1999

Synthesis of proazaphosphatranes and their applications in organic synthesis

Philip Barnaba Kisanga
Iowa State University

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Synthesis of proazaphosphatranes and their applications in organic synthesis

by

Philip Barnaba Kisanga

A dissertation presented to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Major Professor: Dr. John G. Verkade

Iowa State University

Ames, Iowa

1999

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For Major Program

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For the Graduate College

DEDICATION

To my beloved wife Grace Kabang Mikaya, children, family and friends who stood firmly behind me throughout this endeavor.

TABLE OF CONTENTS

CHAPTER 1

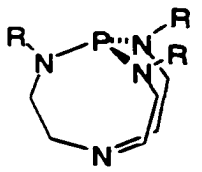
GENERAL INTRODUCTION

Dissertation Organization

This dissertation is made up of ten chapters. The first chapter deals with general introduction and a statement of the purpose of the project. The second chapter is dedicated to the synthesis of three new proazaphosphatranes, while the third chapter describes a modified synthesis of intermediates leading to the proazaphosphatrane $P(i\text{-}PrNCH_2CH_2)_3N$. Subsequent chapters focus on applications of proazaphosphatranes in organic synthesis, namely in the synthesis of glutaronitriles, β-hydroxy nitriles, β-nitroalkanols, *E*-α,β-unsaturated esters and oxazolidines, as well as Michael addition reactions of alcohols, nitroalkanes and imines derived from α-amino esters. The last chapter contains general conclusions and a prospective outlook for the chemistry of proazaphosphatranes. Each of the chapters that describe research, are either papers published or papers still in progress, except for Chapter 3 which discloses a discovery to be submitted as a Record of Invention to Iowa State University Research Foundation (ISURF).

Introduction and Statement of the Project

Proazaphosphatranes (**1**) constitute a class of compounds that is emerging as useful bases for important organic transformations. The strong basicity of these compounds has been attributed to their ability to form a transannular bond leading to the highly stable five-membered azaphosphatrane ring systems **2**.



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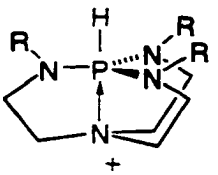

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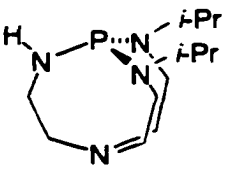
a: R = Me

b: R = *i*-Pr



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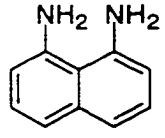
The first proazaphosphatrane $P(MeNCH_2CH_2)_3N$ (**1a**) was synthesized in our group by Lensink *et al.* in 1989.[1] Following its synthesis, this compound was found to be a very strong base with a pK_a of about 26.8 in THF based on competitive deprotonation.[2] However, the pK_a value extrapolated for acetonitrile (41.6) appears to be questionable and will be revisited in Chapter 2 of this dissertation. The proazaphosphatrane **1a** was also found to be a very efficient catalyst for the trimerization of isocyanates.[3] Results of experiments carried out so far suggest that **1a** has a pK_a value higher than that of proton sponge (**4**) and consequently a much stronger base than either DBU (**5**) or TMG (**6**), which are commonly used

nonionic organic bases. The ability of **1a** to equilibrate with P_4-*t*-Bu (**7**) was taken as an indication that this base has a pK_a value close to that of P_4-*t*-Bu.[4] However, the current study (Chapter 2) concludes that this observation was erroneous.



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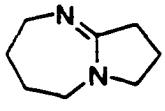

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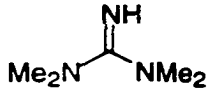

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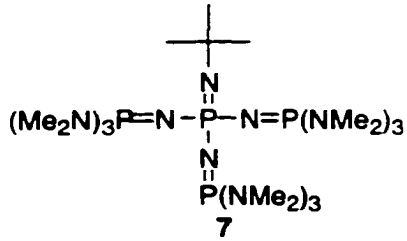

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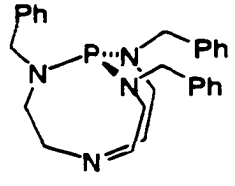
Several new proazaphosphatranes have been prepared over the last decade. Hence, Lensink *et al.*[1] prepared the benzylic derivative **8** while Tang prepared the imidate **9**.[5] Wroblewski[6] and D'Sa[7] were able to place



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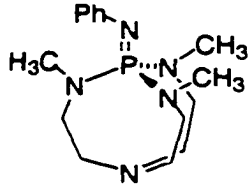

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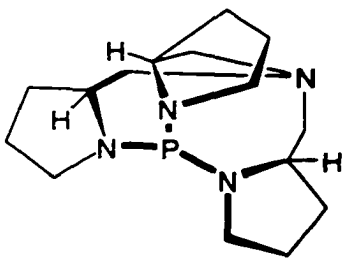
isopropyl groups on the equatorial nitrogens to form proazaphosphatranes **1b** and **3**, respectively, which were also found to be strong bases. With the preparation of these new bases by our group, the list of reactions catalyzed/promoted by proazaphosphatranes grew. D'Sa found that these compounds could function as superior catalysts for the silylation[8] and

acylation[9] of alcohols. An elegant use of proazaphosphatranes discovered by D'Sa *et al.* was the direct synthesis of α,β-unsaturated nitriles.[10] With these results, the proazaphosphatranes caught the attention of other researchers,[11,12] including Yamamoto, who was able to prepare the first C_3 symmetric derivative (**10**) of these compounds.[13] Yamamoto's effort was



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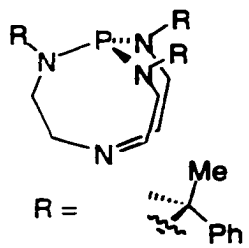

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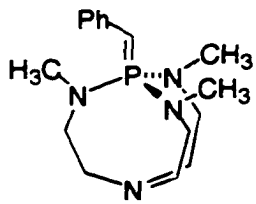

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followed by those Liu *et al.* who successfully prepared a second C_3 symmteric analogue (**11**) that has been found to be an efficient reagent for the determination of enantiomeric excesses of chiral azides.[14] Ilankumaran has found that the proazaphosphatranes can be used as efficient catalysts for transesterification reactions.[15] Studies by Arumugam and McLeod revealed that proazaphosphatranes can be used for dehydrohalogenations that afforded alkenes in excellent yields.[16] In a recent study, D'Sa observed that these bases promote the most efficient synthesis of benzofurans reported to date.[17] He also found that these compounds are capable of isomerizing methylene-interrupted double bonds.[18]

Work by Wang has resulted in the preparation of a novel ylide[19] **12** from the proazaphosphatrane **1a** in addition to using the same proazaphosphatrane as a base for Wittig reactions of aldehydes.[20] Furthermore, Wang *et al.* have been able to prepare homoallylic alcohols from aldehydes and CH_2:$CHCH_2SiMe_3$ in a reaction catalyzed by P(*i*-$PrNCH_2CH_2)_3N$.[21] In other studies, Wang was able to prepare α-cyanohydrins[22] and to induce the reduction of carbonyl compounds with PHMS in the presence of $P(MeNCH_2CH_2)_3N$.[23]

These results show that proazaphosphatranes do offer advantageous alternatives to conventional methodologies. The current study was initiated in an attempt to develop further uses for proazaphosphatranes as reagents and catalysts in organic synthesis. The focus of this study was to identify reactions in which these bases offer improved methodologies. Since the commercially available base $P(MeNCH_2CH_2)_3N$ synthesized by our group is expensive ($238.00/g), we also decided to seek a preparation of analogous bases that could be made more easily at a lower price.

References

1. Lensink, C.; Xi, S. –K.; Daniels, L. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3478.
2. Laramay, M. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1990**, *112*, 9421.
3. Tang, J. -S.; Verkade, J. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 896.
4. (a) For a review see: Verkade, J. G. *Coord. Chem. Rev.* **1994**, *137*, 233. For basicity related studies on these bases see: (b) Milbrath, D. S.; Verkade, J. G. *J. Am. Chem. Soc.* **1977**, *77*, 6607. (c) Leffek, K. T.; Pruszynski, P.; Thanapaalasingham, K. *Can. J. Chem.* **1989**, *67*, 590; and references cited therein. (d) Laramay, M. A.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1991**, *605*, 163.
5. Tang, J. –S.; Dopke, J.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 5015.
6. Wroblewski, A.; Pinkas, J.; Verkade, J. G. *Main Group Chemistry* **1995**, *1*, 69.
7. D'Sa, B.; Verkade, J. G. *Phosphorus Sulfur Silicon* **1997**, *123*, 301.
8. D'Sa, B.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 832.
9. D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963.

10. D'Sa, B.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1997**, *63*, 3691.

11. Memeger, W. U.S. Patent 5,399,662.

12. Russell, T. P.; Mishra, I. B. U.S. Patent Appl. 708,001.

13. Ishikara, K.; Karumi, Y.; Kondo, S.; Yamamoto, H. *J. Org. Chem.* **1998** *63*, 5692.

14. Liu, X.; Ilankumaran, P.; Guzei, I.; Verkade, J. G. manuscript in preparation.

15. Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086.

16. Arumugam, S.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827.

17. D'Sa, B.; Kisanga, P.; Verkade, J. G. submitted.

18. D'Sa, B.; Kisanga, P.; Verkade, J. G. manuscript in preparation.

19. Wang, Z.; Verkade, J. G. *Tetrahedron Lett.* **1998**, *39*, 9331.

20. Wang, Z.; Verkade, J. G. *Heteroatom Chem.* **1998**, *9*, 687.

21. Wang, Z.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* in press.

22. Wang, Z.; Zhang, G.; Verkade, J. G. manuscript in preparation.

23. Wang, Z.; Verkade, J. G. manuscript in preparation.

CHAPTER 2

SYNTHESIS OF NEW PROAZAPHOSPHATRANES AND THEIR APPLICATION IN ORGANIC SYNTHESIS

A paper to be submitted to Tetrahedron

Philip B. Kisanga[a,b] and John G. Verkade[b,c]

Abstract

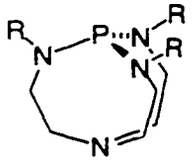
We report herein the synthesis of the new strong bases $P(RNCH_2CH_2)_3N$ (R= Me_3CCH_2, Me_2CHCH_2) and $P(HNCH_2CH_2)_2NCH_2CH_2NCHMe_2$. The new azaphosphatranes $[HP(RNCH_2CH_2)_3N]Cl$ (R= Me_3CCH_2, Me_2CHCH_2) have P-N_{ax} distances of 2.047 and 1.958 Å, respectively. We also report the synthesis of the tetramine precursor to the latter proazaphosphatrane (namely, $(H_2NCH_2CH_2)_2NCH_2CH_2NHCHMe_2$) in a remarkable yield and the use of a novel separation technique to separate it from a mixture with the di- and tri-isopropyl subsituted analogues.

Introduction

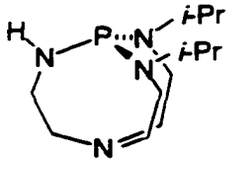
The nonionic superbases **1a**,[1] **1b**,[2] and **1f**,[3a] first synthesized in our laboratories, have been found to be efficient catalysts and promoters for many

[a] Graduate student and University Professor, respectively, Department of Chemistry, Iowa State University.
[b] Primary researcher and author. [c] Author for correspondence.

reactions. Thus, these proazaphosphatranes can catalyze the trimerization of isocyanates,[4] the dehydrohalogenation of alkyl halides,[5] the synthesis of α,β-



1a R = Me
1b R = *i*-Pr
1c R = Piv
1d R = *iso*-Bu
1e R = Et



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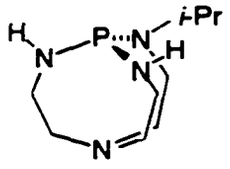
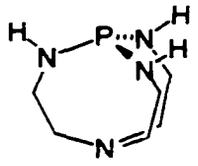


1g



1h

unsaturated nitriles,[6] β-hydroxy nitriles,[7] and homoallylic alcohols,[8] the transesterification of esters,[9] the deprotection of acylated alcohols[10a] and silylated alcohols,[10b] the synthesis of β-nitroalkanols,[11] the synthesis of α,α-dicyano-α,β-olefins,[12] Michael addition reactions,[13] the silylation of hindered alcohols,[14] the conjugation of methylene-interrupted double bonds,[15] the synthesis of glutaronitriles,[16] the synthesis of benzofurans,[17] and the synthesis of oxazolidines.[18] We have also been able to utilize these bases stoichiometrically in other syntheses, such as the Wittig products,[19] Stille coupling products,[20] α,β-unsaturated esters[21] and oxazoles.[22] Compound **1a** (available from Strem Chemicals) has been extensively studied and found to be superior to other nonionic bases, such as DBU and proton sponge.[23]

Recent studies with **1a**, **1b**, and **1f** suggests that these bases have slightly different basicities.[2,3,6] Furthermore, we have found that **1b** is superior to **1a** in a number of reactions as a result of its higher basicity and better stability with respect to oligomerization.[7,8,21] It is imperative that new homologous proazaphosphatranes be synthesized in order to facilitate studies aimed at understanding the effect of the PN_3 nitrogen substituents on the basicity and catalytic properties of this class of compounds. More economical and convenient syntheses of such trisubsituted proazaphosphatranes are also important to investigate, because in our experience, trisubstituted bases are more stable to oligomerization than the less substituted analogues.

We have previously attempted to use acetaldehyde for the synthesis of $N(CH_2CH_2NHEt)_3$ (the precursor to **1e**) through the reduction of the intermediate *tris*-aldimine formed with $N(CH_2CH_2NH_2)_3$ (**2**).[2] However, oligomerization of the intermediate aldimine was faster than its reduction and consequently, the tetramine $N(CH_2CH_2NHEt)_3$ had to be prepared by a less convenient procedure.[24] This was achieved by reacting $N(CH_2CH_2NH_2)_3$ (**2**) with acetic anhydride followed by reducing the *tris*-amide thus produced with lithium aluminum hydride. Although the *tris*-aldimine derived from acetaldehyde proved to be unsuitable, we believed that higher aldehydes might

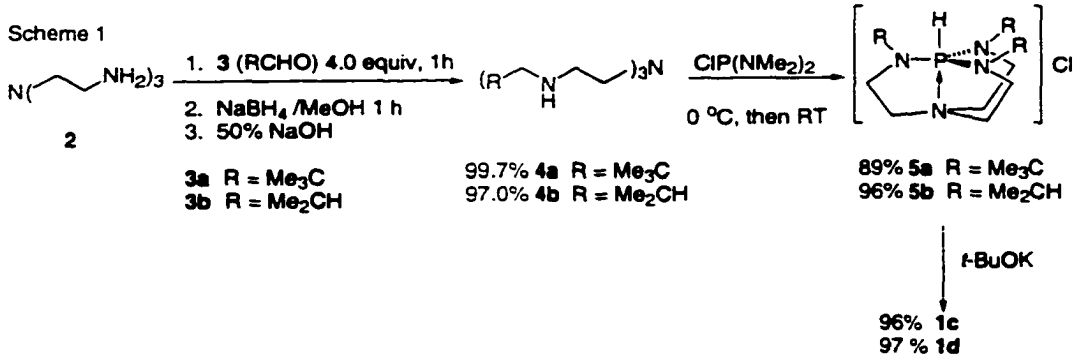
lead to *tris*-aldimines that are less prone to oligomerization because of steric hindrance. We therefore decided to investigate the reaction of pivalaldehyde (**3a**) and isobutyraldehyde (**3b**) with **2** and we report herein the synthesis of proazaphosphatranes **1c** and **1d**, respectively, derived from these aldehydes.

We have previously reported the synthesis of the proazaphosphatrane **1b**[2] and its less substituted analogue **1f**.[3] Preliminary results have also indicated that **1h** is more basic than **1a**, although the pure base could not be isolated.[25] We thus tentatively concluded that if we could prepare proazaphosphatrane **1g**, it might exceed **1a**, **1b** and **1f** in basicity.

Results and Discussion

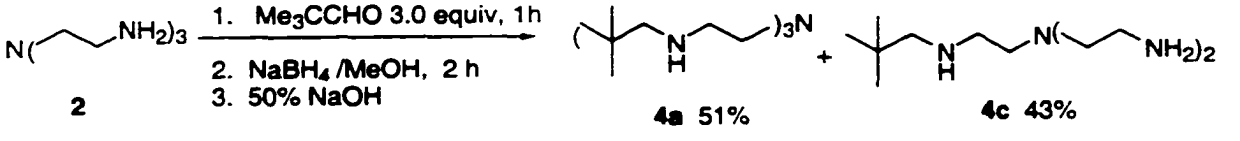
Synthesis of $N(CH_2CH_2NHCH_2CMe_3)_3$ (4a), $[HP(Me_3CCH_2NCH_2CH_2)_3N]Cl$ (5a) and $P(Me_3CCH_2NCH_2CH_2)_3N$ (1c)

The preparation of **4a** was achieved by stirring a 1:4 mixture of **2** and pivalaldehyde for 1 hour and then reducing the intermediate aldimine with



sodium borohydride in methanol. The excess borohydride was quenched with 50% sodium hydroxide to afford **4a** in 99.7% yield (Scheme 1). This synthesis of **4a** is more convenient than that recently reported by Scheer *et al.* (who provided no physical data for the pure tetramine).[26] The Scheer synthesis was carried out by reacting the tetramine **2** with pivaloyl anhydride followed by the reduction of the triamide thus produced with lithium aluminum anhydride. When the amount of pivalaldehyde in Scheme 1 was reduced to 3.0 equiv, conversion to **4a** decreased to 51% owing to the formation of 43% of the less substituted derivative **4c** (Scheme 2). The tetramine **4a** is not appreciably soluble in acetonitrile and as a result, the hydrochloride **5a** was successfully prepared in a solvent system composed of methylene chloride and ethyl ether in

Scheme 2



2 **4a** 51% **4c** 43%

89% yield (Scheme 1) and then deprotonated in THF to afford **1c** in 71% yield. The use of methylene chloride alone led to inconsistent results, while ether failed to induce a clean reaction. Although the reaction was successful in THF, the product thus obtained could not be purified.

The weak acid **5a** displayed a ^{31}P signal at 2.29 ppm, which is significantly downfield (by ~12 ppm) compared with that of the commonly

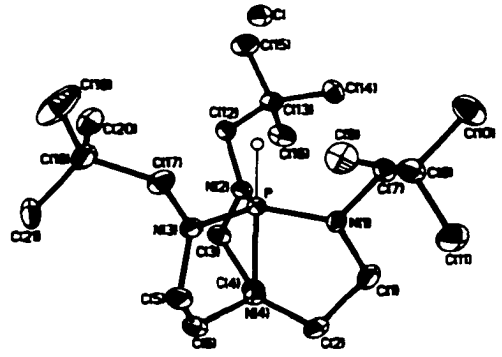
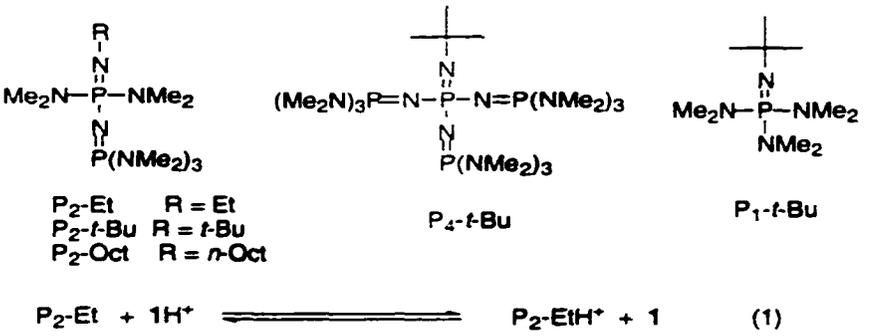


Figure 1. Molecular structure of **5a**. Ellipsoids are drawn at the 50% probability level

used trisubstituted analogues **1a**H^+ and **1b**H^+.[2] However, X-ray crystallography (Figure 1) showed that the P-N_{ax} distance (2.047 Å) was within experimental error (i.e. within 3 x esds) of those found in other analogues [**1a**H^+ (1.967 Å), **1b**H^+ (1.946 Å), **1f**H^+ (2.078 Å) reported previously from our laboratories.[2] The $N_{eq}PN_{eq}$ angles of 118-119 ° are also comparable to those of the other analogues reported previously.[2] The proazaphosphatrane base **1c** displayed a ^{31}P NMR signal at 144.3 ppm in C_6D_6, which upon addition of two drops of nitromethane rapidly disappeared and was replaced by a single ^{31}P signal at 2.29 ppm. This experiment demonstrates that the new proazaphosphatrane has a pK_a value of at least 28 in acetonitrile, since the pK_a of nitromethane in CH_3CN is 28.[27a] The strong basicity of this proazaphosphatrane was confirmed by the ability of its conjugate acid **5a** to equilibrate with P_2-Et in acetonitrile upon

standing at room temperature for 1 h in an experiment monitered in a flame-sealed tube by ^{31}P NMR analysis (equation 1). In the presence of 10 mol % of $Cr(acac)_3$ as a relaxagent, this reaction afforded an equilibrium mixture that could be analyzed accurately by ^{31}P NMR spectroscopy to afford a pK_a of 32.84



in CH_3CN for the conjugate acid **5a** based on the pK_a of P_2-Et phosphazene base reported by Schwesinger *et al.*[27a] The pK_a values (average of at least two measurements) similarly obtained for **1a** through **1g** (except **1e**, which has not yet been found to be synthetically useful) in CH_3CN are shown in Table 1. It is worth mentioning that these pK_a values (32.90 – 34.49) are substantially lower (by ~ 8 pK_a units) than we estimated previously.[27b] In that report, P_4-*t*-Bu, the only phosphazene base commercially available at that time was used in a manner analogous to that described in equation 1. However, for reasons that are not clear, an apparent equilibrium was observed in an experiment utilizing an equimolar amount of each of P_4-*t*-Bu and **1a**H^+. In a repetition of that experiment, we have found that a solution of P_4-*t*-Bu in THF completely

deprotonates an equimolar amount of either **1aH**$^+$ or **1dH**$^+$ (**5b**) in less than 10 min. On the other hand, P_1-*t*-Bu was unable to deprotonate **1aH**$^+$. Therefore, the basicity of proazaphosphatranes is comparable with that of P_2 phosphazene bases such as P_2-Et, P_2-*t*-Bu and P_2-Oct.

Synthesis of N($CH_2CH_2NHCH_2CHMe_2$)$_3$ (4b), [HP(Me_2CHCH_2N-CH_2CH_2)$_3$N]Cl (5b) and P($Me_2CHCH_2NCH_2CH_2$)$_3$N (1d)

The synthesis of **4b** was achieved analogously to that of **4a** as discussed above. Hence **2** was reacted with isobutyraldehyde in a small amount of *t*-butyl alcohol or methanol, followed by reduction with sodium borohydride in methanol to afford a 97% yield of **4b** after distillation (Scheme 1). When isobutyraldehyde was not first dissolved in an alcohol, the isolated yield of **4b** decreased to 89%. Ring closure to **5b** was achieved in acetonitrile in 96% yield in a manner analogous to that described for **5a**. However, scale-up of the reaction led to lower yields as a result of the limited solubility of **4b** in this solvent. This problem was circumvented upon altering the solvent system to methylene chloride or THF. This afforded 87-95% yields of **5b** depending on the scale of the reaction. The P-N_{ax} distance in **5b** is 1.958 Å, which is within experimental error (i.e. within 3 x esds) of those reported for **1aH**$^+$ and **1bH**$^+$.[2] The $N_{eq}PN_{eq}$ angle of 119-120 is also close to those reported for the same

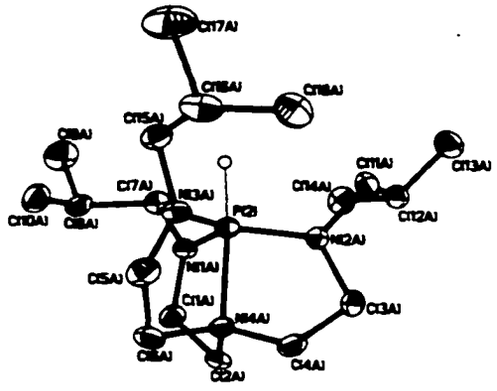


Figure 2. Molecular structure of **5b**. Ellipsoids are drawn at the 50% probability level

analogues.[2] However, the ^{31}P NMR chemical shift of –7.1 ppm is shifted downfield by over 2 ppm compared to that of the commonly used analogues **1a**H^+ and **1b**H^+.[2] The molecular structure of **5b** shows that it crystallizes to form monoclinic crystals in which two molecules crystallize with four solvent ($CHCl_3$) molecules. It is worth mentioning that the ring closure reaction was unsuccessful in ether. Deprotonation of **5b** was achieved using potassium *t*-butyl oxide in THF, followed by extraction with pentane, to afford **1d** in 97% yield as a colorless oil that solidifies to form a white solid upon storing at –4 °C for 24 h. When solid formation did not occur, the colorless liquid was frozen in a dry ice-acetone bath, which was then allowed to warm to –4 °C in the freezer to form a white solid that was kept at or below –4 °C. However, **1d** can be used in the liquid form. So far, we have observed no change in either the

physical data (^{31}P NMR and ^{1}H NMR spectra) or the chemical properties of **1d** upon storing the compound in either the liquid or solid state for up to 30 days. A liquid sample of **1d** stored at room temperature over the same time-period, also showed no change in either the ^{1}H NMR or ^{31}P NMR spectrum. Furthermore, a sample of **1d** left in an open tube for 24 h showed no formation of the oxide as occurs with **1a**, **1b**, and **1f**. The base **1d** showed a single ^{31}P NMR signal at 130.9 ppm. Upon addition of nitromethane to the solution of this compound in C_6D_6, this peak instantaneously disappeared and was replaced by a single peak at –8.2 ppm (**5b**) which is characteristic of pentacoordinate phosphorus.

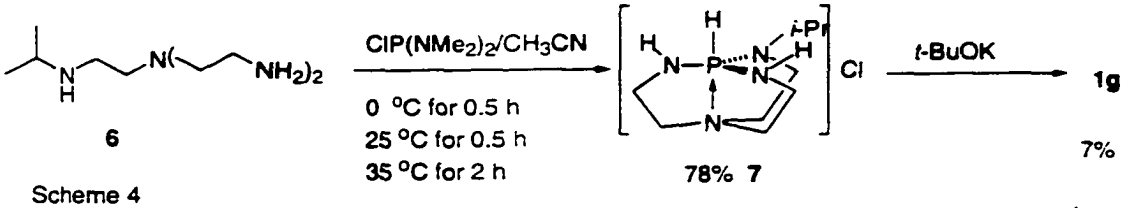
Compound **1d** was thus obtained in three steps in 64 - 90% overall yield. The lower limit occurred in large scale synthesis (0.5 mol) in which stirring difficulties were encountered. Nevertheless, **1d** is the least expensive proazaphosphatrane we have prepared so far.

Synthesis of $(H_2NCH_2CH_2)_2NCH_2CH_2NHCHMe_2$, (6) $HP(HNCH_2CH_2)_2N$-$CH_2CH_2NCHMe_2]Cl$ (7) and $[P(HNCH_2CH_2)_2NCH_2CH_2NCHMe_2]$ (1g)

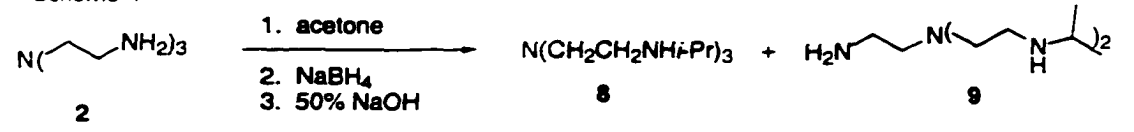
The synthesis of **1g** in Scheme 3 (to be discussed shortly) required a viable route to tetramine **6**. Although syntheses of the more highly subsituted analogues **8**[2] and **9**[3] in Scheme 4 were reported previously from our

laboratories, neither report mentioned the mono-substituted analogue **6**, because we were unable to observe it in the product mixture. We have recently noted its formation in varying amounts during subsequent preparations of both **8** and **9**.

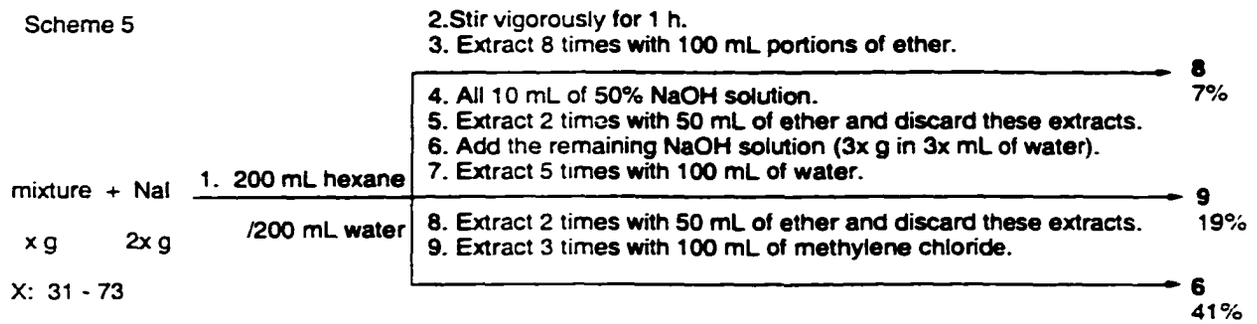
Scheme 3



Scheme 4



Therefore, a study aimed at optimizing the formation of **6** was initiated. Compound **6** was obtained as the major product (Scheme 4) by reducing the amount of acetone used in the reaction to 3.2 equiv and also reducing the time of addition of sodium borohydride to 3 h. However, none of the three products could be isolated from the mixture of products by distillation because of the proximity of their boiling points. Purification based on the difference in the solubility of their sodium iodide complexes was achieved according to Scheme 5. A mixture of **6**, **8** and **9** was stirred in a 1:1 mixture of hexane and water for 1 h in the presence of sodium iodide. Separation of the organic layer, followed by extraction of the aqueous layer with ether afforded **8**, which does not form a complex with sodium iodide that is water-insoluble. The aqueous layer was



then treated with 50% aquesous sodium hydroxide to pH 11 to free **9**. This basic aqueous solution was extracted with ether and dried over anhydrous potassium carbonate. The sodium iodide-**6** complex remained as an insoluble viscous oil above the aqueous layer and was extracted with methylene chloride to afford an oily material that was distilled to afford pure **6**.

The conversion of **6** to its hydrochloride **7** was achieved as shown in Scheme 3. In this process, **6** was added to $ClP(NMe_2)_2$ in acetonitrile at 0 °C. The reaction mixture was stirred for 0.5 h at this temperature, followed by stirring at room temperature for an additional 0.5 h. The reaction mixture was placed in a warm water bath (35 °C) and stirred for 2 hours. The intermediate **7** that precipitated was filtered under vacuum and washed with cold acetonitrile to afford the pure salt. Alternatively, the reaction mixture was stirred at room temperature overnight to afford the hydrochloride salt **7** in comparable yields to that described above. Attempted deprotonation of **7** with potassium *t*-butoxide in THF, followed by extraction with pentane, afforded a liquid material with ^{31}P

NMR spectral peaks at 124 and 134 ppm. The two peaks were found to persist when $MeNO_2$ was added to a solution of the product in C_6D_6 and therefore we concluded that this material could not be **1g**. The second step in Scheme 3 was then repeated in benzene. The product isolated exhibited a ^{31}P NMR chemical shift at 100.9 ppm in C_6D_6. This peak rapidly disappeared on addition of $MeNO_2$ to a C_6D_6 solution of the product with the subsequent appearance of a peak at –32.6 ppm, which is characteristic of **7**. The peak at 100.9 ppm for the mono-isopropyl-substituted **1g** (although slightly shifted in the presence of MeCN to 101.4 ppm) also agrees favorably with the trend observed for disubstituted **1f** and trisubstituted **1b**, whose ^{31}P NMR chemical shifts are 110.5[3a] and 117[2] ppm, respectively.

Compound **1g** was very unstable, oligomerizing even at –4 °C over 24 h, although crude **1g** dissolved in benzene and kept in the freezer for up to seven days did not oligomerize substantially. We previously observed that **1f** oligomerized when kept at room temperature for a week and that it could be kept for longer periods of time when kept below –4 °C.[3] An attempt at preparing the unsubstituted proazaphosphatrane **1h** also has remained unsuccessful so far due to similar oligomerizations, although it could be observed in solution and stable derivatives were isolated.[28] The ^{1}H and ^{13}C

NMR spectra of **1g** were not sufficiently clean to allow elemental analysis and/or HRMS. An attempt at redistillation was unsuccessful because of the small amount of material in hand. However, the observed purity (93% by ^{31}P NMR analysis) was sufficient for NMR characterization. The rest of the material, as determied by ^{31}P NMR analysis was the oxide whose presence is attributed to adventitious oxygen that readily reacted with **1g**.

Comparison of the catalytic properties of 1b, 1c and 1d

Since **1d** is less expensive than any of the other proazaphosphatrane bases we have prepared so far, we selected it for the comparison of its efficiency as a catalyst for a number of reactions for which **1b** has proved to be a superior base. We also compared these key reactions for **1c** as well. Thus, we used both **1c** and **1d** for the synthesis of several β-hydroxy nitriles, β-nitroalkanols, α,β-unsaturated esters and for the oxa-Michael addition of allyl alcohol to some α,β-unsaturated ketones. Pertinent data for these comparative reactions in Table 2 reveal that **1d** is generally as efficient as **1b** and more efficient in some cases. The most noteworthy of these reactions is the preparation of a β-hydroxy nitrile from *p*-anisaldehyde and acetonitrile in the presence of 2.2 equiv of magnesium sulfate. Previously, we found that this

reaction proceeds with relatively modest yield (78%) in the presence of **1b** as the catalyst. In the presence of **1d**, the conversion of *p*-anisaldehyde to the β-hydroxy nitrile is 96% at 0 °C with relatively higher formation of the α,β-unsaturated nitrile (14% compared to 4% using **1b**). However, by reducing the reaction temperature to –5 °C, a similar conversion is obtained with only 3% of the α,β-unsaturated nitrile being observed by ^{1}H NMR integration with a corresponding 91% isolated yield of the β-hydroxy nitrile. Similarly, the β-hydroxy nitrile from the reaction of *p*-chlorobenzaldehyde and acetonitrile was obtained in a superior yield (88%). Likewise, the preparation of β-hydroxy nitriles from 2-methylcyclohexanone and 2-butanone proceeded with superior yields. The reaction of mesityl oxide and 4-hexen-3-one with allyl alcohols provide two other examples in which **1d** is superior to **1b**. We have reported previously[11] a relatively low nitroaldol yield in the reaction of 3-pentanone and nitromethane (see also Table 2). We find here that **1d** affords a much better yield (Table 2). Table 2 also show that **1c** is not a useful catalyst for the synthesis of β-hydroxy nitriles and the synthesis of α,β-unsaturated esters. The poor reactivity of **1c** in acetonitrile is probably due to its lower basicity in addition to its lower solubility in this solvent. However, **1c** is highly effective

for the addition of allyl alcohol to enones[13] and for the promotion of the Henry (nitroaldol) reaction in the presence of magnesium sulfate.[11]

Experimental Section

All ring closure and deprotonation reactions were carried out under nitrogen. *Tris*(2-aminoethyl)amine (**2**) was distilled before use. The aldehydes (Aldrich) were used as received. The solvents THF, pentane, benzene, methylene chloride and acetonitrile were dried according to standard procedures.[29] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker VRX300 or Bruker DRX400 instrument and calibrated using TMS as an internal standard. ^{31}P NMR were recorded on a Bruker DRX400 instrument. The melting and boiling points of the products were obtained in sealed tubes under nitrogen and are uncorrected. The bases **1a**,[1] **1b**,[2] and **1f**[3] were prepared according to previously reported methods, although **1a** is commercially available (Strem).

Procedure for the Synthesis of $N(CH_2CH_2NHCH_2CMe_3)_3$ (4a)

To 14.6 g (0.10 mol) of *tris*(2-aminoethyl)amine (**2**) in a 500 mL round-bottomed flask placed in an ice bath was added over 20 min 49 mL of an 80% commercially available pivalaldehyde solution in *t*-butyl alcohol. The mixture was allowed to stir at room temperature for 1 hour after which 100 mL of

methanol was added. The resulting brownish solution was allowed to cool to 5 °C and then 11.1 g of powdered sodium borohydride was added portion-wise over 1 h at the end of which unreacted sodium borohydride could be seen as a white solid. The reaction mixture was quenched by the addition of 60 mL of a 50% sodium hydroxide solution. At this point, a solid precipitated which was dissolved by the addition of 100 mL of water. The reaction mixture was extracted with hexane (4x100 mL) and the hexane extracts were combined and treated with 50 mL of 1.0 M sodium iodide solution. The hexane layer was separated and the aqueous layer was extracted with 3x50 mL of hexane. The hexane extracts were combined and then dried over anhydrous potassium carbonate. Removal of the volatiles under reduced pressure, followed by distillation under vacuum, afforded 34.9 g (99.7%) of a pale product **4a** (B.P. 160 °C / 2 Torr) that was ^{1}H NMR-pure. ^{1}H NMR ($CDCl_3$): δ 2.64 (t, 6H), 2.48 (t, 6 H), 2.34 (s, 6 H), 0.99 (s, 27 H),. ^{13}C NMR ($CDCl_3$): δ 63.2, 55.7, 49.9, 32.3, 28.5. HRMS Calcd for $C_{21}H_{49}N_4$ 357.39573. Found *m/e* ($M+H^+$) 357.39558.

Procedure for the Preparation of a mixture of $N(CH_2CH_2NHCH_2CMe_3)_3$ (4a) and $(H_2NCH_2CH_2)_2NCH_2CH_2NHCH_2CMe_3$ (4c)

To 14.6 g (0.10 mol) of *tris*(2-aminoethyl)amine (**2**) in a 500 mL round-bottomed flask placed in an ice bath was added 36.0 mL of an 80% commercially available pivalaldehyde solution in *t*-butyl alcohol over 20 min. The mixture was allowed to stir for 1 hour after which 100 mL of methanol was added. The resulting brownish solution was allowed to cool to 5 °C and then 9.50 g of powdered sodium borohydride was added portion-wise over 1 h at the end of which unreacted sodium borohydride was present as a white solid. The reaction mixture was quenched by the addition of 60 mL of a 50% sodium hydroxide solution. At this point, a solid precipitated which was dissolved by the addition of 100 mL of water and the reaction mixture was extracted with ether (4x100mL). The ether extracts were combined and dried over anhydrous potassium carbonate. Removal of the volatiles under reduced pressure afforded a mixture of the title products. The separation of these products was accomplished as follows. The product mixture was dissolved in 50 mL of hexane in a 500 mL round-bottomed flask followed by the addition of 50 mL of 1.00 M solution of NaI. The mixture was stirred for 0.5 h, the organic layer was separated and the aqueous layer extracted with 4x100 mL of hexane to

afford a solution of $N(CH_2CH_2NHCH_2CMe_3)_3$ (**4a**) that was purified as detailed above to afford a 51% yield (14.6 g) of the tetramine **4a**. The aqueous layer was placed in a water bath and 50 mL of 50% sodium hydroxide was added slowly (to avoid a strong exotherm) and then the mixture was extracted with 4x60 mL of ether. The ether extracts were combined and dried over anhydrous potassium carbonate. Removal of the volatiles under reduced pressure followed by distillation at 140 °C/500 milliTorr afforded 9.31 g (43%) of **4c**. ^1H NMR (C_6D_6): δ 2.52-2.61 (overlapping region, 6H), 2.40 (t, 2 H), 2.30 (s, 2H), 2.25 (t, 4 H), 0.96 (s, 9 H). ^{13}C NMR (C_6D_6): δ 63.3, 58.5, 55.3, 49.7, 41.0, 32.2, 28.4.

Preparation of $[HP(Me_3CCH_2NCH_2CH_2)_3N]Cl$ (5a)

To 50.0 mmol of $ClP(NMe_2)_2$ prepared *in situ* in 125 mL of methylene chloride by the slow addition of 1.5 mL (16.7 mmol) of PCl_3 to 6.1 mL (33.3 mmol) of $P(NMe_2)_3$ at 0 °C in an ice bath, was added 17.8 g (50 mmol) of $N(CH_2CH_2NHCH_2CMe_3)_3$ (**4a**) dissolved in 50 mL of methylene chloride under nitrogen. The flask was equipped with an outlet for the escape of the byproduct Me_2NH. After addition of **4a**, 100 mL of dry ether was added and the reaction mixture was stirred for 48 h at room temperature after which the volatiles were removed under reduced pressure. The residue was partitioned between 10 mL of water and 50 mL portions of methylene chloride until the methylene chloride

extracts afforded no residue. The organic extracts were combined and dried over anhydrous magnesium sulfate and then the volatiles were removed under reduced pressure to afford an oily material that was dissolved in 30 mL of methylene choride. Ether was added until a slight turbidity was seen. The flask was then placed in the freezer for at least 2 h. After decantation of the supernatant, the white material that precipitate was washed with 2x15 mL of ice-cold ether to afford 18.3 g (89%) of **5a**. ^{1}H NMR ($CDCl_3$): δ 3.63 (s, 6 H), 3.26 (t, 6 H), 2.68 (td, 6 H), 0.89 (s, 27 H). ^{13}C NMR ($CDCl_3$): δ 61.1 (d, J = 11 Hz), 48.0 (d, J = 7.4 Hz), 42.2 (d, J = 6.0 Hz), 33.5 (d, J = 3.8 Hz). ^{31}P NMR ($CDCl_3$): δ 2.29.

Procedure for the Preparation of $P(Me_3CCH_2NCH_2CH_2)_3N$ (1c)

To a mixture of 6.77 g (16.1 mmol) of $[HP(Me_3CCH_2NCH_2CH_2)_3N]Cl$ (**5a**) and 3.60 g (32.2 mmol) of *t*-BuOK in a Schlenk flask was added 100 mL of dry THF under nitrogen. The reaction mixture was stirred for 2 h at room temperature after which THF was distilled off under vacuum. Then 150 mL of pentane was added to the reaction mixture under nitrogen and stirring was continued for one more hour. The reaction mixture was allowed to settle and the clear upper layer was vacuum transferred by means of a canula into a 500 mL Schlenk flask through a fritted glass. Another portion of pentane (100 mL)

was added under nitrogen and the mixture stirred for 0.5 h after which the whole mixture was transferred by canula onto the fritted glass under nitrogen. The mixture was allowed to filter slowly under vacuum. After filtration was complete, the solvent was removed under vacuum to afford 4.71 (97% yield) of the base **1c** as a white solid that was found to be 98% pure by ^{1}H NMR spectrospcopy and essentially pure by ^{31}P NMR spectroscopic analysis. ^{1}H NMR (C_6D_6): δ 2.86-2.95 (overlapping region, 18 H), 1.01 (d, 27 H). ^{13}C NMR (C_6D_6): δ 66.6 (d, J = 43.8 Hz), 51.8 (d, J = 1 Hz), 51.2 (d, J = 6.8 Hz), 34.4 (d, J = 2.8 Hz), 28.3 (d, J = 2.5 Hz). ^{31}P NMR (C_6D_6): δ 144.3.

Preparation of $N(CH_2CH_2NHCH_2CHMe_2)_3$ (4b)

To 14.6 g (0.1 mol) of *tris*(2-aminoethyl)amine (**2**) in a 500 mL round-bottomed flask was added dropwise. 36 mL (28.8 g, 0.40 mol) of isobutyraldehyde dissolved in 10 mL of *t*-butyl alcohol over 20 minutes. The mixture was allowed to stir at room temperature for 1 h after which 100 mL of methanol was added. The resulting colorless solution was allowed to cool to 5 °C in an ice bath and then 11.1 g of powdered sodium borohydride was added portion-wise over 1 h at the end of which unreacted sodium borohydride was present as a white solid. The reaction mixture was quenched by the addition of 60 mL of aqueous 50% sodium hydroxide followed by the addition of 100 mL

of water to dissolve the precipitated inorganic material. The reaction mixture was extracted with 4x100 mL of hexane. The hexane extracts were combined and then treated with 50 mL of 1.0 M sodium iodide. The hexane layer was separated and then the aqueous layer was washed with 3x50 mL of hexane. The hexane extracts were combined and dried over anhydrous potassium carbonate and then the volatiles removed under reduced pressure. The crude product was distilled under vacuum to afford 30.5 g (97%) of **4b** as a pale liquid (B.P. 160 ^{0}C / 2 Torr). ^{1}H NMR ($CDCl_3$): δ 2.60 (t, 6H), 2.46 (t, 6 H), 2.40 (d, 6 H), 1.72 (m, 3 H), 1.25 (s, 3H), 0.95 (d, 18 H),. ^{13}C NMR ($CDCl_3$): δ 59.1, 55.2, 48.9, 29.5, 21.4. HRMS Calcd for $C_{18}H_{45}N_4$ 315.34787. Found *m/e* ($M+H^+$) 315.34856.

Procedure for the Preparation of [HP($Me_2CHCH_2NCH_2CH_2$)$_3$N]Cl (5b)

To 50 mmol of $ClP(NMe_2)_2$ prepared *in situ* in 125 mL of acetonitrile by the slow addition of 1.5 mL (16.7 mmol) of PCl_3 to 6.1 mL (33.3 mmol) of $P(NMe_2)_3$ at 0 °C in an ice bath, was slowly added 15.7 g (50 mmol) of tetramine **4b** dissolved under nitrogen in 50 mL of acetonitrile. The flask was equipped with an outlet for the escape of the byproduct Me_2NH. A white precipitate was observed to form gradually. After completion of the addition, the reaction mixture was stirred for 2 h at room temperature after which 100 mL

of ether was added. Stirring was continued for two additional hours after which the volatiles were removed under reduced pressure. The residue was then partitioned between 100 mL of acetonitrile and 100 mL of hexane. The hexane fraction, upon removal of the volatiles afforded 0.3 g of unreacted $N(CH_2CH_2NHCH_2CHMe_2)_3$ (**4b**). The acetonitrile fraction afforded a residue, which was dissolved in the least amount of THF and then ether added until no more precipitation was observed with further addition of ether (total ~150 mL). The flask was then placed in the freezer for at least 2 h after which the clear layer was decanted from the residue. The residue was washed with 20 mL of cold THF and then was dried under vacuum to afford 18.1 g (96% yield) of white solid **5b**. ^{1}H NMR ($CDCl_3$): δ 0.85 (d, 18 H), 1.83 (septet, 2 H), 2.61 (d, 6H), 3.10 (t, 6 H), 3.56 (t, 6 H). ^{13}C NMR ($CDCl_3$): δ 55.7 (d, J = 12.7), 47.0 (d, J = 7.8 Hz), 39.6 (d, J = 5.9 Hz), 26.8 (d, J = 4.7 Hz), 20.0 (s). ^{31}P NMR ($CDCl_3$): δ -7.1 (s).

Procedure A for a large scale synthesis of $[HP(Me_2CHCH_2NCH_2CH_2)_3N]Cl$ (5b)

To 192 mmol of $ClP(NMe_2)_2$ prepared *in situ* in 200 mL of methylene chloride by the slow addition of 5.7 mL (64 mmol) of PCl_3 to 23.4 mL (128 mmol) of $P(NMe_2)_3$ at 0 °C in an ice bath, was added slowly under nitrogen

60.0 g (191 mmol) of tetramine **4b** dissolved in 150 mL of methylene chloride. The flask was equipped with an outlet for the escape of the byproduct Me_2NH. After completion of the addition, the reaction mixture was stirred for 6 h at room temperature after which the reaction mixture was kept in the refrigerator overnight. The volatiles were removed *in vacuo*, the residue was dissolved in 100 mL of methylene chloride and then water was added slowly until two layers were seen. The layers were separated and the aqueous layer was extracted with 6x50 mL portions of methylene chloride. The organic extracts were combined and dried over anhydrous magnesium sulfate, and then the volatiles were removed under reduced pressure. The residue was dissolved in the least amount of methylene chloride and then precipitated with 200 mL of dry ether. After decantation, the residue was dried under vacuum to afford 62.9 g (87% yield) of a white product (**5b**) whose ^1H NMR, ^{13}C NMR and ^{31}P NMR spectra were identical to those given above.

Procedure B for a large scale synthesis of $[HP(Me_2CHCH_2NCH_2CH_2)_3N]Cl$ (5b)

To 192 mmol of $ClP(NMe_2)_2$ prepared *in situ* in 300 mL of THF by the slow addition of 5.7 mL (64 mmol) of PCl_3 to 23.4 mL (128 mmol) of $P(NMe_2)_3$ at 0 °C in an ice bath, was slowly added 60.0 g (191 mmol) of

tetramine **4b** dissolved in 200 mL of THF under nitrogen. The flask was equipped with an outlet for the escape of the byproduct Me_2NH. After completion of the addition, the reaction mixture was stirred for 6 h at room temperature after which 200 mL of ethyl ether was added. The reaction mixture was then refrigerated overnight. The reaction mixture was then filtered through a medium glass frit, the precipitate was washed three times with cold THF and then the product was dried under vacuum to afford 53.5 g (74.1%) of compound **5b**. The ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were identical to those given above.

Preparation of $P(Me_2CHCH_2NCH_2CH_2)_3N$ (1d)

To a mixture of 13.7 g (136 mmol) of **5b** and 8.09 g (72.2 mmol) of *t*-BuOK in a 500 mL Schlenk flask was added under nitrogen 100 mL of dry THF. The reaction mixture was stirred for 2 h at room temperature after which THF was distilled off under vacuum. Pentane (150 mL) was then added to the reaction mixture under nitrogen and stirring was continued for an additional hour. The reaction mixture was then allowed to settle and the clear upper layer was vacuum transferred by means of a canula into a 500 mL Schlenk flask through a glass frit. Another portion of pentane (100 mL) was added under nitrogen to the residue in the reaction flask and the mixture stirred for 0.5 h

after which it was transferred by canula into the fritted glass tube under nitrogen. After the mixture was allowed to filter slowly under vacuum, the solvent was removed under vacuum and the crude base transferred under nitrogen by means of a syringe (or pipette) into a 50 mL round-bottomed flask. Distillation at 132 °C/ 210 milliTorr afforded 12.0 g (97% yield) of the product **1d**. ^{1}H NMR (C_6D_6): δ 0.93 (d, 18 H), 1.82 (septet, 3 H), 2.75 (overlapping region, 12H). ^{13}C NMR (C_6D_6): δ 59.1 (d), 52.1 (d), 47.2 (d), 29.2 (d), 21.2 (d). ^{31}P NMR (C_6D_6): δ 130.9.

Preparation of a mixture of 6, 8, and 9

To a solution of 76 g (0.52 mol) of *tris*(2-aminoethyl)amine (**2**) and 81.0 g of anhydrous sodium acetate in 500 mL of water was added 225 mL of glacial acetic acid in a 3.0 L three-neck flask. The mixture was stirred by means of a mechanical stirrer at 500 rpm while it cooled to room temperature. The mixture was then placed in an ice/salt bath and cooled to 5 °C after which 110 mL (1.67 mol) of acetone was added over 15 min. The solution was allowed to stir for 5 minutes and then 55 g (1.50 mol) of powdered sodium borohydride was added portion-wise over 3 h and the temperature was kept to 5-10 °C. After completion of the addition, the reaction mixture was allowed to stir in the ice bath for 30 additional min and then it was quenched with 200 g of sodium

hydroxide dissolved in 300 mL of water. Extraction of the mixture with 4x100 mL of methylene chloride, drying of the extract over anhydrous potassium carbonate and removal of the extract solvent under reduced pressure afforded 73.1 g of the product mixture.

Separation of the mixture of 6, 8 and 9

To the above mixture of **6**, **8**, and **9** (73.1 g) dissolved in 200 mL of hexane in a 1.0 L round-bottomed flask was added 142 g of sodium iodide followed by 200 mL of water. The mixture was stirred vigorously for 1 h and then extracted with 6x100 mL of ether. After the addition of 10 mL of 50% sodium hydroxide solution, two more extracts obtained with 2x50 mL of ether were collected and dried over anhydrous potassium carbonate. The volatiles were removed under reduced pressure to afford 329 mg of a material that was discarded. When these last extracts contained substantial amounts of **8**, as determined by ^{1}H NMR spectroscopy of the residue, extraction was continued until the extracts produced no more residue upon removal of the volatile components. The organic layers were then combined, dried over anhydrous potassium carbonate and the volatiles removed under reduced pressure to afford crude **8** that was distilled at 85-90 °C/200 milliTorr to afford 9.91 g (7% yield) of **8**. To the aqueous layer was then carefully added (slow addition to avoid an

exothermic reaction) 210 g of sodium hydroxide dissolved in 220 mL of water. The reaction mixture was allowed to cool to room temperature, and then it was extracted with 6x100 mL of ether while making sure that no oily droplets were collected with the organic fraction. The ether extracts were combined and dried over anhydrous potassium carbonate. The volatiles were removed under reduced pressure and the crude product was distilled at 110-120 °C /250 milliTorr affording 22.7 g (19% yield) of **9**. The aqueous layer remaining at this point also displayed the presence of a viscous oily layer which was extracted with 3x100 mL of methylene chloride. The extracts were dried over anhydrous potassium carbonate followed by removal of the solvent under reduced pressure to afford crude **6** that was distilled to afford 40.1 g (41% yield) of **6** as a yellowish liquid (B.P. 137 °C/200 milliTorr) that was 98% pure by ^{1}H NMR spectroscopy. ^{1}H NMR (C_6D_6): δ 2.89 (septet, 1 H), 2.54 (t, 6 H), 2.39 (s, 2 H), 2.24 (t, 4 H), 0.98-1.05 (overlapping region, 11 H). ^{13}C NMR (C_6D_6): δ 58.4, 55.4, 49.5, 46.2, 40.9, 23.8.

Procedure for the Preparation of [HP(NHCH$_2$CH$_2$)$_2$NCH$_2$CH$_2$NCHMe$_2$]Cl (7)

To 50 mmol of ClP(NMe$_2$)$_2$ prepared *in situ* in 100 mL of dry acetonitrile by the slow addition of 1.5 mL (16.7 mmol) of PCl$_3$ to 6.1.mL (33.3 mmol) of

$P(NMe_2)_3$ at 0 °C in an ice bath, was added under nitrogen 9.40 g (50.0 mmol) of **6** dissolved in 50 mL of acetonitrile. The flask was equipped with an outlet for the escape of the byproduct Me_2NH. The reaction mixture was stirred for 0.5 h at 0 °C and then for 0.5 h at room temperature. The reaction flask was then placed in a water bath warmed to 35 °C and stirring continued for 2 additional hours during which a white precipitate was formed. The precipitate was filtered by means of a medium glass frit, washed with 2x20 mL portions of ice-cold dry acetonitrile and then dried under vacuum to afford 9.96 g (78%) of **7**. ^{1}H NMR (D_2O): δ 5.61 (d, 1 H J = 320 Hz), 3.46 (septet, 1 H), 2.96 (overlapping region, 12 H), 1.00 (d, 6 H). ^{13}C NMR (D_2O): δ 49.0 (d, J = 11.3 Hz), 47.7 (d, J = 8.3 Hz), 47.4 (d, J = 15.1 Hz), 32.9 (d, J = 5.3 Hz), 32.5 (d, J = 2.3 Hz), 20.3 (d, J = 5.3 Hz). ^{31}P NMR (D_2O): δ 32.7.

Procedure for the Preparation of 1g

To a mixture of 6.31 g (25.0 mmol) of **7** and 2.80 g (25.0 mmol) of *t*-BuOK in a 500 mL Schlenk flask, was added under nitrogen 100 mL of dry benzene. The reaction mixture was stirred for 2 h at room temperature and then it was allowed to stand until separation into two layers occurred. The clear upper layer was transferred under vacuum by means of canula into a 500 mL Schlenk flask through a glass frit. Another portion of benzene (100 mL) was

added to the residue of the reaction mixture and then the mixture was stirred for 0.5 h after which the mixture was transferred under nitrogen by canula into the glass frit and filtered slowly under vacuum. After filtration was completed, the solvent was distilled under vacuum and the crude base transferred under nitrogen by means of a syringe into a 50 mL round-bottomed flask. Distillation at 143 °C/ 200 milliTorr afforded 378 mg (7% yield) of **1g**. ^{1}H NMR (C_6D_6): δ 2.67 (septet, 1 H), 2.55 (t, 6 H), 2.39 (t, 2 H), 2.24 (t, 4H), 1.23 (d, 6 H), 0.92 (bs, 2H). ^{13}C NMR (C_6D_6): δ 58.4 (d, J = 11.3 Hz), 55.3 (d, J = 12.1 Hz), 49.5 (d, J = 2.3 Hz), 46.2 (s), 40.9 (s), 23.9 (d, J = 0.8 Hz). ^{31}P NMR (C_6D_6): δ 100.9.

Procedure A for the determination of pK_a

To 100 mg (0.3 mmol) of P_2-Et weighed under nitrogen in an NMR tube was added 0.30 mmol of the protonated proazaphosphtrane followed by 0.03 mmol of the relaxagent $Cr(acac)_3$. The NMR tube was sealed with a rubber septum and 0.75 mL of dry CH_3CN or CD_3CN was added under nitrogen. The tube was then flame-sealed under reduced pressure (< 760 Torr but > 5 Torr) and the mixture was shaken vigorously for 0.3 - 1 h. ^{31}P NMR integration of the signals representing the four species shown in equation 1 afforded their molar ratios. The pK_a was then calculated from the derived relationship

$$K_{1H^+} = \frac{10^{-32.94} \times [P_2\text{-}EtH^+][1]}{[P_2\text{-}Et][1H^+]} = \frac{10^{-32.94} \times [1]^2}{[1H^+]^2}$$

and the definition $pK_a = -\log K_a$. The ^{31}P NMR integration values were substituted for the concentrations of the individual species in the above relationship. Because P_2-Et is unstable under atmospheric conditions, the pK_a value calculated using a fresh sample of the phosphazene base with **5b** (33.53) was used as secondary reference to check the pK_a values determined for other proazaphosphatranes. Unlike P_2-Et, **1a**, and **1f**, **1d** has been found to be stable with respect to oligomerization, oxidation and hydrolysis at atmopsheric conditions.

Procedure B for the determination of pK_a

To 103 mg (0.3 mmol) of **1d** weighed under nitrogen in an NMR tube was added 0.30 mmol of the protonated proazaphosphtrane followed by 0.03 mmol of the relaxagent $Cr(acac)_3$. The NMR tube was sealed with a rubber septum and 0.75 mL of dry CH_3CN or CD_3CN was added under nitrogen. The tube was then flame-sealed under reduced pressure (< 760 Torr but > 5 Torr) and the mixture was shaken vigorously for 0.3 - 1 h. ^{31}P NMR integration of the signals representing the four species shown in equation 1 afforded their molar ratios. The pK_a was then calculated as shown in **A** above.

Acknowledgements

The authors are grateful to the Hampshire Chemical Co. for a research sample of *tris*(2-aminoethyl)amine and to the Iowa State Center for Advanced Technology for research support.

References

1. Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989,** *578*, 75.
2. Wroblewski, A.; Pinkas, J.; Verkade, J. G. *Main Group Chemistry* **1995**, *1*, 69.
3. D'Sa, B.; Verkade, J. G. *Phosphorus Sulfur Silicon* **1997**, *123*, 301.
4. Tang, J. –S.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 4931.
5. Arumugam, S.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827.
6. D'Sa, B.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3691.
7. Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3090.
8. Wang, Z.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* in press.
9. Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086.
10. D'Sa, B.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 832.
11. Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4298.

12. McLaughlin, P.; Verkade, J. G. manuscript in preparation

13. Kisanga, P.; Verkade, J. G. manuscript in preparation.

14. D'Sa, B. Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963.

15. D'Sa, B.; Kisanga, P. G.: Verkade, J. G. manuscript in preparation.

16. Kisanga, P.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 10057.

17. D'Sa, B.; Kisanga, P.; Verkade, J. G. manuscript in preparation.

18. Kisanga, P.; Verkade, J. G. manuscript in preparation.

19. (a) Wang, Z.; Verkade, J. G. *Heteroat. Chem.* **1998**, *9*, 687. (b) Wang, Z.; Verkade, J. G. *Tetrahedron Lett.* **1998**, *39*, 9331.

20. McLaughlin, P.; Verkade, J. G. *Organometallics* **1998**, *17*, 5037..

21. Kisanga, P.; D'Sa, B.; Verkade, J. G. manuscript in preparation.

22. Tang, J. –S.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 7793.

23. Laramay, M. A.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1991**, *605*, 163.

24. Krakowiak, K.; Bradshaw, J. S.: Izatt, R. M. *J. Org. Chem.* **1990**, *55*, 3364.

25. Laramay, M. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1990**, *112*, 9421.

26. Scheer M.; Müller, J.; Baum, C.: Häser, M. *Chem. Commun.* **1998**, 2505.

27. (a) Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G.-Z.;

Peters, E.-M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, 1055. (b) Tang, J.; Dopke, J.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 5015.

28. (a) Schmidt, C.; Lensink, C.; Xi, S. –K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75. (b) Schmidt, C.; Xi, S. –K.; Lensink, C.; Verkade, J. G. *Phosphorus Sulfur Silicon* **1990**, *49-50*, 163.

29. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals, 3rd Ed.* Permagon Press: New York, 1988.

Table 1. The pK_a of the conjugate acids of some proazaphosphatranes of interest in CH_3CN.

base	pK_a in CH_3CN	base	pK_a in CH_3CN
1a	32.9	**1d**	33.53
1b	33.63	**1f**	33.00
1c	32.84	**1g**	34.49

Table 2. Comparison of the efficiency of **1b** as a catalyst or promoter versus **1c** and **1d**.

reaction	mol % **1**/°C/h	% yield with **1d**	% yield with **1c**	% yield with **1b**[a]
2-methylcyclohexanone + MeCN	10/25/6[b]	93	-[c]	84[7]
2-butanone + MeCN	10/25/6[6]	96	-[c]	88[7]
p-anisaldehyde + MeCN	30/-5/6[b]	91	trace	60[7]
p-chlorobenzaldehyde + MeCN	30/0/6[b]	89	trace	71[7]
3-pentanone + $MeNO_2$	10/25/3[b]	76	78	60[11]
benzaldehyde + *n*-$PrNO_2$	20/25/2[b]	96	95	97[11]
p-anisaldehyde + CH_3CO_2Et	30/50/6	91(96)	trace	60[21]
p-chlorobenzaldehyde + $EtCO_2Me$	30/50/6	95	trace	95[21]
4-hexen-3-one + CH_2:$CHCH_2OH$	20/70/3	96	96	71[13]
mesityl oxide+ CH_2:$CHCH_2OH$	20/70/3	88	81	40[13]

[a]Obtained from previous reports from our laboratories. [b]In the presence of 2.2 equiv of $MgSO_4$. [c]No detectable amount of product formed.

CHAPTER 3

MODIFIED SYNTHESIS OF INTERMEDIATES LEADING TO $P(i\text{-}PrNCH_2CH_2)_3N$

A discovery to be disclosed to ISURF[a] in a Record of Invention

Philip Kisanga[b,c] and John G. Verkade[b,d]

The proazaphosphatrane $P(i\text{-}PrNCH_2CH_2)_3N$[1] is emerging as a strong competitor for the commercially available (Strem) analog $P(MeNCH_2CH_2)_3N$.[2] In several reactions, the former compound either promotes a much more cleaner reaction or supersedes the latter in both yield and ability to effect the reaction.[3] It is therefore, highly desirable to develop a more convenient, efficient and economical synthesis for this compound.

To this end, we have modified the synthesis of the intermediate $(i\text{-}PrNHCH_2CH_2)_3N$ and of $[HP(i\text{-}PrNCH_2CH_2)_3N]Cl$ which is the precursor to $P(i\text{-}PrNCH_2CH_2)_3N$. Furthermore, we have eliminated the use of methylene chloride that has been recently classified as a possible health hazard. In our method published earlier,[1] the reaction of 32 g of tren $[N(CH_2CH_2NH_2)_3]$ required 10 hours of continuous addition of sodium borohydride. Thus, the

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[a] Iowa State University Research Foundation.
[b] Gradauate studenbt and University Professor, respectively, Department of Chemistry, Iowas State Univeristy.
[c] Primary researcher and author
[d] Author for correspondence

time required to run this rather small-scale reaction was inconveniently long and hence an impediment in developing a large scale synthesis of P(*i*-$PrNCH_2CH_2)_3N$. In the modified version described here, this reaction is carried out on a 96 g (0.66 mol) scale of tren and the time required for attending the reaction is about 8 hours although the reaction is run over about 48 hours. The amount of sodium borohydride required for the reaction of 96 g of tren using our previous method is about 312 g (8.4 mol). With the modification described here, the amount of sodium borohydride required is 99 g (2.68 mol) with an estimated 67% savings (equivalent to at least $173 based on the Aldrich price) on this reactant alone.

Preparation of (*i*-$PrNHCH_2CH_2)_3N$

In a 3.0 L 3-neck flask provided with a mechanical stirrer and a thermometer was added 500 mL of water followed by 96 g (0.66 mol) of tren. To this solution was added 86 g of anhydrous fused sodium acetate followed by 235 mL of glacial acetic acid (an equimolar amount of $NaOAc•6H_2O$ could in principle also be used). The mixture was stirred at 500 rpm and the temperature of the solution was monitored until it reached 20 °C. To this mixture was then added (over 20 min) 500 mL of acetone from a freshly opened bottle. The solution was allowed to stir for 30 minutes and then it was placed in an ice/salt

bath until the temperature of the solution reached 10 °C. To this solution was then added 25 g of sodium borohydride portionwise over 1.5 h. The solution was then allowed to stir overnight while the temperature of the bath was allowed to warm to room temperature slowly. After about 12 h, the ice/salt bath was renewed and the addition of sodium borohydride continued. After the portionwise addition of a maximum 30 g of sodium borohydride (or until the appearance of a solid, which ever comes first), 200 mL of acetone was added with continuous stirring. Sometimes some solid appears before completion of addition of 30 g of sodium borohydride, the remainder of the 30 g of $NaBH_4$ was added following the addition of the 200 mL of acetone. This was followed by the addition of more 15 g of sodium borohydride over 1 h. After the addition was complete (regardless of the appearance of solid), the mixture was allowed to stir overnight. Renewal of the ice/salt bath to 10 °C and the addition of 15 g of sodium borohydride led to the formation of a small amount of solid if a solid had not already appeared. The reaction mixture was allowed to stir for 30 minutes and then 50 mL of acetone was added whereupon any solid that may have been formed disappeared. The mixture was allowed to stir for 15 minutes after which an additional 15 g of sodium borohydride was added. The reaction mixture was allowed to stir for 30 more minutes and then it was quenched with

400 g of a 50% solution of sodium hydroxide. If a solid formed upon quenching, the solution was decanted and the residue washed with 3x100 mL of ether. The decantate was then extracted with ether (6x200 mL) and dried over anhydrous potassium carbonate. The solvent and 2-propanol that had formed was removed under vacuum to afford 172 g (0.63 mol, 96%) of ^{1}H NMR-pure (i-PrNHCH$_2$CH$_2$)$_3$N.

Synthesis of [HP(i-PrNCH$_2$CH$_2$)$_3$N]Cl

To 182 mmol of ClP(NMe$_2$)$_2$ prepared in situ in 175 mL of ether by the slow addition of 5.3 mL (61.0 mmol) of PCl$_3$ to 22.0 mL (122 mmol) of hexamethylphosphorus amide (P(NMe$_2$)$_3$) at 0 °C in an ice bath, was added 33.1 g (122 mmol) of (i-PrNHCH$_2$CH$_2$)$_3$N under nitrogen. The flask was equipped with an outlet for the escape of the byproduct Me$_2$NH. A white precipitate was observed to form immediately. After completion of the addition, the reaction mixture was stirred for 12 h at room temperature after which it was filtered and then washed with 2x50 mL of ice-cold ether followed by 2x20 mL of ice-cold THF. Removal of the THF afforded 39.4 g (96%) of the salt which was converted to the title base as reported previously from our laboratories.[1]

References

1. Wrobleski, A.; Pinkas, J.; Verkade, J. G. *Main Group Chemistry* **1995**, *1*, 69.

2. Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75.

3. (a) Wang, Z.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* in press. (b) Kisanga, P.; D'Sa, B.; Fei, X.; Verkade, J. G. submitted. (c) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3090.

CHAPTER 4

$P(RNCH_2CH_2)_3N$-CATALYZED α,β–DIMERIZATION OF UNSATURATED NITRILES: FORMATION OF 2-ALKYLIDENE-3-ALKYLGLUTARONITRILES

A paper published in the Journal of Organic Chemistry **1998**, *63*, 10057.[a]

Philip Kisanga,[b,c] Bosco D'Sa[d] and John Verkade[b,c]

Abstract

The title syntheses are efficiently catalyzed by strongly basic pro-azaphosphatranes of the type $P(RNCH_2CH_2)_3N$ via Michael addition. A plausible reaction mechanism is proposed for the formation of the glutaronitriles.

Introduction

The oligomerization and polymerization of olefins has been of interest to researchers for decades. Of specific interest are processes that lead to the formation of dimers that can be utilized in copolymerization reactions. Such

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[a] Reproduced with permission from Journal of Organic Chemistry. Copyright 1999, American Chemical Society.

[b] Graduate student and University Professor, respectively, Department of Chemistry, Iowa State University.

[c] Primary researcher and author.

[d] Schering-Plough Research Institute, 1011 Morris Avenue, Union, NJ 07083.

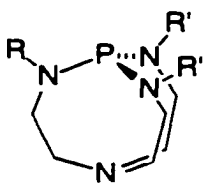
[e] Author for correspondence.

dimers are often observed as byproducts in Michael addition reactions. Among dimer formations unsaturated nitriles are those produced by electrolytic processes[1,2] and those catalyzed by transition metal complexes.[3,4] trialkyl phosphines,[4] isocyanide-copper(I) oxide binary systems[4,5,6] and bases.[7] Reactions catalyzed by trialkyl phosphines or transition metal complexes suffer from the major drawback that they are restricted to the dimerization of β-unsubstituted-α,β-unsaturated acrylonitrile and the corresponding acrylate. Moreover, the isocyanide-copper(I) system requires a lengthy reaction time and a high temperature, and the conversion ratio is disappointing. Electrolytic reactions produce glutaronitriles as a minor product and are therefore inefficient routes to this class of compounds. Reports of the use of bases in the dimerization of nitriles are scanty. The report by White[7] *et al.* describes a rapid reaction that is catalytic in R_3NCN, but provides very low to modest yields (15-54%) along with several byproducts. Shabtai[8] and co-workers reported on the dimerization of crotononitrile and allyl cyanide using a catalyst system consisting of potassium-benzylpotassium ($K/PhCH_2K$). However, these reactions produce the corresponding dimers in apparently very low (unreported) yields along with other products including trimers. The method reported by A. Daweal[9]

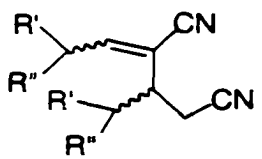
utilizes a condensation between propionaldehyde and cyanoacetic acid to produce 3-ethyl-2-propylideneglutaronitrile in low yield.

Results and Discussions

We have shown previously that acetonitrile can be deprotonated by the nonionic bases **1a**,[10] **b**[11] and **c**[12] giving a low concentration[13,14] of the anion $[CH_2CN]^-$. It has also been demonstrated that this anion adds to carbonyl



1a: R = R' = Me
1b: R = H, R' = *i*-Pr
1c: R = R' = *i*-Pr



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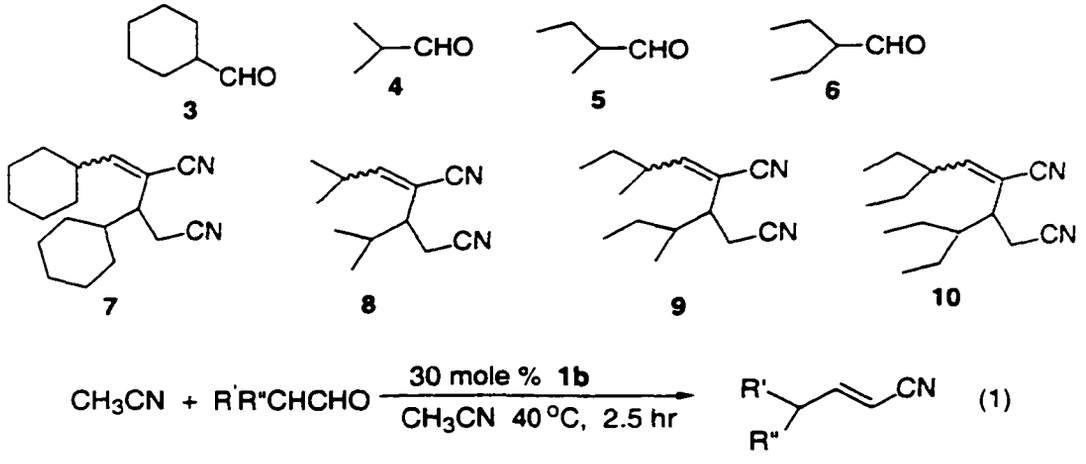
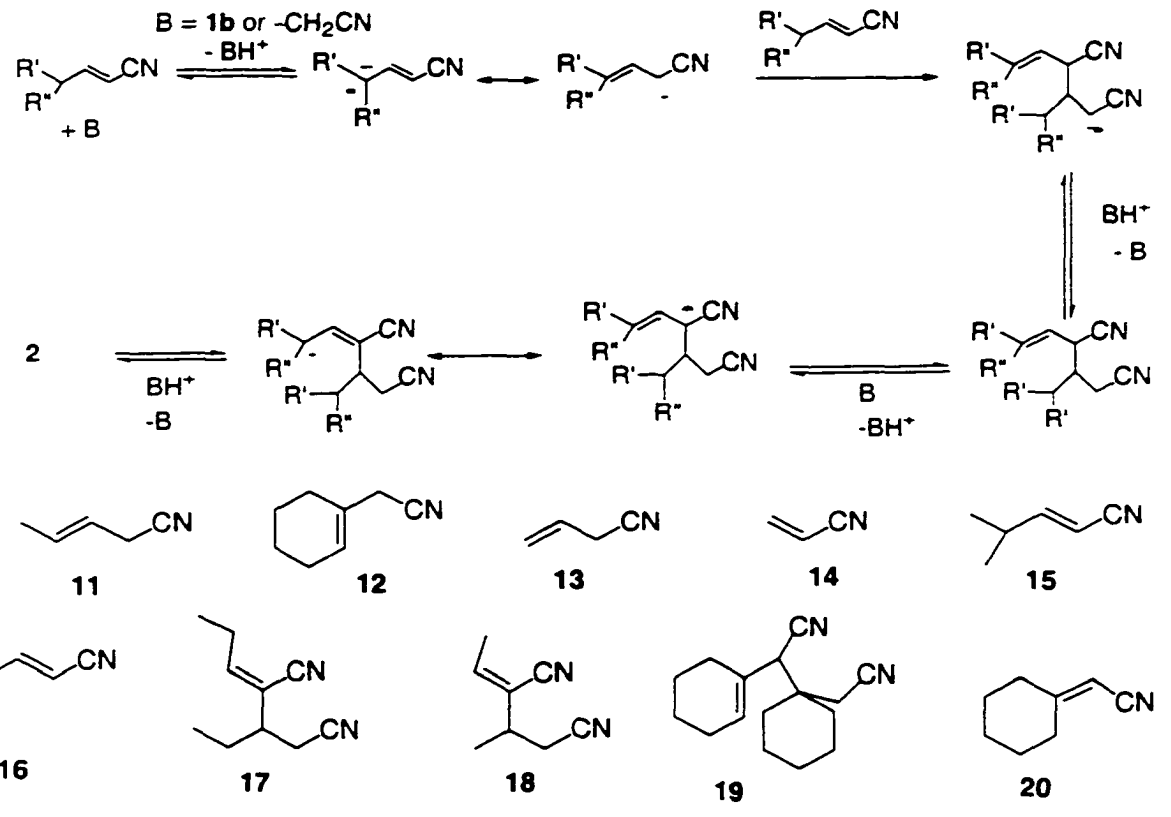
compounds to form α,β–unsaturated nitriles[13] or β–hydroxynitriles.[14] In the formation of α,β-unsaturated nitriles,[16] we reported that aldehydes lacking an α–hydrogen (e.g. trimethylacetaldehyde and aromatic aldehydes) react to form α,β-unsaturated nitriles,[16] while primary aldehydes form the aldol products.[13] Here we show that secondary aldehydes in the presence of **1b** afford 2-alkylidene-3-alkylglutaronitriles (**2**), which are α,β-dimers of the α,β–unsaturated nitriles we expected originally. We observed no β,β-dimer in our reaction (a product that accompanies the copper(I)oxide-isocyanide process[4]). Thus commercially available **3-6** are converted to the high yields

shown for their corresponding glutaronitriles **7-10**, respectively. These products are assumed to form via the corresponding α,β-unsaturated nitriles (equation 1) which are subsequently deprotonated by **1b** to from an allylic



anion that can then Michael add to another molecule of the α,β–unsaturated nitrile. This process is depicted in Scheme 1. The isomerization of the double bond as shown in this scheme is consistent with our previous observation that **1b** is capable of conjugating methylene-interrupted double bonds.[14] In accordance with this finding, we expected **1b** to be able to produce Michael addition products from substrates possessing double bonds poised to conjugate. The results of these experiments are shown for substrates **11-16** in Table 1. Scheme 1 further shows that $^{-}CH_2CN$ acts as a base in catalyzing the formation of the glutaronitriles. This was proved in reactions in which the substrates **11**, **12** and **13** were reacted separately with 10 mole percent of **1b** in CD_3CN. The ^{31}P NMR of the reaction mixture showed the existence of **1b**, **1b**H^+, and

Scheme 1



1bD^+. The ^{13}C NMR spectrum of the reaction mixture showed the existence of CD_3CN and a substantial amount of CD_2HCN which can be formed only if the $^-CD_2CN$ produced by the deprotonation of CD_3CN deprotonates the substrate. However, reactions in the presence of acetonitrile is slower requiring up to 12 hours to achieve yields similar to thosse obtained with reactions carried out in benzene that requites 1-3 hours only. This is probably because of the solvation of the anions in the more polar acetonitrile.

As shown in this Table 1, both **1a** and **1b** can function as catalysts for Michael addition reactions. Likewise, **1c** catalyzes the reaction of **3** and **4**

with acetonitrile to produce the corresponding glutaronitriles **7** and **8** in 97% and 93% (estimated by ^{1}H NMR integration) respectively in 2.5 hours. As postulated in Scheme 1, the γ- rather than the α-hydrogen is deprotonated at the α,β-unsaturated nitrile stage of these Michael additions. This assumption receives support from the lack of reaction in Table 1 of substrates **14** and **16** which lack a γ-hydrogen. Substrate **15**[15] on the other hand produces the dimer in excellent yield. The reaction of the methylene interrupted unsaturated nitrile **12** in the presence of catalytic amounts of **1a** or **1b** produces the dimer **19** in 90% yield in addition to the isomerized monomer **20** in 10% yield. Evidence for the isomerization of the β,γ-unsaturated glutaronitrile produced in the penultimate step of Scheme 1 to the more stable final α,β-unsaturated isomeric product is therefore provided by product **19**. The failure of product **19** to undergo conjugation may be due to the sterically hindered environment of the α-hydrogen owing to the presence of the two six-membered rings. The formation of compound **19** also serves as evidence for the postulated reaction pathway shown in Scheme 1. The isolation of product **20** on the other hand supports our previous findings that **1b** is capable of isomerizing double bonds. In a similar way, the production of the glutaronitriles **17** and **18** from the substrates **11** and **13** respectively using **1a** or **1c** as bases indicate that they (**1a** and **1c**) are capable of isomerizing double bonds.

Although further experiments along the above lines are underway, we have thus far recovered only starting materials in attempted dimerizations of methylene interrupted β,γ-unsaturated esters or ketones. Diphenyl acetaldehyde and 2-phenylpronionaldehyde have so far also failed to give the glutaronitriles under the reaction conditions above in which secondary aldehydes are used. Primary aldehydes undergo aldol condensation as we previously reported.[13]

Experimental Section

The aldehydes and nitriles (from Aldrich Chemical Company) were used as received. Acetonitrile was distilled from calcium hydride and stored over 4Å molecular sieves. All reactions were carried out under nitrogen.

General procedure for the preparation of glutaronitriles from aldehydes

In a typical experiment, 30 mg (0.12 mmol) of **1b** was weighed under nitrogen in a round bottomed flask containing a magnetic stirring bar. Dry acetonitrile (2 mL) was then added and the solution was warmed to 40 °C in an oil bath. The aldehyde (0.40 mmol) was added in one portion and the reaction mixture was stirred for 2.5 h. After the volatiles were removed under vacuum, the glutaronitriles were eluted on a silica gel column with Et_2O

in hexane. The ratio of Et_2O was gradually increased from 0% to 60% in 5% portions. The dinitriles eluted with about 40% Et_2O in hexane to afford 43-48% of a mixture of isomers and 45-51% of diastereomers of the *Z*-isomer. Attempts to isolate the *E*-isomer form the mixture by column chromatography failed.

General procedure for the preparation of glutaronitriles from nitriles.

This reaction was carried out by weighing 25 mg (0.12 mmol) of **1a** or 30 mg of **1b** (0.12 mmol) under nitrogen in a 10 mL round bottomed flask containing a magnetic stirring bar. To this was added 2 mL of the solvent and the resulting solution was warmed to the required temperature (Table 1). The nitrile was then added in the ratio required and the mixture was stirred for the time shown in Table 1. Removal of the volatiles under vacuum followed by column chromatography using ether and hexane as mentioned above afforded the glutaronitriles.[16]

Ackowledgements

The authors thank the Donors of the Petroleum Research Fund administered by the American Chemical Society and the Iowa State Center for Advanced Technology Development for grant support of this work.

References

1. Baizer, M.; Anderson, *J. Org. Chem.* **1965**, *30*, 1357.
2. Baizer, M.; Chruma, L.; White, A. *Tetrahedron Lett.* **1973**, *52*, 5209.
3. Misorro, A.; Uchida, Y.; Tamai, K.; Hidai, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 931.
4. Saegusa, T.; Ito, Y.; Tomita, S.; Kinoshita, H. *J. Org. Chem.* **1970**, *35*, 670.
5. Saegusa, T.; Ito, Y.; Tomita, S. *J. Am. Chem. Soc.* **1971**, *93*, 5656.
6. Saegusa, I.; Ito, Y.; Tomita, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 830.
7. White, A.; Baizer, M. M. *J. Chem. Soc., Perkins Trans. 1* **1973**, 2231.
8. Shabtai, J.; Ney-Igner, *J. Org. Chem.* **1975**, *40*, 1158.
9. Dewael, A. *Bull. Soc. Chim. Belg.* **1932**, 324.
10. Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75.
11. D'Sa, B.; Verkade, J. G. *Phosphrus Sulfur Silicon* **1997**, *123*, 301.

12. Wroblewski, A. E.; Pinkas, J.; Verkade, J. G. *Main Group Chem.* **1995**, *1*, 69.

13. D'Sa, B.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3961.

14. Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. G.,*J. Org. Chem.* **1999**, *64*, 3090.

15. Palomo, C.; Aizpuruo, J.; Garcia, J.; Ganboa, I.; Cossio, F. B.; Leua, B.; Lopez, C. *J. Org. Chem.* **1990**, *55*, 2498.

16. See Supporting Information for spectral data for these compounds.

Table 1. Conditions and yields for the preparation of glutaronitriles.[a]

substrate	solvent	T (°C)	cat.[b]	product (yield %)
3	CH_3CN	30	**1a** or **b**	**7** (98)[c]
4	CH_3CN	30	**1a** or **b**	**8** (81)[c]
5	CH_3CN	30	**1a** or **b**	**9** (85)[c]
6	CH_3CN	30	**1a** or **b**	**10** (95)[c]
11	C_6H_6	40	**1a**	**17** (98)[d]
12	C_6H_6	40	**1b**	**19** (90)[e]
12	MeOH[f]	50	**1a**	**19** (90)[e]
13	C_6H_6	30	**1c** or **1a**	**18** (94)[d]
14	C_6H_6 [g,h]	40	**1a** or **1b**	0
15	C_6H_6	25	**1b**	**8** (96)
16	CH_3CN[g]	25	**1b**	0

[a]The time was 2.5 h unless stated otherwise. [b]Present in 10 mole per cent concentration unless stated otherwise. [c]The amount of based used was 30 mole percent. [d]The reaction time was 1 hour in the presence of 10 mole percent of **1a** or **1c**. [e]In addition to the glutaronitrile **19**. 10% of isomerized substrate was isolated (see text). [f]The reaction time was ten minutes. [g]Several solvents were tried (MeOH, C_6H_6, CH_3CN, THF, Et_2O). [h]The reaction was also attempted at room temperature.

Supporting Information

^{1}H NMR and ^{13}C NMR Data

7. ^{1}H NMR ($CDCl_3$): 0.80-1.30 overlapping region (10H), 1.52-1.80 overlapping region (11H), 2.1-2.2 (m, 1H), 2.34-2.65 (m, 3H), 6.09 (d, 1H). ^{13}C NMR ($CDCl_3$): 20.23, 25.27, 25.31, 25.98, 26.09, 30.58, 30.77, 32.20, 32.25, 38.28, 39.61, 41.08, 47.59, 112.28, 116.01, 118.03, 156.77, 157.16 ppm. Anal. Calcd. for $C_{18}H_{26}N_2$ C, 79.95; H, 9.69; N, 10.36. Found C, 80.15; H, 9.91; N, 10.08. HR MS (EI) *m/e* (M^+) calcd for $C_{18}H_{26}N_2$ 270.20960, obsd 270.20896.

8. ^{1}H NMR ($CDCl_3$): 0.88-0.97 overlapping region (6H), 1.03-1.12 overlapping region (6H), 1.65-1.83 (m, 1H), 2.08-2.16 (m, 1H), 2.36-2.45 (m, 1H) 2.57-2.65 (m, 1H) 2.80-2.88 (m, 1H), 6.09 (d, 1H). ^{13}C NMR ($CDCl_3$): 20.29, 20.43, 20.66, 22.22, 22.24, 30.72, 31.73, 48.59, 112.18, 115.83, 117.91, 158.58 ppm. Anal. Calcd. for $C_{12}H_{18}N_2$ C, 75.74; H, 9.53; N, 14.72. Found C, 76.65; H, 9.67; N, 13.68. HR MS (EI) *m/e* (M^+) calcd for $C_{12}H_{18}N_2$ 190.14700, obsd 190.14685.

9. Obtained as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$): 0.88-0.98 overlapping region (9H), 1.10 (t, 3H), 1.32-1.67 overlapping region (4H), 2.3-2.55 (m, 2H), 2.64-2.71 (m, 2H), 6.12 (d, 1H). ^{13}C NMR ($CDCl_3$): 10.85, 10.88, 10.95, 11.93, 12.05, 12.09, 16.06, 16.10, 16.18, 16.29, 20.13, 20.21,

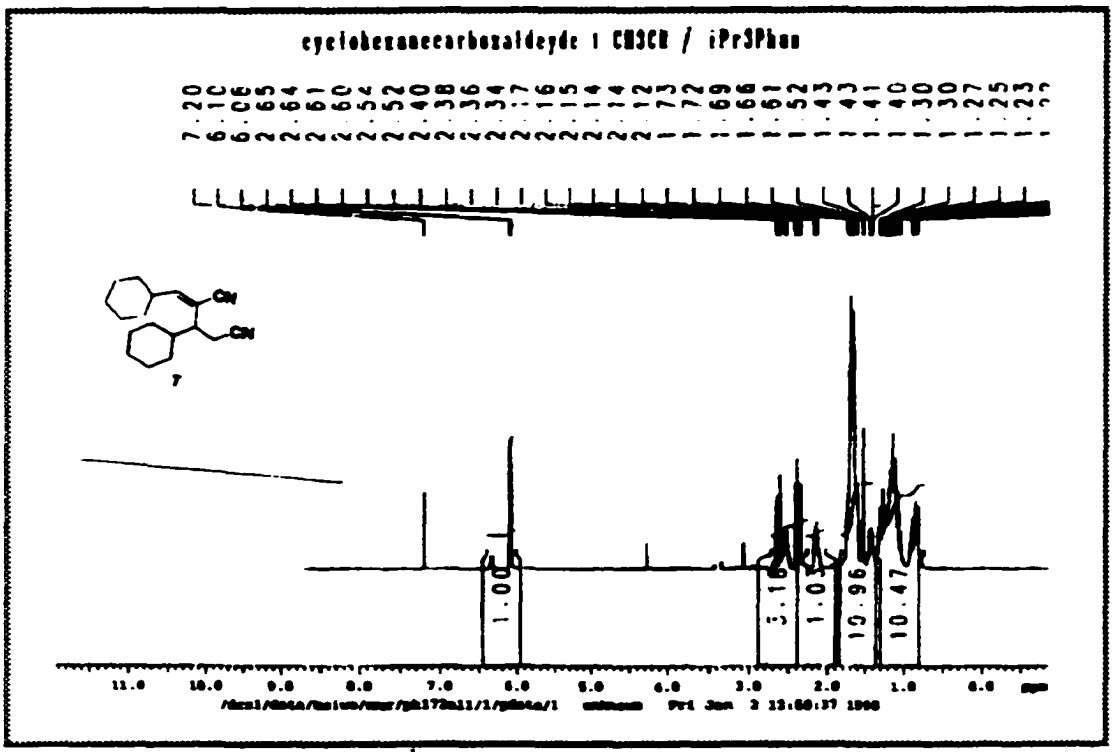
20.25, 20.33, 20.57, 20.63, 26.48, 26.50, 26.60, 26.66, 29.57, 29.58, 29.60, 36.63, 36.75, 36.80, 36.85, 38.77, 38.83, 46.48, 46.63, 47.02, 47.21, 113.12, 113.62, 116.08, 116.10, 116.22, 116.26, 117.93, 117.97, 118.06, 118.10, 157.33, 157.42, 157.62, 157.71 ppm. HR MS (EI) *m/e* (M^+) calcd for $C_{14}H_{22}N_2$ 218.17830, obsd 218.17812.

10. ^{1}HNMR ($CDCl_3$): 0.84-0.98 overlapping region (13H), 1.27-1.40 overlapping region (4H), 1.44-1.61 (m, 4H), 2.44-2.52 (m, 3H), 2.60-2.72 (dd, 1H), 6.07 (d, 1H). ^{13}C NMR ($CDCl_3$): 10.31, 10.47, 11.92, 12.05, 20.49, 21.44, 22.19, 27.85, 27.88, 42.28, 44.57, 46.31, 115.13, 116.47, 118.21, 156.42 ppm. HR MS (EI) *m/e* (M^+) calcd for $C_{16}H_{26}N_2$ 246.20960, obsd 246.20958.

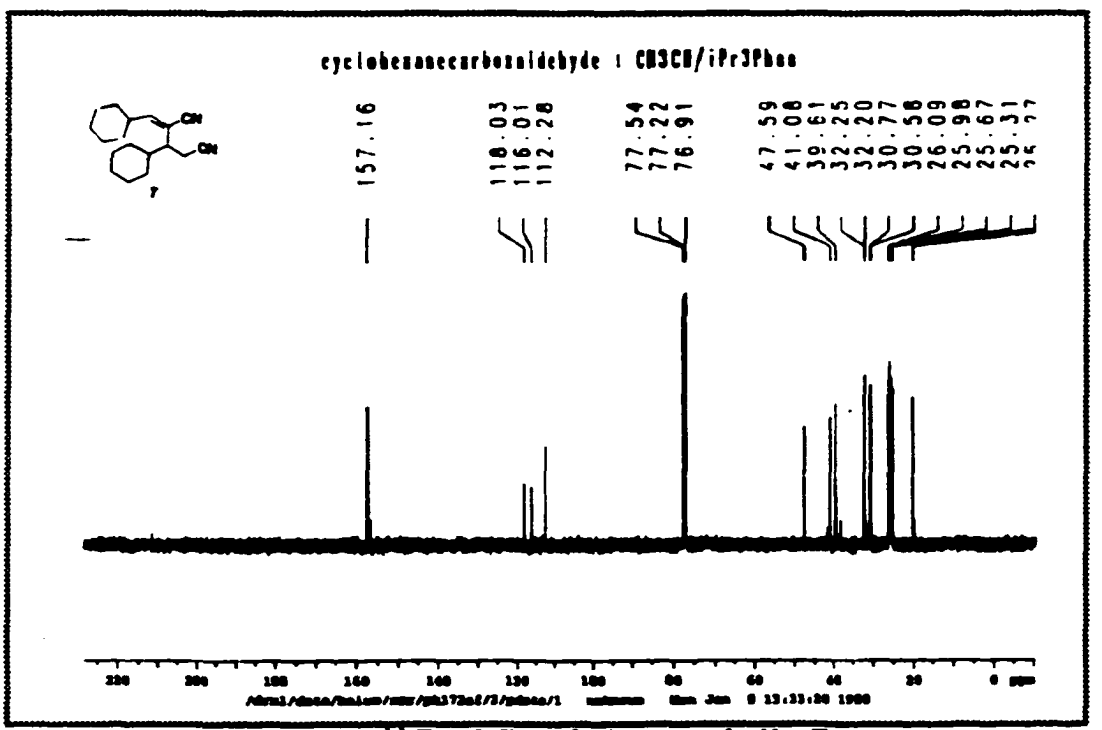
17. ^{1}H NMR ($CDCl_3$ 0.93 (t, 3H), 1.11 (t, 3H), 1.55-1.70 (m, 2H), 2.44-2.54 (m, 5H0, 6.37 (t, 1H). ^{13}C NMR ($CDCl_3$ 11.51, 13.24, 22.55, 25.17, 25.90, 43.29, 114.50, 115.26, 117.56, 152.69 ppm. HR MS (EI) *m/e* (M^+) calcd for $C_{10}H_{14}N_2$ 162.11570, obsd 162.11569.

18. Both ^{1}H NMR and ^{13}C NMR Compared favorably with that reported in *J. Org. Chem.* **1970**, 670.

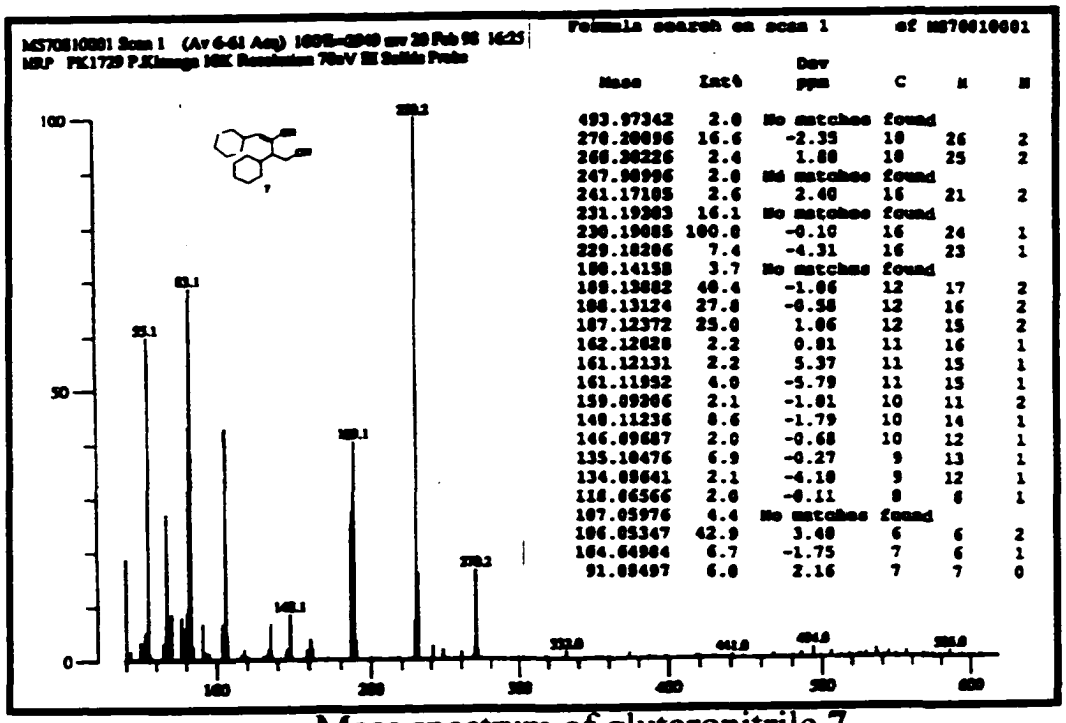
19. ^{1}H NMR ($CDCl_3$) 1.26-1.35 overlapping region (3H), 1.51-1.63 overlapping region (11H), 1.99 (m, 4H), 2.38 (AB q, 4H), 3.28 (s, 1H), 5.79 (t, 1H).



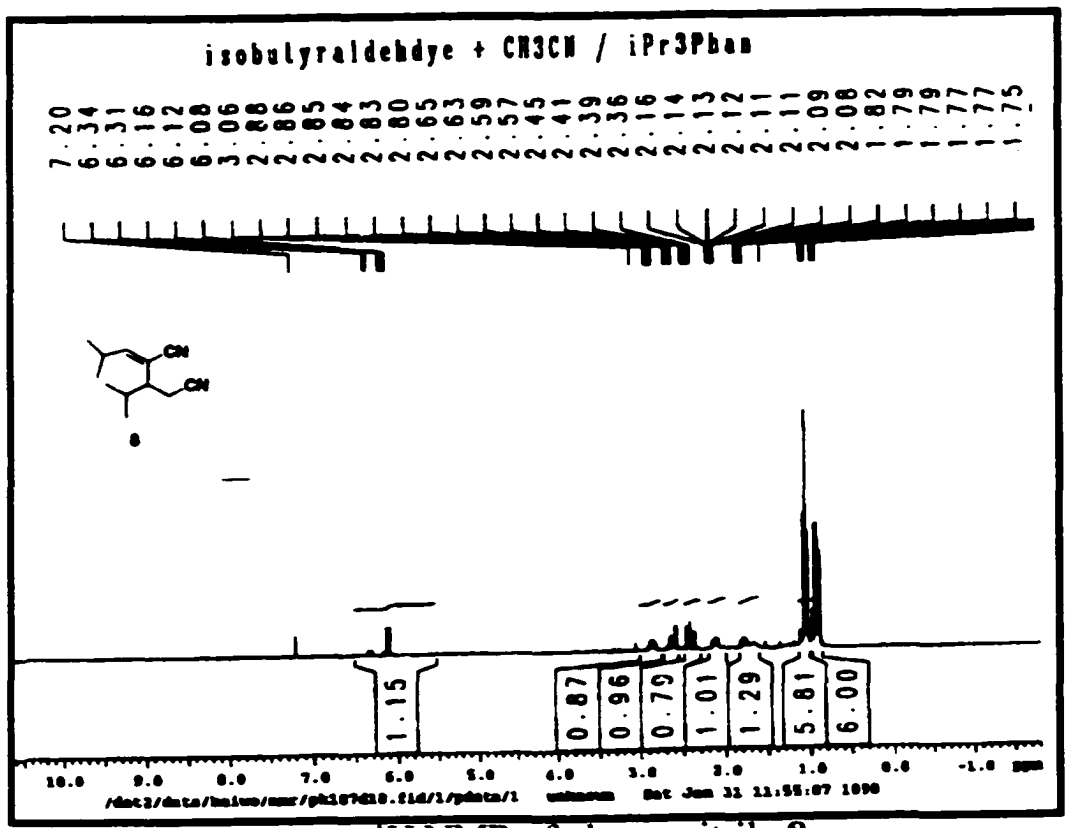
^{1}H NMR of glutaronitrile 7



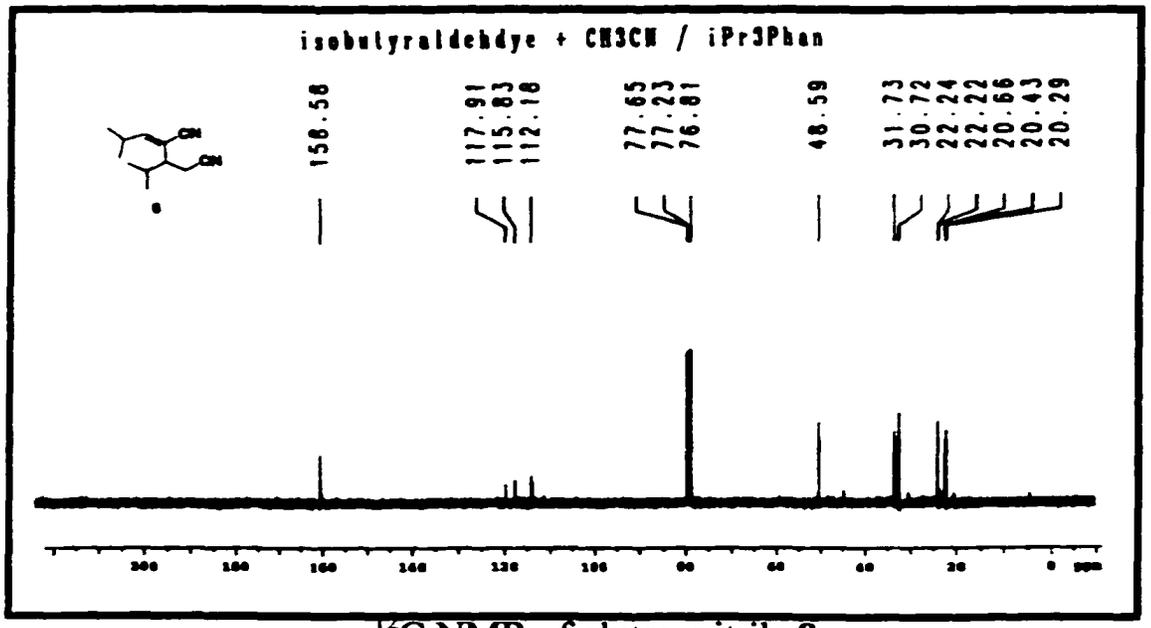
^{13}C NMR of glutaronitrile 7



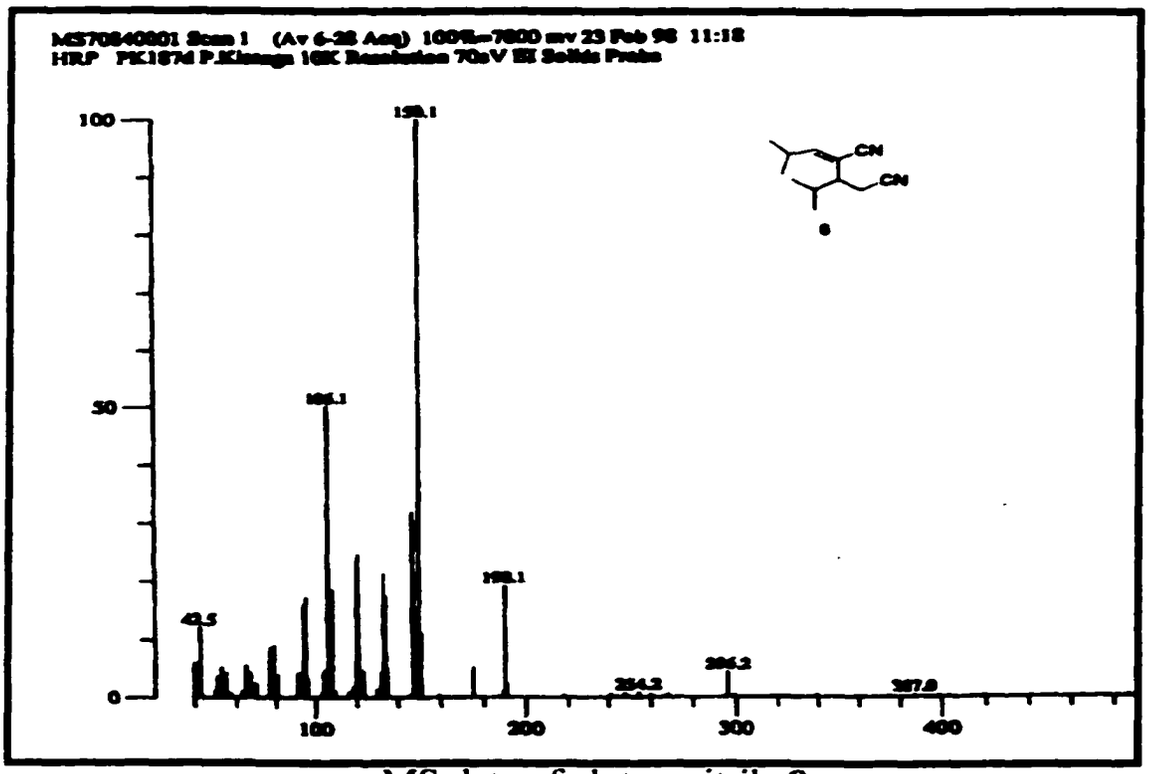
Mass spectrum of glutaronitrile 7



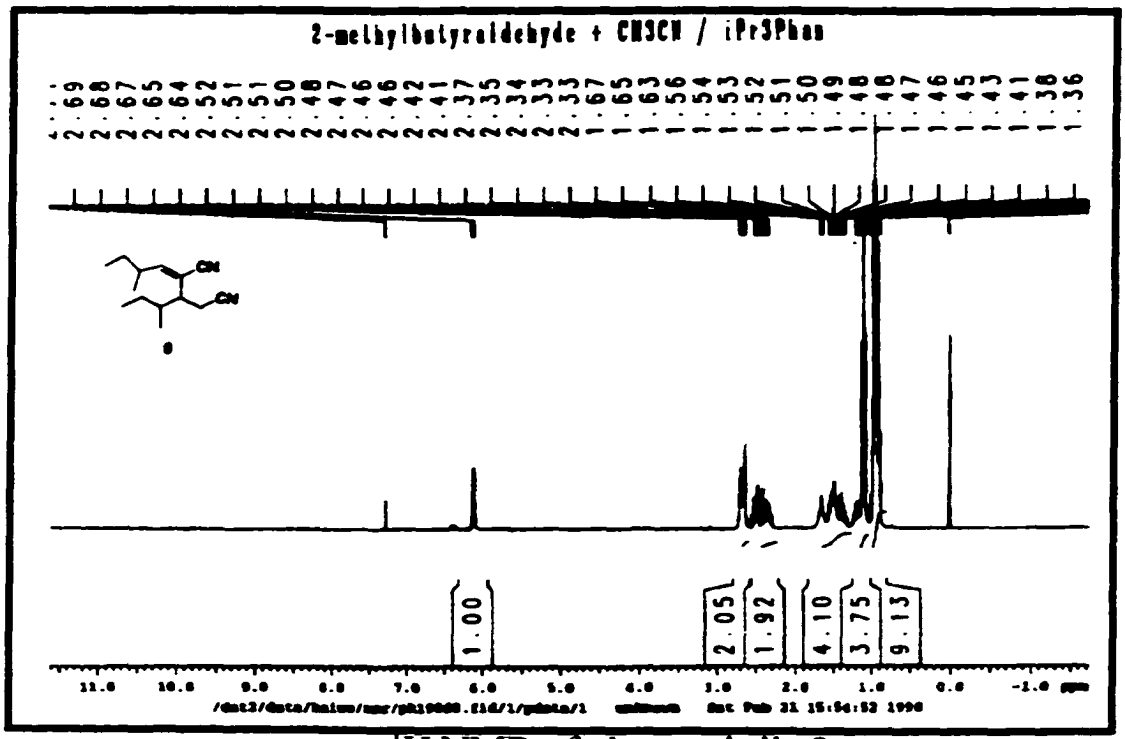
^{1}H NMR of glutaronitrile 8



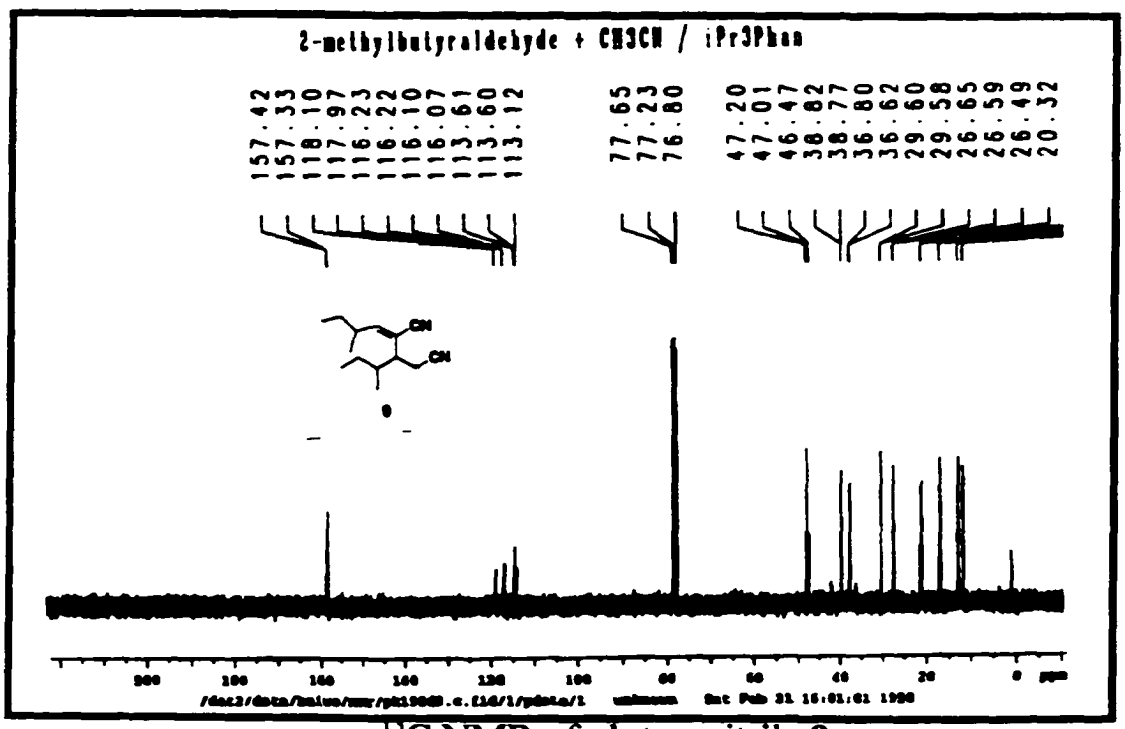
^{12}C NMR of glutaronitrile **8**



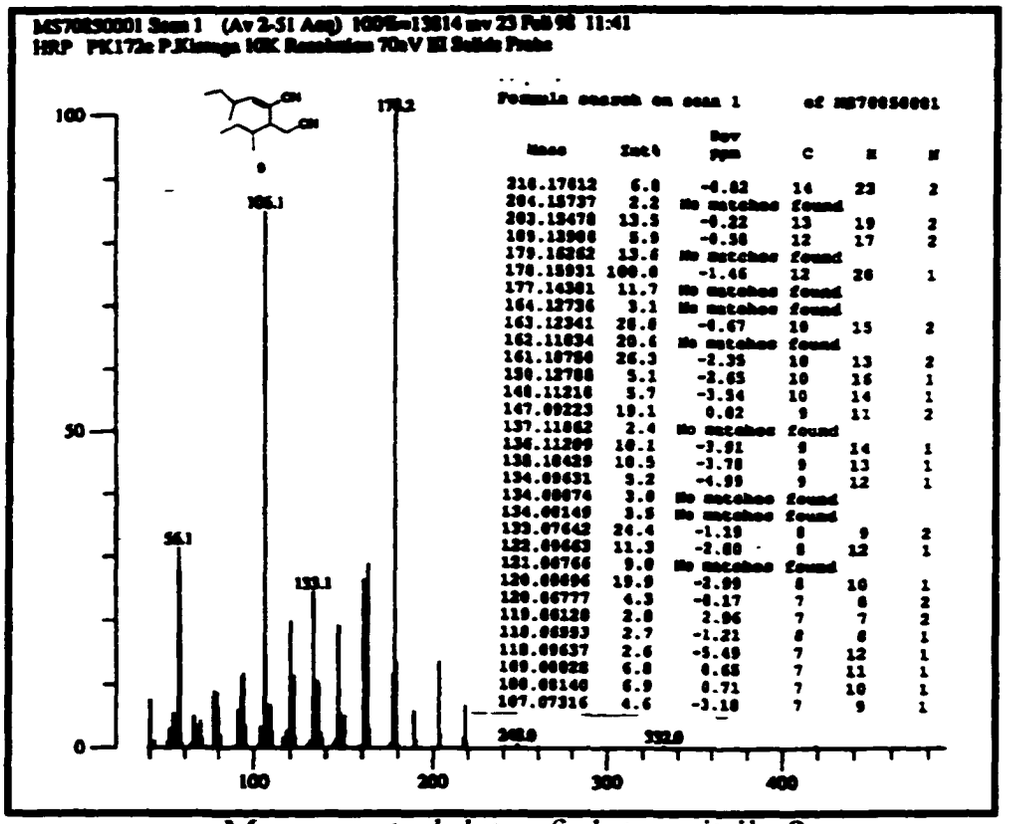
MS data of glutaronitrile **8**



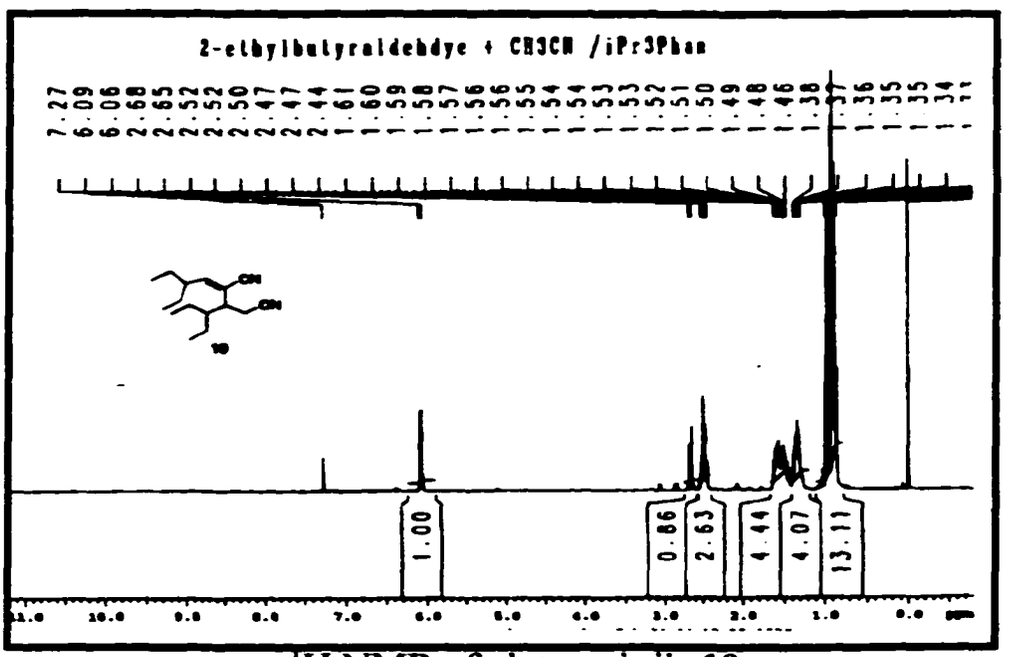
^{1}H NMR of glutaronitrile **9**



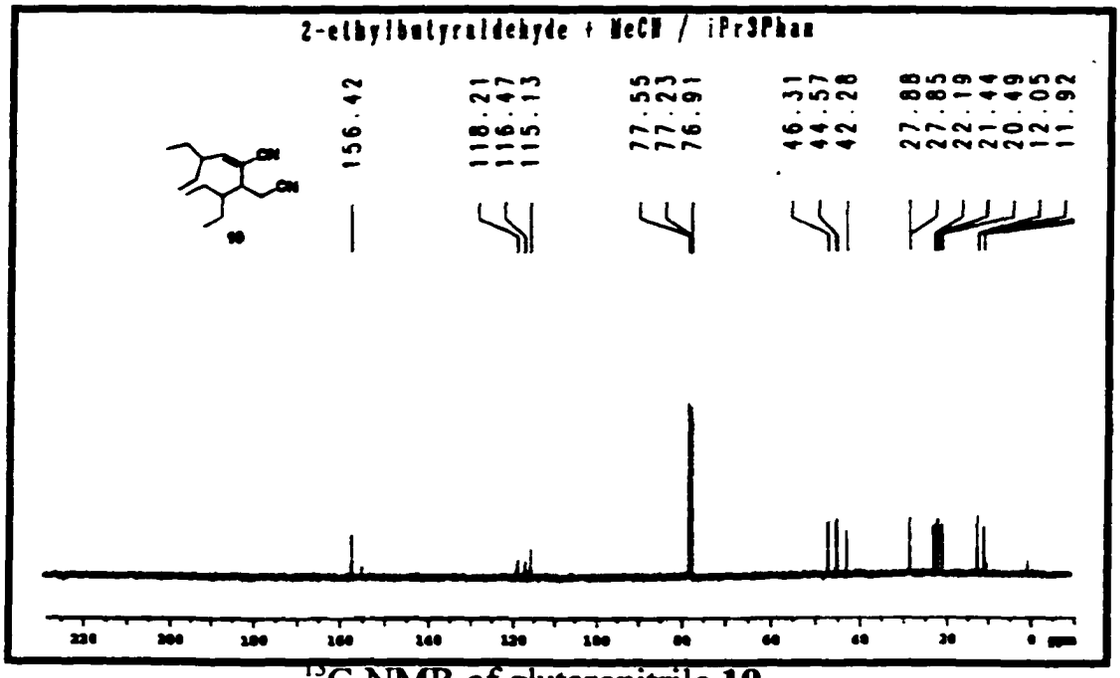
^{13}C NMR of glutaronitrile **9**



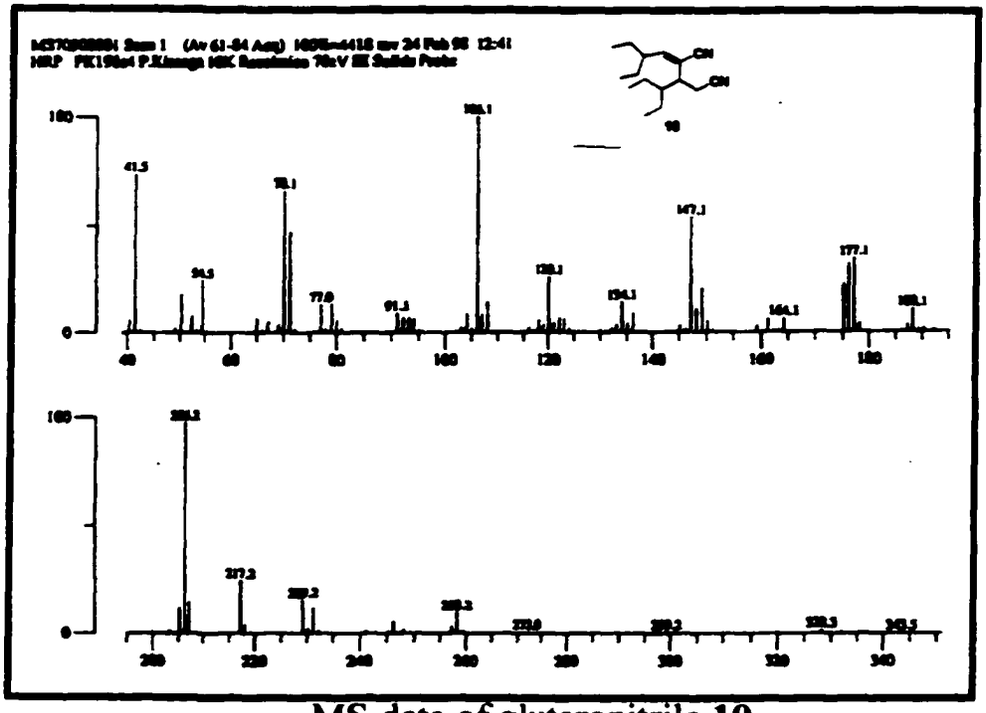
Mass spectral data of glutaronitrile **9**



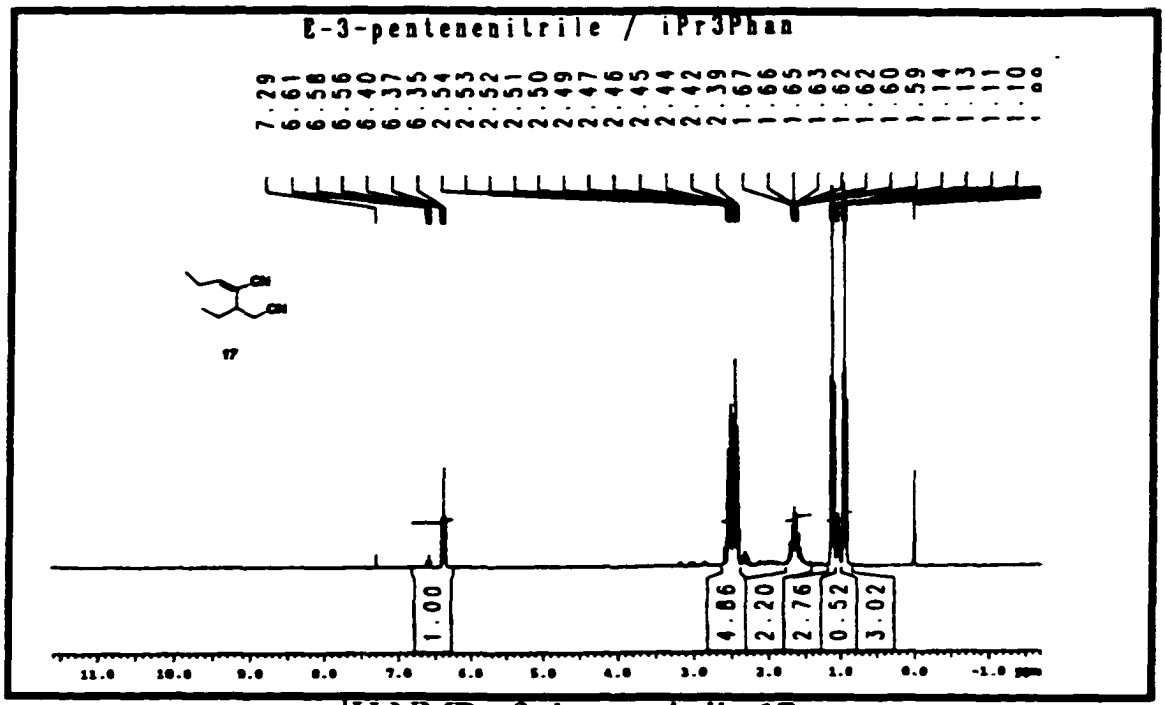
^{1}H NMR of glutaronitrile **10**



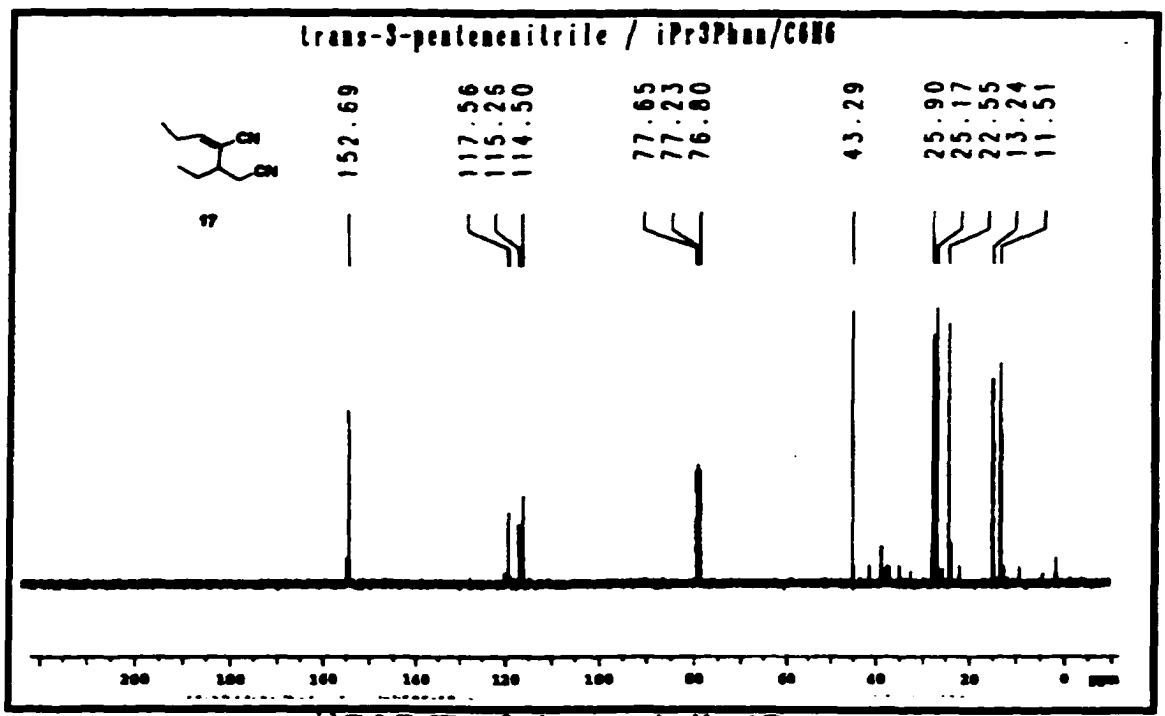
^{13}C NMR of glutaronitrile **10**



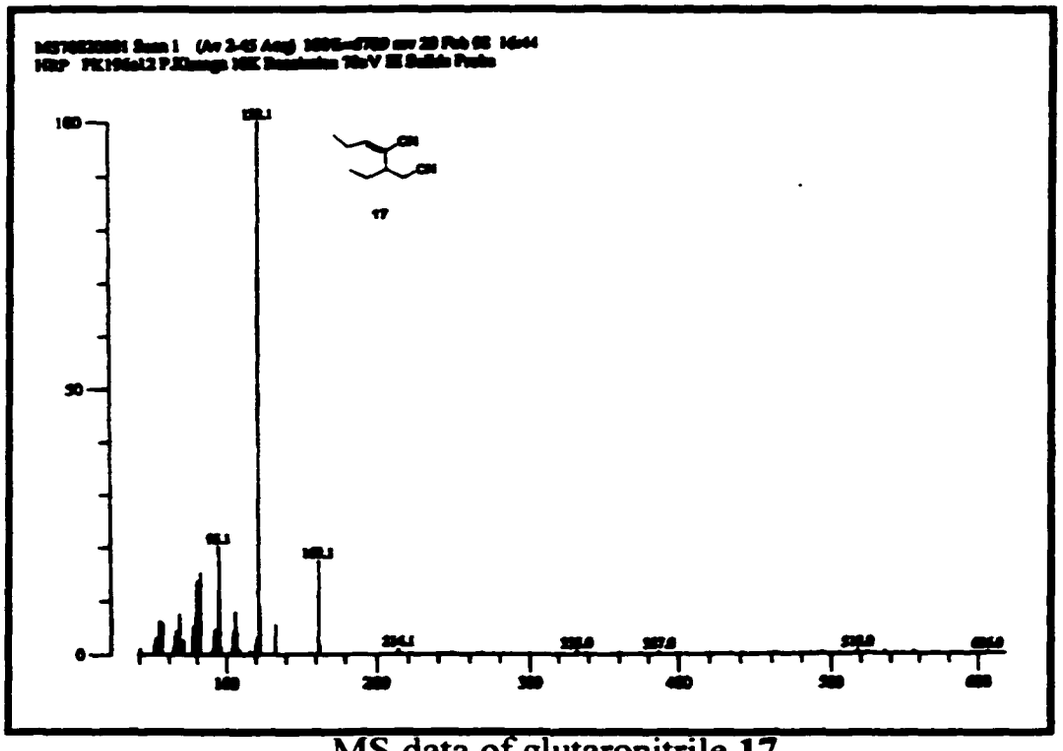
MS data of glutaronitrile **10**



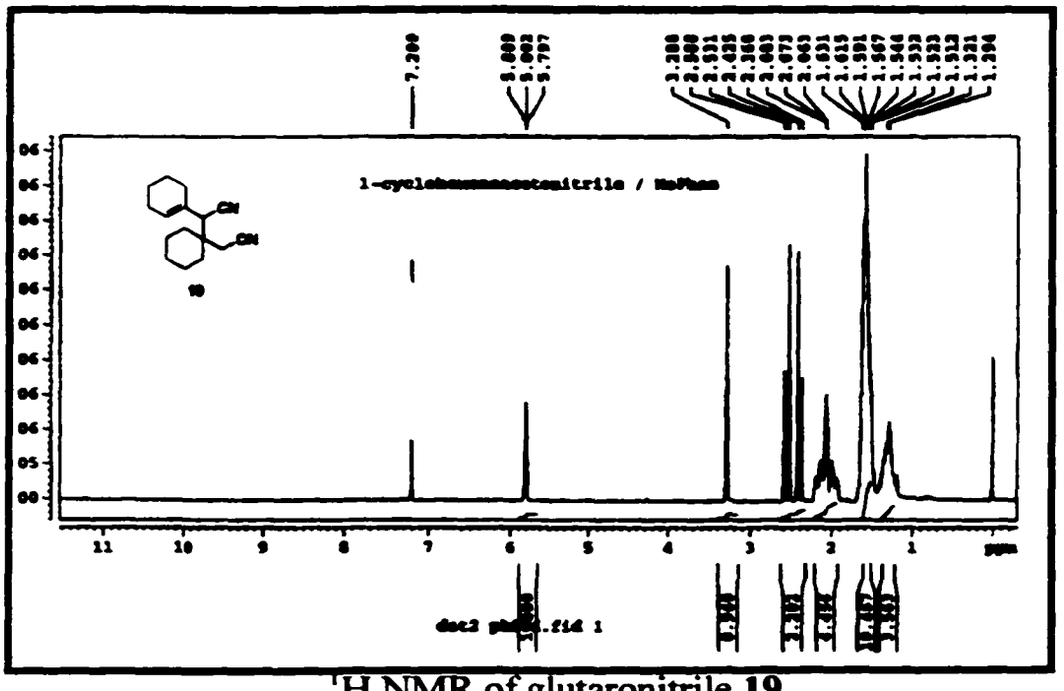
^{1}H NMR of glutaronitrile 17



^{13}C NMR of glutaronitrile 17



MS data of glutaronitrile **17**



^{1}H NMR of glutaronitrile **19**

CHAPTER 5

P(RNCH$_2$CH$_2$)$_3$N-CATALYZED SYNTHESIS OF β-HYDROXY NITRILES

A paper published in the Journal of Organic Chemistry **1999**, *64*, 3090[a]

Philip Kisanga,[b,c] Dale McLeod,[d] Bosco D'Sa[e] and John Verkade[b,f]

Abstract

We herein report the successful synthesis of β-hydroxy nitriles in very good to excellent yields from aldehydes and ketones in a simple reaction that is promoted by strong non-ionic bases of the title type. The reaction occurs in the presence of magnesium salts which activates the carbonyl group and stabilizes the enolate thus produced.

Introduction

β-Hydroxy nitriles are useful intermediates in organic synthesis as, for example, in the synthesis of 1,3-aminoalcohols.[1] As a result, several methods have been developed for their synthesis. The most common methods for

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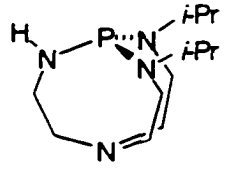
[b] Graduate student and University Professor, respectively, Department of Chemistry, Iowa State University.
[c] Primary researcher and author.
[d] Pfizer Corporation.
[e] Schering-Plough Research Institute, 1011 Morris Avenue, Union, NJ 07083.
[f] Author for correspondence.

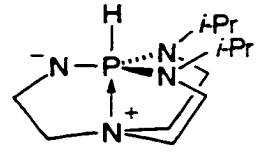
preparing β-hydroxy nitriles involve the reaction of a 1,2 epoxide[2] with a nitrile in the presence of metal salts such as $LiClO_4$/KCN,[3] using lanthanide(III) alkoxides as catalysts[4] or with acetone cyanohydrin under mildly basic conditions.[5] However, these approaches succeed only with simple aliphatic epoxides and the yields range from poor (35%) to very good good (95%) with the exception of the $LiClO_4$/KCN reagent that leads to yields ranging from 80-98%. Another recent method for the synthesis of β-hydroxy nitriles includes the use of a manganese-lead system to promote the coupling of an alkyl iodide, acrylonitrile and a ketone.[6] The toxicity of lead and DMF (used as the solvent) make this method environmentally unsafe. A mercucry-assisted reaction has also been reported. In this process an electron deficient alkene is treated with mercury fulminate and lithium bromide and the reaction mixture is heated at 50 °C to afford the β-hydroxy nitriles in low to moderate yields.[7] However, the toxicity of mercury and the lengthy reaction times required render this method unattractive. Bahradi *et al.*[8] utilize aryl halides as the precursors of electrogenerated bases which are then used to deprotonate acetonitrile. The anion thus produced can add to acetone or aldehydes in DMF to produce the title compounds in 52-74% yield. β-Hydroxy nitriles can also be synthesized by ionization of an α-hydrogen of acetonitrile by *n*-butyllithium (sold as a

flammable solution) or alkali amides, followed by condensation with ketones and aldehydes.[9] When *n*-butyllithium is employed, a temperature of -80 °C is required to give the best yields (47-89%) and if alkali amides are employed, a temperature of -33 °C is required to provide yields up to 93%. A simple room temperature procedure was developed by Maasalu *et al.*[10] which involved reacting acetonitrile with carbonyl compounds in the presence of powdered KOH. However, the yields for the reaction were moderate ranging from 43-68%. Although several other methods exist for the preparation of β-hydroxy nitriles, they involve a multi-step synthesis,[11,12] they make use of highly toxic compounds,[13-15] they proceed with poor to moderate overall yields,[16] or they require low[17] temperatures.

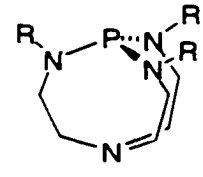
The proazaphosphatranes **1a/1a'**,[18] **b**,[19] and **c**[20] have recently been shown to be strong non-ionic bases capable of deprotonating acetonitrile,[21] benzyl nitrile,[21] nitroalkanes[22] and other activated methylenes,[23] thereby providing



1a



1a'



1b: R = *i*-Pr
1c: R = Me

access to anions that we have successfully employed in useful transformations. In our continued search for reactions in which these proazaphosphatranes

provide improved synthetic methodology over conventional approaches, we have found that bases of type **1** are efficient catalysts for the preparation of β-hydroxy nitriles.

Results and Discussions

We previously reported that ketones do not react with acetonitrile in the presence of bases of type **1**.[21] In hopes of activating the carbonyl function of this class of compounds to attack by $^{-}CH_2CN$, we investigated the use of Lewis acids such $AlCl_3$, BF_3, BF_3•OEt_2, $MgBr_2$ and HgI_2. Thus we were able to detect the formation of 1-2% of β-hydroxy nitriles (estimated by ^1H NMR spectroscopic integration) in the reaction of cyclohexanone with acetonitrile in the presence of one equiv of BF_3•OEt_2 or HgI_2 and 30 mole percent of **1a**. The other Lewis acids either induced no detectable reaction or produced complicated reaction mixtures. When the reaction was repeated in the presence of one equiv of magnesium sulfate or magnesium bromide and 30 mole percent of **1a**, the reaction mixture produced about 40% of the α,β-unsaturated nitrile in addition to 59% of the products identified by ^1H NMR spectroscopy as β-hydroxy nitrile. When the concentration of the base was reduced to 15 mole percent in the same reaction, the conversion to β-hydroxy nitrile increased to 72%. At 10 mole percent in another repetition of this reaction, 88% of the

products produced was observed to be the β-hydroxy nitrile while 11 percent was identified by ^{1}H NMR spectroscopy as the α,β-unsaturated nitrile. Increasing the amount of the magnesium compound to 2.2 equiv led to the production of 96% of the β-hydroxy nitrile in 4 hours and no ^{1}H NMR detectable unsaturated nitrile. Seventeen carbonyl compounds were then treated under these optimized conditions and the results are shown in Table 1. The reaction is assumed to proceed through the pathway shown in Scheme 1.

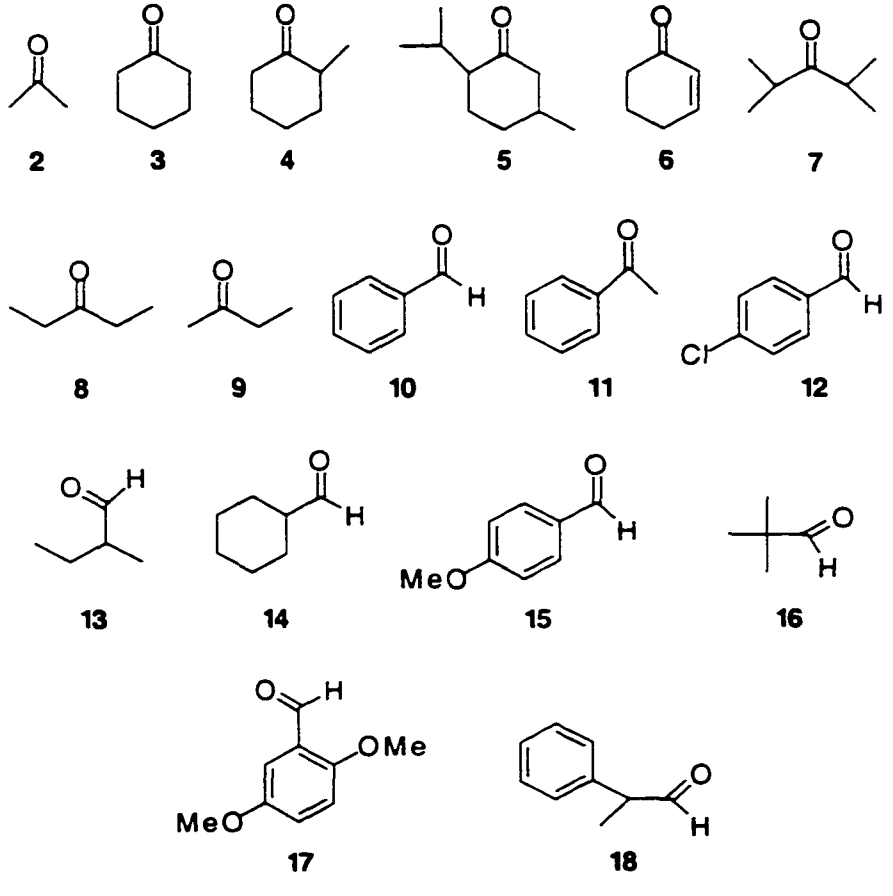
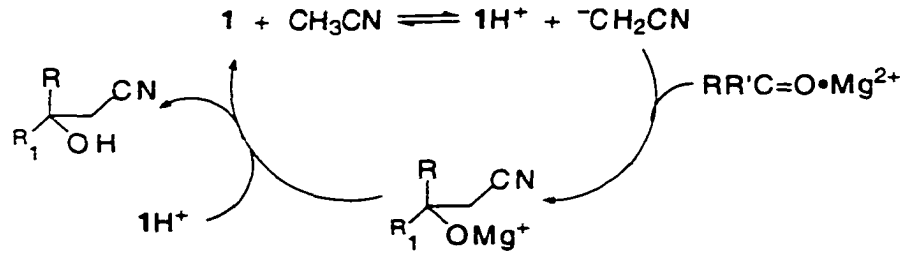


Table 1 shows that ketones participating in this reaction afford β-hydroxy nitriles as the only products. This is due to the sterically hindered nature of the tertiary alcohols produced which prevents further deprotonation by the bulky

Scheme 1



base **1a**. β-Hydroxy nitriles formed from aldehydes on the other hand, (i.e., secondary alcohols) are less sterically hindered and can be deprotonated by **1a** (Scheme 2) leading to α,β-unsaturated nitriles.

Scheme 2

Sterically hindered ketones **5** (menthone) and **7** (2,4-dimethyl-3-pentanone) did not react with acetonitrile in the presence of **1a** under our conditions. This is because the approach of the nucleophilic $^{-}CH_2CN$ ion to the ketonic carbonyl is hampered by the bulk of the alkyl groups. Acetophenone (**11**) was unreactive, presumably as a result of its resonance stabilization. The enolizable aldehyde **18** (2-phenylpropionaldehyde) produced no detectable β-hydroxy nitrile. The protonated **1a** that was detected in the reaction mixture by

^{31}P NMR spectroscopy is attributable to the protonation of **1a** that occurs in the pre-equilibrium shown for the general case in Scheme 1. However, the $^{-}CH_2CN$ that is formed here apparently does not attack the carbonyl. Combination of a solution of 2-phenylpropionaldehyde (**18**) with a solution of **1a** in acetonitrile leads to deprotonation of 2-phenylpropionaldehyde (**18**) by either **1a** or $^{-}CH_2CN$ to give a resonance stabilized enolate. The involvement of $^{-}CH_2CN$ in the deprotonation of 2-phenylpropionaldehyde (**18**) was shown by carrying out the reaction in CD_3CN. ^1H NMR analysis of the reaction mixture after 2 hours revealed the presence of a substantial amount of CHD_2CN. The dimerization of 2-cyclohexenone (**6**) in the presence of the catalysts of type **1** is under further investigation in our laboratories. The reaction of primary aldehydes (represented in this study by *n*-heptanal) to form the corresponding aldol product isolated in 99% yield had been reported previously in a separate study.[21] The reaction of 2-methylcyclohexanone (**4**) to form the corresponding novel β-hydroxy nitrile in 91% yield testifies to the efficiency of our methodology. Both **1b** and **1c** are also catalysts for the preparation of β-hydroxy nitriles. The results of the reaction of carbonyl compounds with acetonitrile in the presence of **1b** and magnesium sulfate are given in Table 2. Contrary to our observation with **1a**, the reaction of acetonitrile with trimethyl

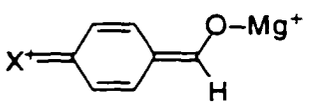
acetaldehyde in the presence of **1b** and 2.2 equiv of magnesium sulfate does not produce substantial amounts of the corresponding undesired α,β-unsaturated nitrile and gives higher yields of the corresponding β-hydroxy nitrile. This is attributable to the relatively stronger basicity of **1a** (resulting from its ability to exist in a zwitterionic amide form **1a'**) which is less sterically hindered.[18,22] Base **1a'** is thus better capable of effecting dehydration of the desired product.

The reaction of aromatic aldehydes produces a mixture of β-hydroxy nitriles and α,β-unsaturated nitriles. This is attributed to resonance stabilization of the α,β-unsaturated nitriles derived from the aryl ring compared with that of the corresponding β-hydroxy nitriles. We reasoned that this propensity of aromatic aldehydes is probably due to the presence of the alkoxide anion that deprotonates the α-methylene in the products, thus leading to the elimination of water during work-up. We therefore decided to quench the reaction of benzaldehyde (**10**) with acetonitrile in the presence of 20 mole percent of **1b**, with MeOH prior to work-up. However, this resulted in only a modest improvement in the distribution of products (i.e., an 82% conversion to the desired β-hydroxy nitrile in addition to 5% of the α,β-unsaturated nitrile). We finally decided to use the less basic **1c** instead of **1b** in the reaction of **10** with acetonitrile, and then quenched the reaction with MeOH prior to work-up. This

produced the β-hydroxy nitrile and the α,β-unsaturated nitrile in conversions of 83% and 3% respectively as estimated by ^{1}H NMR integration of the reaction mixture. When the reaction was carried out at 0 ^{0}C for six hours and then quenched at this temperature with MeOH before passing through a silica gel column, the production of β-hydroxy nitriles from benzaldehyde (**10**) increased to 86%. Upon increasing the concentration of **1c** to 30 mole percent a 92 percent conversion to the desired product was observed with only a trace amount of the α,β-unsaturated nitrile formed. The results of the reactions of aromatic aldehydes with CH_3CN in the presence of **1a** -**1c** are shown in Table 3. The data in this table demonstrate that the dependence of this reaction on the base used (**1a**, **1b**, or **1c**) is minimal. This table also shows that increasing the reaction time to 18 hours at 0 ^{0}C increases the conversion by an average of 5% while the amount of the α,β-unsaturated nitriles increases by only 1-2%. Therefore, the rate of elimination of water is effectively suppressed at this temperature.

The reactions of p-chlorobenzaldehyde (**12**) and *p*-anisaldehyde (**15**) proceeded in an unexpected manner. One would have expected **12** to be more reactive than benzaldehyde (**10**), which in turn would be more reactive than **15** based on inductive effects. However, we find that while **10** reacts

quantitatively, both **12** and **15** have lower reactivities. The cause of this anomalous reactivity is unclear at this time. Since both **10** and **12** have proven to be highly reactive towards $^{-}CH_2CN$ in the absence of magnesium ion.[21] we suspected that coordination of Mg^{2+} to the carbonyl group induces greater resonance effects (as shown in **19** and **20**) which offset the -I effects in p-chlorobenzaldehyde (**12**), *p*-anisaldehyde (**12**). and 2,5-dimethoxybenzaldehyde (**17**), thereby reducing the reactivity of these compounds. The –I effect due to the *p*-chloro, *p*-methoxy and *o*-methoxy groups are expected to activated these aldehdyes towards nucleophilic attack by $^{-}CH_2CN$, whereas, the +R effects deactivates them. Since the result observed here is deactivation, it can be assumed that +R effect predominates.



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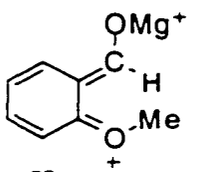


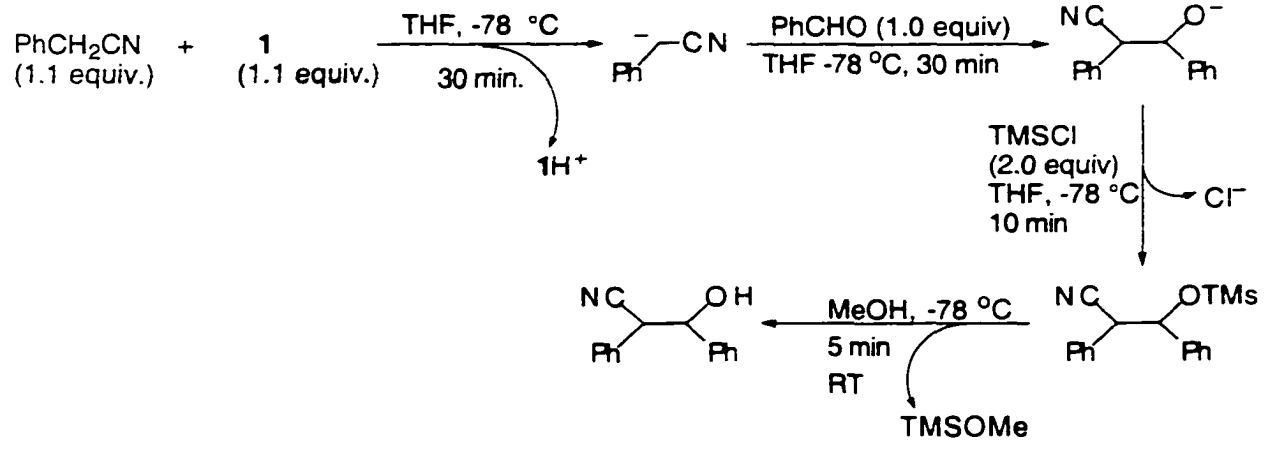
20

To support this assumption, 4-fluorobenzaldehyde and *o*-anisaldehyde were reacted under the same conditions. An 85% and an 83% conversion to the corresponding β-hydroxy nitrile were observed. respectively, which are in accord with such a resonance effect. Despite steric hindrance of the carbonyl group in 2,5-dimethoxybezaldehyde (**17**), the corresponding β-hydroxy nitrile is formed in 84% yield. Although the *o*-OMe group is expected to deactivate the

carbonyl group by both induction and resonance effects, the yields with **17** and *o*-anisaldehyde are slightly higher since resonance will produce the unfavorable geometry shown in **20**. The yields are lower (than that of **10**) as a result of a +R effect.

When the reaction of benzyl cyanide was attempted with PhCHO in the presence of 1 mole % of **1c** and 2.2 equiv of $MgSO_4$, the quantitative production of the corresponding α,β-unsaturated nitrile was recorded in less than one hour in a ^{1}H NMR experiment. However, the preparation of the desired β-hydroxy nitrile was achieved in 99% yield by carrying the reaction at -78 °C in THF as indicated in Scheme 3.

Scheme 3



Conclusion

Nonionic superbases of type **1** are superior catalysts for the synthesis of β-hydroxy nitriles under mild conditions using CH_3CN and sterically unhindered carbonyl substrates that are not easily enolized. The advantages of such catalysts are: (1) The yields of the desired products are high. (2) The reaction occurs at room temperature in a relatively short period of time. (3) The catalyst can be recovered in high yields. (4) The reaction consists of one step. (5) Except for two of the catalysts, which are easily synthesized, all materials are readily commercially available including **1a** (Strem). (6) Reagents known to be toxic are avoided.

Experimental Section

CH_3CN was distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen. $MgSO_4$ was purchased from Fischer Scientific and used as received. All the substrates were purchased from Aldrich Chemical Co. and were used as received. The bases **1a-1c** were prepared according to our previously published methods.[18-20]

General procedure for the preparation of β-hydroxy nitriles using acetonitrile

In a round-bottom flask 3 mL of CH_3CN, 528 mg $MgSO_4$ (2.2 equiv) and 2 mmol of carbonyl substrate were mixed under nitrogen. In a second round-bottomed flask 3 mL of CH_3CN and **1**, (0.4 equiv) were mixed. The contents of the latter flask were then added to the first flask and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was then loaded directly onto a silica gel column and flashed with 100 % ethyl acetate with the exception of 3-hydroxy-3-methylpentanenitrile and 3-hydroxy-3,3-dimethylpentanenitrile which were eluted with MeOH/Et_2O (5:95).

Preparation of β-hydroxy nitriles from aromatic aldehydes

To a mixture of the aldehyde (2.0 mmol) and anhydrous magnesium sulfate (528 mg 4.4 mmol) contained in a round-bottom flask, was added 2.0 mL of dry acetonitrile under nitrogen. The suspension was placed in a constant temperature bath at 0 °C and the mixture was stirred for 5 minutes. A solution of **1** (0.6 mmol) in acetonitrile was added and the mixture was stirred for 6 hours at the end of which 1.0 mL of MeOH was added and stirring continued for 5 more minutes. The reaction mixture was then loaded on to a silica gel

column and eluted with 100% ethyl acetate. The crude product was then purified (when necessary) by column chromatography (*vide infra*).

Preparation of PhCH(OH)CH(CN)Ph using 1c and benzyl nitrile

In a round-bottom flask, 1.2 g (5.5 mmol) of **1c** was dissolved in 10 mL dry THF under nitrogen and the solution was cooled to -78 °C. To the clear solution was added 0.6 mL (5.3 mmol) of benzyl nitrile followed by stirring for 0.5 hr. To the resulting yellow solution was added 0.5 mL (5.0 mmol) of benzaldehyde and the mixture was stirred for an additional 10 minutes. At this point 1.0 mL (8.0 mmol) of TMSCl was added and the mixture was stirred for 10 minutes. This was followed by the addition of 2.0 mL of MeOH at -78 °C and then the reaction mixture was allowed to warm slowly to room temperature over 2 hours. Most of the THF was evaporated under reduced pressure and then 20 mL of dry ether was added to precipitate [H**1c**]Cl that was isolated by filtration. After the removal of ether from the filtrate under reduced pressure, the crude product was eluted through a silica gel column using EtOAc:hexane (70:30) to obtain 1.1 g (99% yield) of the product.

Purification of β-hydroxy nitriles

The crude β-hydroxy nitriles were loaded onto a silica gel column and the starting materials and α,β-unsaturated nitriles eluted with 60 mL of 30% ether in hexanes. The β-hydroxy nitriles were then eluted with ethyl acetate in hexane (70:30). Each of the products from isobutyraldehyde and trimethylacetaldehyde were first eluted with Et_2O/hexane (30:70) followed by 80 mL MeOH/Et_2O (30:70).

(1-Hydroxy-2-methylcyclohexyl)acetonitrile: Isolated as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$): δ 0.93 (d, 3H), 1.3-1.95 (m, 9H), 2.01, (bs, 1H), 2.56 (ABq, 2H). ^{13}C NMR ($CDCl_3$): δ 14.86, 15.07, 21.45, 23.04, 25.27, 30.13, 30.16, 37.09, 38.35, 77.79, 72.75, 117.87. mp 77-78 °C. HR MS (EI) m/*e* (M^+) calcd for $N_9H_{15}NO$ 153.11536, obsd 153.11551.

Catalyst recovery

After the reaction, magnesium sulfate was filtered from the reaction mixture and the residue on the filter paper was washed with 10 mL of chloroform. The solvents were removed under vacuum and 5 mL of water was added. The products were then extracted with 4 x 10 mL portions of ether. The organic layer was then dried over anhydrous magnesium sulfate and the

volatiles removed under reduced pressure to afford the β-hydroxy ntriles. To the aqueous solution containing [1H]OH was added 0.1 mL of 37% aq HCl and the mixture was extracted with 4 x 10 mL portions of methylene chloride to afford [1H]Cl which was then purified and converted to **1** according to previously published methods.[18-20]

Acknowledgments

The authors are grateful to the Iowa State University Center for Advanced Technology for a grant supporting this research.

References

1. Fülöp, F.; Huber, I.; Bernáth, G.; Hönig, H.; Senger-Wasserthal, P. *Synthesis* **1991**, 43.
2. a) Gorzynski Smith, J. *Synthesis* **1984**, 629. b) Ciaccio, J.; Stanescu, C.; Bontemps, J. *Tetrahedron Lett.* **1992**, *33*, 1431.
3. Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1991**, *32*, 4775.
4. Ohno, H.; Mori, A.; Inoue, S. *Chem. Lett.* **1993**, *6*, 975.
5. Mitchell, D.; Koenig, T. *Tetrahedron Lett.* **1992**, *33*, 3281.

6. Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990.

7. You, Z.; Lee, H. *Tetrahedron Lett.* **1996**, *37*, 1165.

8. Barhdadi, R.; Gal, J.; Heintz, M.; Troupel, M.; Perichon, J. *Tetrahedron* **1993**, *49*, 5091.

9. Kaiser, E. W.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 3402.

10. Maasalu, A.; Valimae, T.; Loiveke, I.; Teng, S.; Laats, K. *Easti NSF Tead. Akad. Toim. Keem.* **1988**, *37*, 248; *Chem. Abstr.* 111, 38854e.

11. Wade, P.; Bereznak, J. *J. Org. Chem.* **1987**, *52*, 2973.

12. Araki, S.; Yamada, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1126.

13. Zhang, X.L.; Han, Y.; Ying, T.; Wen-Tian, H.; Yao-Zeng, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, *3*, 189.

14. Gostevskii, B. A.; Kruglaya, O. A.; Albanov, A. I.; Vyazankin, N. S. *Zh. Org. Khim.* **1979**, *15*, 1101; *Chem. Abstr.* 91, 91318c.

15. Cuvingy, T.; Hullot, P.; Larcheveque, M. *J. Organometal. Chem.* **1973**, *57*, C36.

16. Goasdowe, N.; Gaudemar, M. *J. Organomet. Chem.* **1972**, *39*, 17.

17. a) Kasatkin, A. N.; Biktimirov, R.; Tolstikov, G. A.; Nikoneko, A. *Zh. Org. Khim.* **1990**, *26*, 201; *Chem. Abstr.* 114, 42230c. b) Kauffmann. T.: Kieper, H.; Pieper, H. *Chem. Ber.* **1992**, *125*, 899. c) Li, N-S.: Yu, S.: Kabalka, W. *J. Org. Chem.* **1995**, *60*, 5973.

18. D'Sa, B.; Verkade, J. G. *Phosporus Sulfur Silicon* **1997**, *123*, 301.

19. Wroblewski, A. E.; Pinkas, K.: Verkade, J. G. *Main Group Chemistry*. **1995**, *1*, 69.

20. Schmidt, H.; Lensink, C.; Xi, S. K.: Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75.

21. D'Sa, B.; Kisanga, K.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3961.

22. Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4298.

23. Arumugam, S.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827.

Table 1. The reaction of carbonyl compounds with acetonitrile in the presence of **1a**[a] and 2.2 equiv of magnesium sulfate at 25 °C for 4 hours.

substrate	β-hydroxy nitrile % yield	α,β-unsaturated nitrile % yield	% starting material[b]
acetone (2)[c]	94	0	2
cyclohexanone (3)[c]	94	0	4
2-methylcyclohexanone (4)[c]	91	0	8
5, 7, 11, 18	0	0	100
2-cyclohexenone (6)[d]	0	0	0
3-pentanone (**8**)	87	0	9
2-butanone (**9**)	88	0	10
benzaldehyde (**10**)	79	6	13
p-chlorobenzaldehyde (**12**)	71	3	21
2-methylbutyraldehyde (**13**)	95	0	0
cyclohexanecarbocaldehyde (**14**)	76	<1	20
p-anisaldehyde (**15**)	36[b]	10[b]	54[b]
pivalaldehyde (**16**)	83	15	<1
2,5-dimethoxybenzaldehyde (**17**)	62	<1	36

[a]The amount of the catalyst was 10 mole percent unless stated otherwise.

[b]Estimated by ^{1}H NMR integration. [c]The amount of catalyst used was 15%.

[d]Only the dimer of the α,β-unsaturated enone was isolated in 95% yield.

Table 2. The reaction of carbonyl compounds with acetonitrile in the presence of **1b**[a] and 2.2 equiv of magnesium sulfate at 25 °C for 4 hours.

substrate	β-hydroxy nitrile % yield	α,β-unsaturated nitrile % yield	% starting material[b]
acetone (**2**)	99	0	0
cyclohexanone (**3**)	99	0	0
2-methylcyclohexanone (**4**)	54	22	20
5, 7, 11, 18	0	0	100
2-cyclohexenone (**6**)[c]	0	0	0
3-pentanone (**8**)	98	0	0
2-butanone (**9**)	97	0	0
benzaldehyde (**10**)	68	7	20
p-chlorobenzaldehyde (**12**)	50[b]	0	50
2-methylbutyraldehyde (**13**)	97[d]	0	0
cyclohexanecarbocaldehyde (**14**)	95	0	<1
p-anisaldehyde (**15**)	33[b]	33[b]	33
pivalaldehyde (**16**)	95[d]	3	0

[a]The ratio of catalyst used was 20 mole percent unless stated otherwise. [b]Estimated by ^{1}H NMR integration. [c]The only isolated product was the dimeric enone in 99% yield. [d]The concentration of **1b** was 10 mol %.

Table 3. The reaction of aldehydes with acetonitrile in the presence of **1a-1c**[a] and 2.2 equivalents of magnesium sulfate at 0 °C.

starting material[c]	base	β-hydroxy nitrile % yield[b]	% α,β-unsaturated nitrile[c]	starting material[c]
benzaldehyde (**10**)	**1a**	96(98)[d]	2	0
benzaldehyde (**10**)	**1a**	(98)	2	0
benzaldehyde (**10**)	**1b**	(98)	2	0
benzaldehyde (**10**)	**1c**	88 (92)	3	5
benzaldehyde (**10**)	**1c**	(97)[d]	3	0
p-chlorobenzaldehyde (**12**)	**1b**	82(84)	4	12
p-chlorobenzaldehyde (**12**)	**1c**	77 (80)	4	16
cyclohexanecarboxaldehyde (**14**)	**1a**	88(92)	4[e]	0
p-anisaldehyde (**15**)	**1a**	71(75)[d]	6	19
p-anisaldehyde (**15**)	**1b**	(78)	5	17
p-anisaldehyde (**15**)	**1c**	78 (80)	4	16
2,5-dimethoxybenzaldehyde (**17**)	**1a**	81 (85)	0	15
2,5-dimethoxybenzaldehyde (**17**)	**1c**	84 (87)[d]	0	13

[a]The amount of **1c** used was 30 mole percent and the reaction time was 6 h unless stated otherwise. [b]Values in parenthesis are conversions estimated by ^{1}H NMR integration . [c]Estimated by ^{1}H NMR integration. [d]The reaction time was 18 hours. [e]A small amount of unidentified material was observed.

Supporting Information

^{1}H NMR and ^{13}C NMR spectral data with peak assignments

3-Hydroxy-3-methylbutyronitrile: These NMR spectra compared favorably with that reported in *J. Org. Chem.* **1996**, *62*, 4087.

3-Ethyl-3-hydroxypentanenitrile: These spectra compared favorably with that reported in *J. Org. Chem.* **1968**, *33*, 3402.

3-Hydroxy-3-methylpentanenitrile: The boiling point compared favorably to that reported in *Bull. Chim. Belg.* **1932**, *41*, 251. No NMR spectra reported. ^{1}H NMR ($CDCl_3$): δ 0.97 (t, 3H), 1.35 (s, 3H), 1.66 (m, 2H), 2.18 (bs, 1H), 2.51 (d, 2H). ^{13}C NMR ($CDCl_3$): δ 8.10, 26.10, 30.83, 34.16, 71.34, 117.81.

3-Phenyl-3-hydroxyproprionitrile: ^{1}H NMR compared favorably to that reported in *Synth. Comm.* **1994**, *24*, 1433. ^{13}C NMR compared favorably to that reported in *Tetrahedron Lett.* **1994**, *35*, 3447.

3-(4-Chlorophenyl)-3-hydroxypropionitrile: ^{1}H NMR compared favorably with that reported in *J. Org. Chem.* **1991**, *56*, 1381.

3-Hydroxy-4-methylhexananenitrile: These NMR spectra compared favorably with that reported in *J. Org. Chem.* **1995**, *60*, 5973.

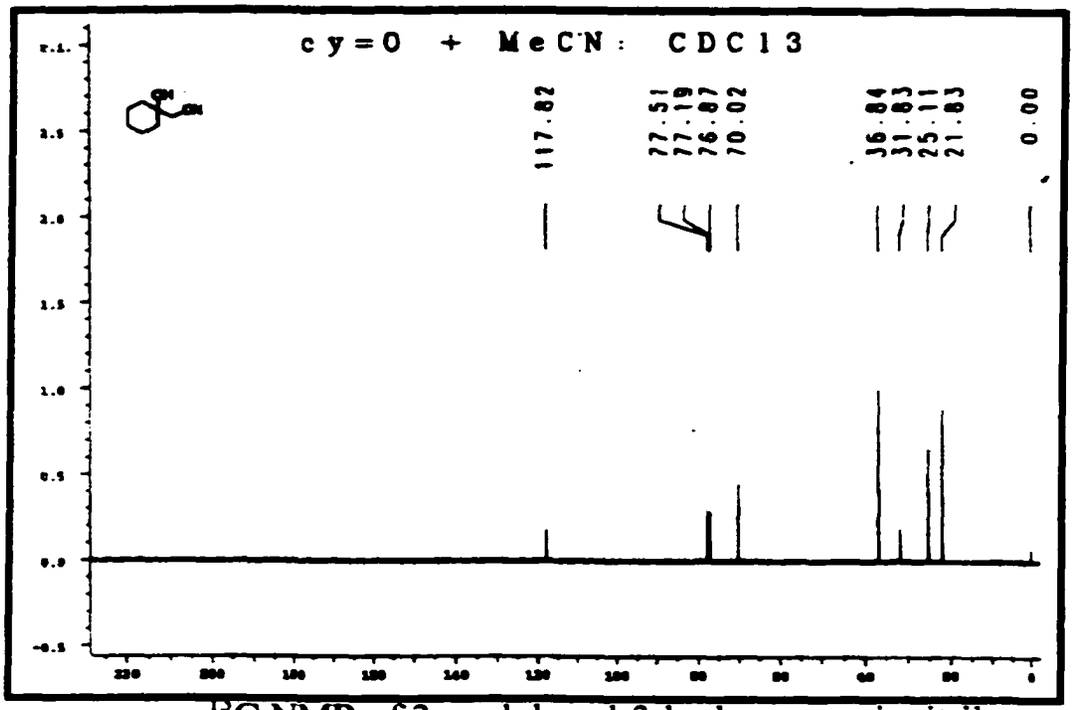
3-Cyclohexyl-3-hydroxypropionitrile: ^{1}H NMR compared favorably to that reported in *J. Chem. Soc., Perkins Trans 1.* **1991**, 1931.

3-(4-Methoxyphenyl)-3-hydroxyproprionitrile: ^{1}H NMR compared favorably with that reported in *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1126.

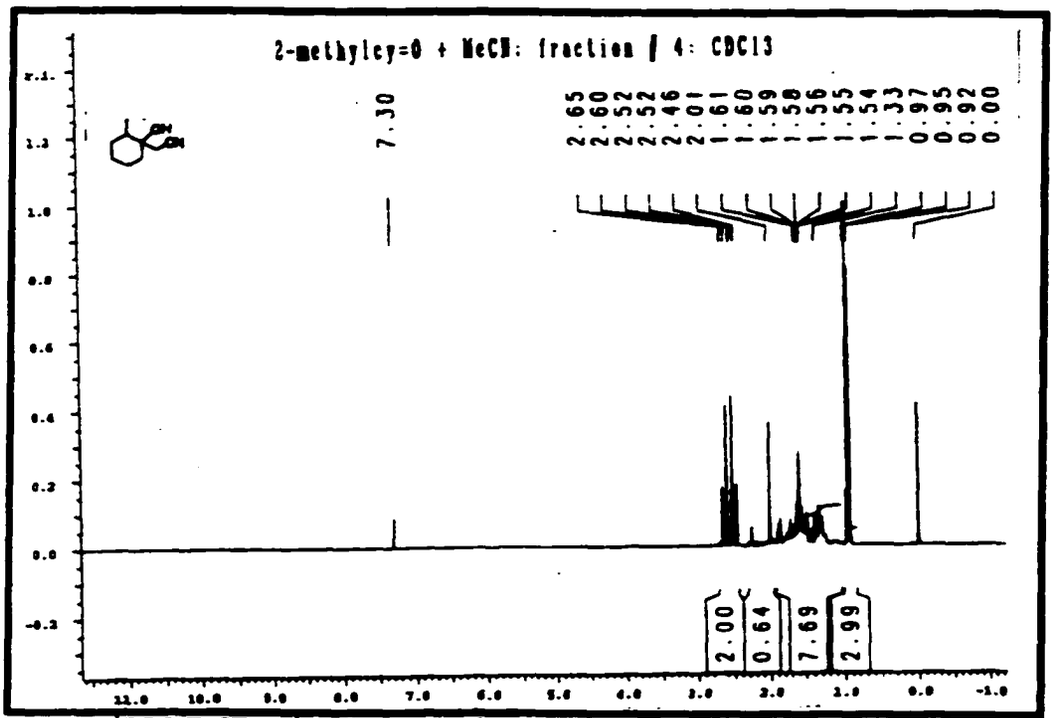
3-Hydroxy-4,4-dimethylpentanenitrile: These NMR spectra compared favorably with that reported in *J. Org. Chem.* **1995**, *60*, 5973.

3-(2,5-Dimethoxyphenyl)-3-hydroxypropionitrile: ^{1}H NMR compared favorably with that reported in *J. Org. Chem.* **1995**, *60*, 2261.

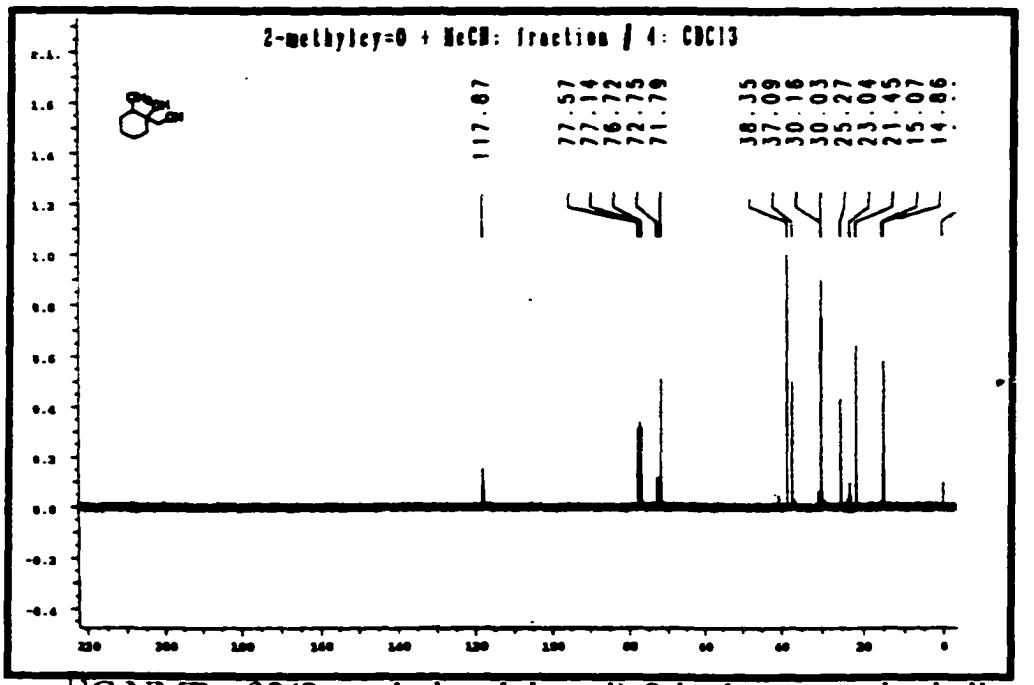
2,3-Diphenyl-3-hydroxyproprionitrile: These NMR spectra compared favorably with that reported in *J. Org. Chem.* **1995**, *60*, 2261.



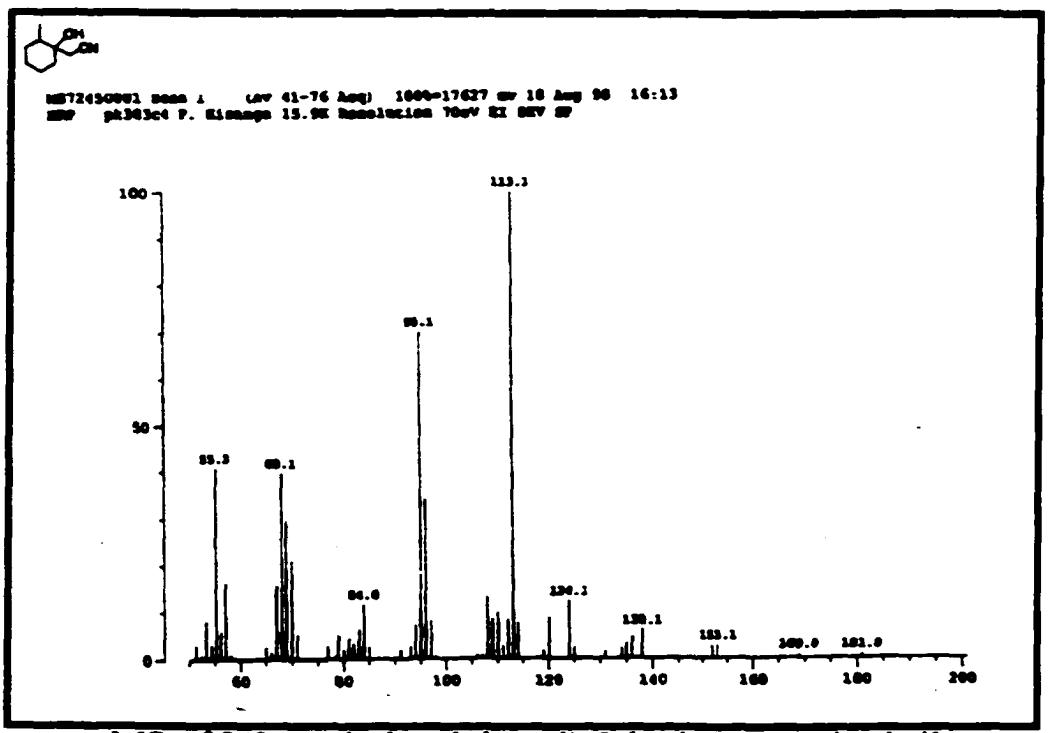
^{13}C NMR of 3-cyclohexyl-3-hydroxypropionitrile



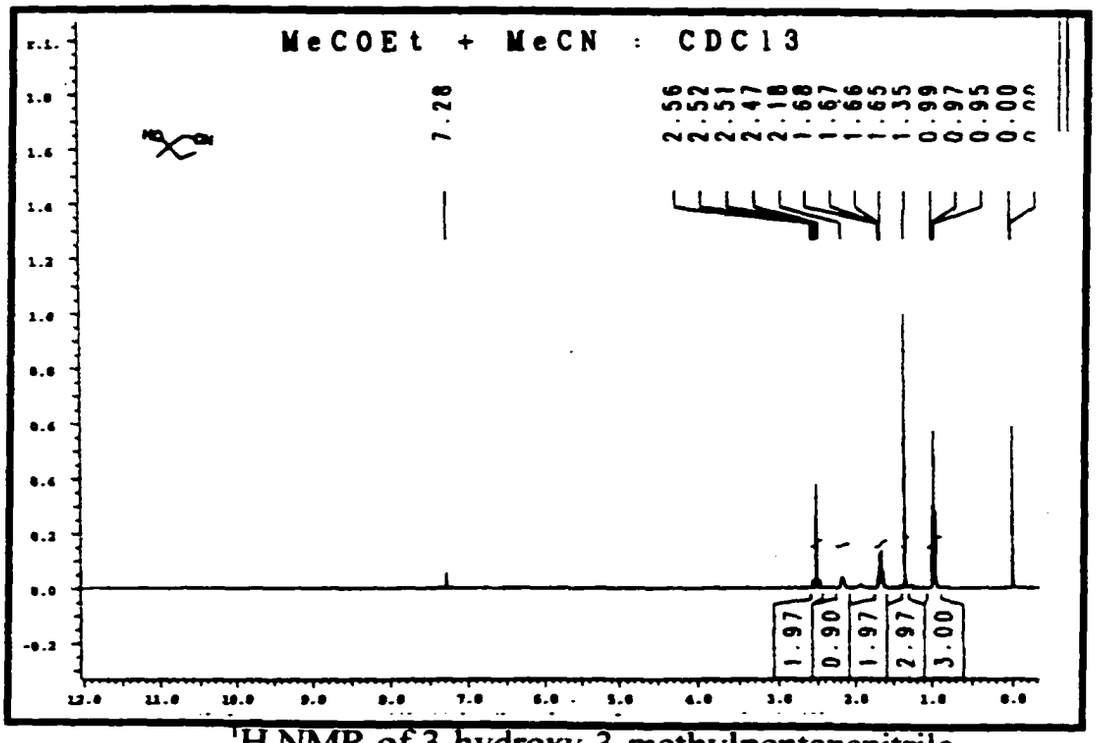
^{1}H NMR of 3(2-methylcyclohexyl)-3-hydroxypropionitrile



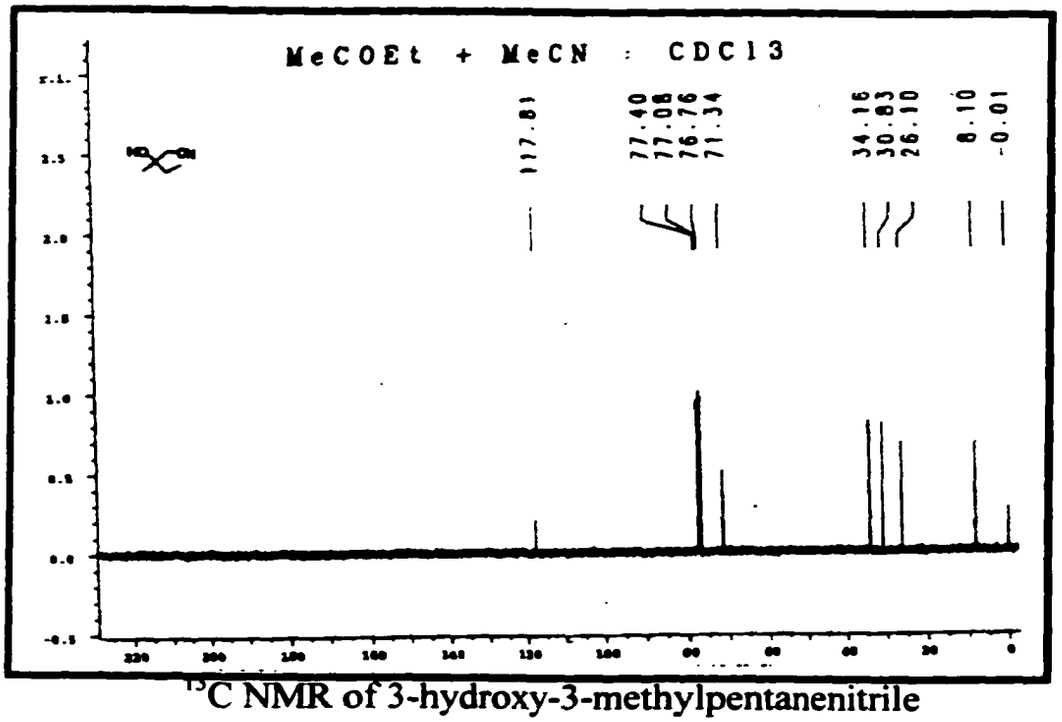
^{13}C NMR of 3(2-methylcyclohexyl)-3-hydroxypropionitrile



MS of 3(2-methylcyclohexyl)-3-hydroxypropionitrile



^{1}H NMR of 3-hydroxy-3-methylpentanenitrile



^{13}C NMR of 3-hydroxy-3-methylpentanenitrile

CHAPTER 6

$P(RNCH_2CH_2)_3N$: AN EFFICIENT PROMOTER FOR THE NITROALDOL (HENRY) REACTION

A paper published in the Journal of Organic Chemistry **1999**, *64*, 4298[a]

Philip B. Kisanga[b,c] and John G. Verkade[b,d]

Abstract

The use of catalytic amounts of the proazaphosphatranes $P(MeNCH_2CH_2)_3N$, $P(i\text{-}PrNCH_2CH_2)_3N$ and $P(HNCH_2CH_2)(i\text{-}PrNCH_2CH_2)_2N$ as nonionic bases in the reaction of nitroalkanes with carbonyl compounds is reported. The reaction proceeds at room temperature in the presence of 2.2 equivalents of magnesium sulfate to produce the corresponding β-nitroalkanols in generally superior yields. Aldehydes react quantitatively in 5-60 mins, whereas ketones require up to 3 hours, and up to 7 hours for the reaction of ketones with higher nitroalkanes.

Introduction

β-Nitroalkanols are important and versatile intermediates in the synthesis of nitroalkenes, 2-amino alcohols and α-nitro ketones.[1] 2-Amino

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alcohols are of particular significance in the synthesis of biologically important compounds such as epinephrine[2] and anthracycline antibiotics[3], while α-nitroketones are valuable intermediates in the synthesis of several natural products.[4] β-Nitroalkanols are also important because of their properties as fungicides[5] and because of their utility as intermediates in the synthesis of aminosugars,[6] antibiotics such as ezomycins[7a] and tunicamycin[7b], and in the synthesis of alkaloids.[8]

Classical methods for preparing β–nitroalkanols include the condensation of the carbonyl substrates and a nitroalkane in the presence of an ionic base, such as alkali metal hydroxides, alkaline earth oxides, carbonates, bicarbonates, alkoxides, alkaline earth hydroxides, or magnesium and aluminum alkoxides.[1] While this approach is quite simple and inexpensive, its limitations often render it unattractive. For example, base-catalyzed elimination of water can occur to form nitroolefins which unfortunately polymerize readily. Moreover, it is not easy to remove the base before work-up because acidification of the reaction mixture may lead to the Nef[9] reaction if it is not done with extreme care. The use of primary amines and triethylamine as condensing agents has also been reported.[1] Although this methodology leads to high yields of the β-nitroalkanol, the production of unsaturated nitro compounds through base-catalyzed

elimination of water has been observed as well as formation of 1,3-dinitro compounds. The latter substrances are also the predominant products when diethylamine is used as a base.[1]

Several variations of the nitroaldol reaction have recently been developed which include the use of tetramethylguanidine,[10] dendritic catalysts,[11] Amberlyst A-21,[12] and a sodium hydroxide-catalyzed process in the presence of cetyltrimethylammonium chloride (CTACl).[13] Although these methods afford high yields of the nitroaldol with aldehydes, they suffer from their inability to produce high product yields with alicyclic or aliphatic ketones when such reactions are even observed. Self-condensation[10] of aliphatic ketones has been cited as a possible reason for the inability of this class of compounds to form the nitroaldol product in appreciable amounts.

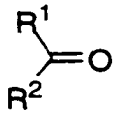
The proazaphosphatranes **1a**,[14] **b**,[15] and **c**[16,17] have recently been shown to be strong non-ionic bases. Thus, they are able to deprotonate acetonitrile,[18,19] benzyl nitrile[18] and other activated methylene compounds,[20] thereby providing access to carbanions that can in turn participate in interesting and useful transformations. In our continued search for reactions in which these proazaphosphatranes provide improved synthetic methodology over conventional approaches, we have found that bases of type **1** also catalyze the Henry reaction in a superior manner.

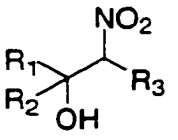
Results and Discussion

The simplicity of reaction 1 stems from the fact that the catalytic amount of the base used is protonated during the reaction to form the salt shown that is easily separated chromatographically; a process that requires neither acidic nor aqueous work-up. Self-condensation of ketones is not possible under the reaction condition since none of the promoter (**1**) is present in unprotonated form at the concentrations employed. Because the basicity order of **1a-c** is **1c < 1b < 1a**,[15] we focus our attention here mainly on **1a** and **1b**. It is worth mentioning that the pK_a of **1a-1c** has been estimated to have a lower limit of 25[15] and an upper limit of 26.8[16b] in DMSO based on competetitive deprotonation.

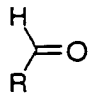
The reaction of carbonyl compounds with nitromethane in the presence of 1a

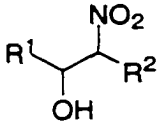
The reaction of aldehydes with nitromethane in the presence of **1a** is fast and virtually quantitative. Thus for example, aldehyde **2k** forms **3k** (via the plausible pathway shown in Scheme 1) in less than 5 minutes in the presence of 2.2 equivalents of $MgSO_4$ and 20 mole percent of **1a**. The decision to use $MgSO_4$ as a Lewis acid was based on another study[18b] in which we found that $MgBr_2$ and $MgSO_4$ were the only Lewis acids found to

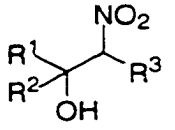




	R^1	R^2		R^1	R^2	R^3
2a:	$(CH_2)_5$		**3a**:	$(CH_2)_5$		H
2b:	$(CH_2)_4$		**3b**:	$(CH_2)_4$		H
2c:	Me	Me	**3c**:	Me	Me	H
2d:	Me	Et	**3d**:	Me	Et	H
2e:	Et	Et	**3e**:	Et	Et	H
2f:	*i*-Pr	*i*-Pr	**3f**:	*i*-Pr	*i*-Pr	H
2g:	$(CH_2)_4CH(Me)$		**3g**:	$(CH_2)_4CH(Me)$		H
2h:	$CH(Me)(CH_2)_3CH(Me)$		**3h**:	$CH(Me)(CH_2)_3CH(Me)$		H
2i:	Ph	Me	**3i**:	Me	Me	H

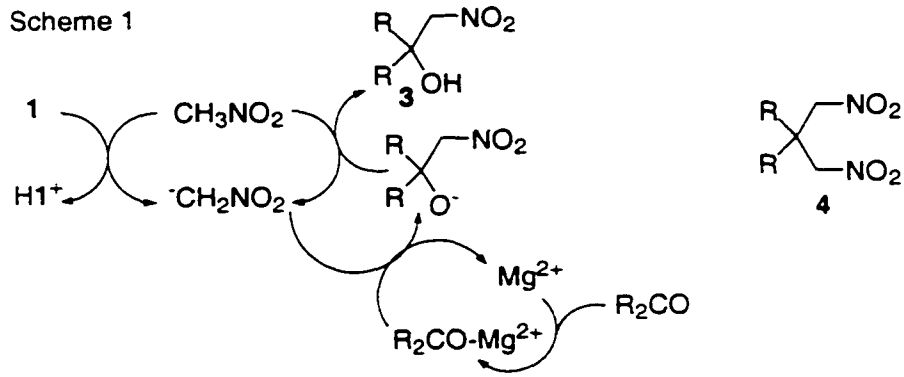






	R		R^1	R^2		R^1	R^2	R^3
2j:	*p*-$MeOC_6H_4$	**3j**:	*p*-$MeOC_6H_4$	H	**3r**:	$(CH_2)_5$		Me
2k:	*p*-$O_2NC_6H_4$	**3k**:	*p*-$O_2NC_6H_4$	H	**3s**:	H	*i*-Pr	Me
2l:	*n*-Pr	**3l**:	*n*-Pr	H	**3t**:	$(CH_2)_5$		Et
2m:	*i*-Pr	**3m**:	*i*-Pr	H	**3u**:	H	Ph	Et
2n:	Ph	**3n**:	Ph	H	**3v**:	H	$CH_3(CH_2)_5$	Et
2o:	2.5-$Me_2C_6H_3$	**3o**:	2.5-$Me_2C_6H_3$					
2p:	PhCH(Me)	**3p**:	PhCH(Me)	H	**3w**:	$Me(CH_2)_5CH(OH)C(NO_2)Me_2$		
2q:	$CH_3(CH_2)_5$	**3q**:	$CH_3(CH_2)_5$	H	**3x**:	$PhCH(OH)C(NO_2)Me_2$		

Scheme 1



activate carbonyl groups in the synthesis of β-hydroxy nitriles catalyzed by bases of type **1**. Since $MgSO_4$ is less expensive and more convenient to handle and its insolubility allows it to be easily filtered by column filtration. we have thus far preferred to use it over $MgBr_2$. Moreover, $MgBr_2$ in the present study did not appear to be effective. The reaction of cyclohexanone **2a** (employed as a model ketone) with nitromethane in the presence of 10 mole percent of **1a** is rather sluggish requiring 18 hours at room temperature to achieve a yield of **3a** (48%) that is comparable to literature values (48-74%[10,21]). Although the yield of **3a** increased to 64% when the amount of **1a** was increased to 20 mole percent, 8% of the corresponding dinitro derivative **4a** is also formed. When this reaction was repeated in the presence of 30% mole percent of **1a**, the yield of the nitroaldol product increased to 68% while the production of the dinitro product **4a** increased to 20%. In the

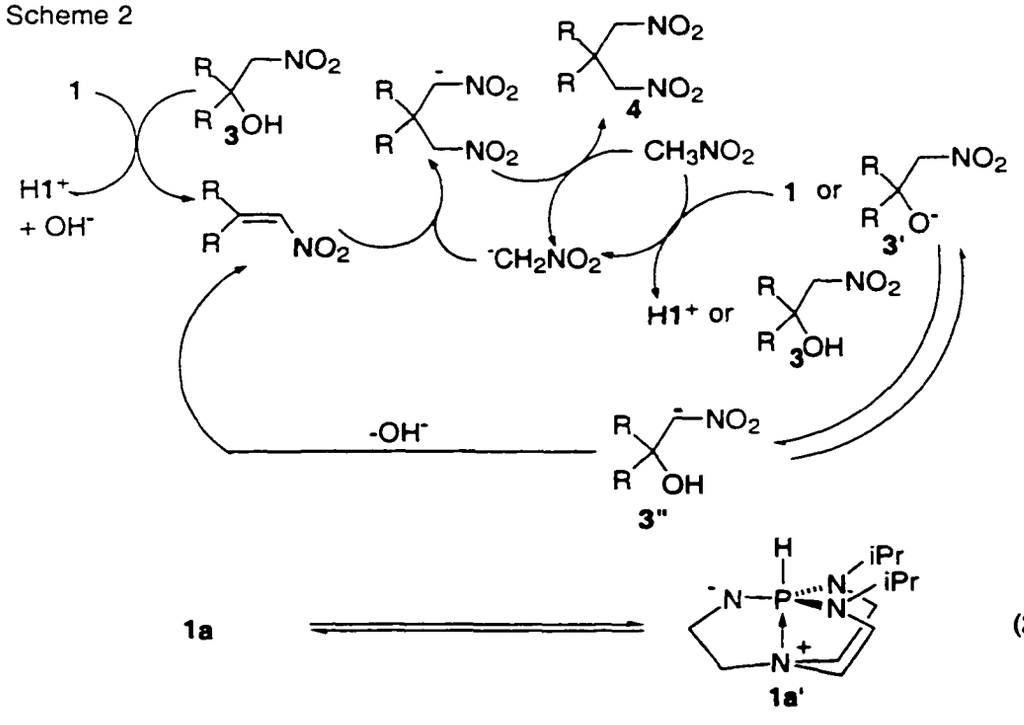
presence of 2.2 equivalents of anhydrous magnesium sulfate (in which the Mg^{2+} presumably acts as a carbonyl group activator) and 30 mole percent of **1a**, the conversion was quantitative and a 96% isolated yield of the nitroaldol product **3a** was obtained in about 3 hours. Reducing the amount of **1a** to 10 mole percent did not materially affect the yield (95%) of **3a**. At concentrations lower than 10 mole percent of **1a**, some of the starting material was still observed after 3 hours. The reactions of cyclopentanone, acetone, 2-butanone, and 3-pentanone with nitromethane in the presence of 10 mole percent of **1a** and 2.2 equivalents of Mg^{2+} were equally successful. Pertinent data for these reactions are shown in Table 1.

Since the formation of the dinitro compounds (**4**) has been reported in several syntheses of β-nitroalkanols,[1] we decided to investigate the limitations such reactions might have on our methodology. At a higher concentration of **1a** (30 mole percent), the formation of the dinitro compounds was observed to begin at reaction times greater than 5 hours. When the reaction was allowed to proceed for 18 hours in the presence of 30 mole percent of **1a** and 2.2 equivalents of magnesium sulfate, an 84% yield of the nitroaldol **3a** and a 14% yield of the dinitro derivative **4a** was realized. The reactions of cyclopentanone, acetone, and 2-butanone with nitromethane in the presence of 30 mole percent of **1a** and 2.2 equivalents of

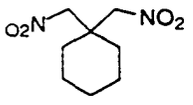
Mg^{2+} were equally successful. With 3-pentanone (**2e**), only 43% of the nitroaldol product **3e** was isolated in addition to 23% of the corresponding dinitro product **4e**, with the rest being unidentified material. Therefore, even with longer reaction times, the formation of the nitroaldol products still predominates. The sterically hindered ketones **2f** and **2h** (as a mixture of diastereomers) have so far failed to form the corresponding nitroaldol products when reacted with nitromethane in the presence of **1a** and 2.2 equivalents of magnesium sulfate. Starting materials were recovered quantitavively.

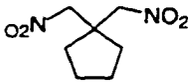
The formation of the dinitro products (via the plausible pathway shown in Scheme 2) in the reaction of ketones with nitromethane in the

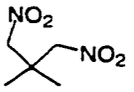
Scheme 2



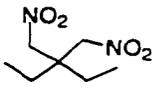
(2)


4a


4b


4c


4d


4e

presence of catalytic amounts of **1a** can be rationalized in terms of the relative basicities and steric features of **1a-1c**.[15] In addition to the superior base strength of **1a**, which is attributed to its ability to exist as an amide base in tautomeric form (equation 2),[14] this base is also less sterically hindered because of the more open amide site in **1a'**. At higher concentrations (30 mole percent) the free base present induces a base assisted dehydration. At longer reaction times, the alkoxide **3'** produced can tautomerize to **3''**, leading to the elimination of OH^- and subsequent formation of the dinitro system **4** as shown in Scheme 2. The results of reactions of nitromethane with some of the ketones involved in this study with 30 mole percent of **1a** in the presence of 2.2 mole equivalents of magnesium sulfate for 18 hours at room temperature are shown in Table 2.

The reaction of carbonyl compounds with nitroalkanes in the presence of 1b

The reaction of aldehydes is fast and quantitative in the presence of **1b**. Thus, **2k** reacts with nitromethane in the presence of 20 mole percent of **1b** and 2.2 equivalents of magnesium sulfate in less than 5 minutes at room

temperature to form **3k** as the only product. When **2a** was reacted with nitromethane in the presence of 10 mole percent of **1b** and 2.2 equivalents of magnesium sulfate for 3 hours, a 95% yield of **3a** was isolated and no dinitro derivative **4a** was observed. Scheme 1 suggests that the reaction requires catalytic amounts of magnesium ions. In the presence of 1 mole percent of $MgSO_4$, **2a** reacted with nitromethane in the presence of 10 mole percent of **1b** to form **3a** (ca 70% conversion as estimated by ^1H NMR integration) in 3 hours at room temperature. When the temperature was raised to 40 °C, the conversion in 2 hours was 73%. Increasing the reaction time beyond 2 hours led to no significant change in the conversion. On the other hand, increasing the amount of magnesium sulfate to 1 mole equivalent increased the conversion to 83% in 2 hours at the same temperature. At mole ratios greater than 2.0 equivalents of magnesium sulfate and 10 mole percent of **1b**, the conversion in 2 hours at 40 °C was estimated by ^1H NMR integration to be 95%. This dependence of the nitroaldol reaction of ketones on Mg^{2+} concentration is attributable to its activation of the carbonyl group via oxygen coordination and its subsequent stabilization of the alkoxide produced upon C-C bond formation. This dual role of $MgSO_4$ is again demonstrated in the reaction of **2m** with $MeNO_2$ in the presence of 1 mole percent of magnesium sulfate and 10 mole percent of **1b**. Although this

reaction is complete in about 1 hour at 40 °C, several spots were observed on TLC. In the presence of 2.2 mole equivalents of magnesium ions, however, the conversion is complete in less than 1 hour at room temperature with **3m** as the only product. Results of the reactions of **2a-2q** with nitromethane in the presence of **1b** and 2.2 mole equivalents of magnesium sulfate are summarized in Table 3.

That high concentrations of **1** deprotonate the methylene group in products of type **3** (leading to the formation of the corresponding dinitro compound **4** as shown in Scheme 2) is demonstrated by our observation of the reactions of nitromethane with some of the ketones used in this study. The results of these reactions in the presence of 40 mole percent of **1b** and 2.2 equivalents of magnesium sulfate for 18 hours at room temperature are given in Table 4. No corresponding of the dinitro products were observed at reaction time of less than 5 hours.

In a similar way to that described above, nitroethane reacts with cyclohexanone (**2a**) and isobutyraldehyde (**2m**) in the presence of 10% of **1b** and 2.2 equivalents of magnesium sulfate to form the corresponding nitroaldols **3r** and **3s** in 82% and 98%, respectively. However, we found that 1-nitropropane requires 1.25 h to undergo a quantitative reaction with heptanal (**2q**) to form a 3:2 mixture of the threo and erythro diastereomers,

respectively. The diastereomeric ratio was determined by ^{1}H NMR integration based on a comparison of both the ^{1}H NMR and ^{13}C NMR spectral data for the diastereomeric mixture with the those reported by Seebach *at al*[22] for the reaction of *n*-hexanal with 1-nitropropane. The reaction of benzaldehyde under similar conditions, afforded only 85% conversion to the desired β-alkanol as observed by ^{1}H NMR integration of the reaction mixture. Upon increasing the amount of the base to 0.2 equiv, this substrate also reacted quantitatively in 2.25 h to afford a 3:1 (*threo: erythro*) diastereomeric mixture of **3u** in 97% yield. The observed preference for the threo diastereomer is probably due to the favorable intramolecular hydrogen bonding in this diastereomer. The reaction of cyclohexanone as a model ketone under similar conditions proceeded with 43% conversion but afforded the nitroaldol **3t** in 93% yield upon increasing the ratio of **1b** to 0.3 equiv and carrying out the reaction for 7 hours (Table 3). However, nitrocyclohexane did afford the corresponding nitroaldols when reacted with each of benzaldehyde, *n*-heptanal, 2-butanone and cyclohexanone. Thus benzaldehyde and cyclohexanone were quantitatively isolated after reaction for 6 hours and 72 hours, respectively, unreacted 2-butanone was lost on evaporation of the volatiles and work-up afforded nitrocyclohexane quantitatively. *n*-Heptanal, however, afforded the

corresponding aldol product in 91% yield. The formation of the aldol product from primary aldehydes has been observed in our laboratories in previous studies.[18] The lack of reactivity of nitrocyclohexane in these reactions is assumed to be the result of steric hindrance. Although protonation of **1b** is observed by ^{31}P NMR analysis, the nitronate anion thus produced, which is associated with the azaphosphatrane counter cation (equation 1) form a bulky ion pair that is too sterically hindered to approach a carbonyl group. The use of magnesium bromide (the only other Lewis acid we have so far found to be compatible with our system[18b]) was also fruitless. The reaction of 2-nitropropane with *n*-heptanal on the other hand proceeded to afford the corresponding nitroaldol **3w** in 99% yield in 1.5 h while the reaction with benzaldehyde required 4 hours to afford a 95% yield of the desired product **3x**. The reaction of 2-nitropropane with 2-butanone afforded only the starting nitroalkane after workup and removal of the volatiles while the reaction of cyclohexanone afforded a mixture of the starting materials after work-up. The inability of the 2-nitropropane to produce 2-nitroalkanols is again explained in terms of the steric hindrance of the ion pair formed after deprotonation. An attempt at employing magnesium bromide as the carbonyl activator for this substrate was also fruitless.

The reaction of carbonyl compounds with nitromethane in the presence of 1c

The yields of β-nitroalkanols using **1c** as a base are equal, within experimental error, to those obtained with **1b**. For example, **2a** or **2b** reacted with nitromethane in the presence of 10 mole percent of **1c** and 2.2 mole equivalents of magnesium sulfate to afford a 95% and a 91% yield of the nitroaldol products **3a** and **3b**, respectively. The yields of the same two products in the presence of 10 mole percent of **1b** were 96% and 93% respectively (Table 3). However, in contrast to our observation with **1b**, increasing the concentration of **1c** from 10 up to 40 mole percent did not lead to the formation of the corresponding dinitro product. Thus when the ratio of **1c** was increased from 10 up to 40 mole percent in the reaction ketones in the presence of 2.2 equivalents of magnesium sulfate, the yield of the nitroaldol product did not appear to change appreciably. For example, **2a** gave a 97% yield of **3a** in 18 hours while **2b** produced a 92% yield of the corresponding nitroaldol in the presence of 40 mole percent of **1c**. The yields of the same two products with 10 mole percent of **1c** (*vide supra*) were 95% and 91%, respectively. This result is consistent with the relatively weaker basicity of **1c** relative to **1b** and **1a**.

We have so far been unable to induce the nitroaldol reaction with aromatic ketones. Only starting materials were recovered upon reacting acetophenone (**2i**) with nitromethane in the presence of 30 mole percent of either **1a** or **1b** and 2.2 mole equivalents of magnesium sulfate. Warming the reaction mixture to 40 °C also did not lead to the production of the expected β-nitroalkanol. This result can be attributed to resonance stabilization of the carbonyl group by the benzene ring in the substrate.

Conclusion

We have shown here that the proazaphosphatranes **1a**, **1b**, and **1c** are highly efficient promoters at room temperature for the Henry reaction in the presence of 2.2 equivalents of magnesium sulfate. While the reaction of primary nitroalkanes and 2-nitropropane proceed with excellent yields, the reaction of nitrocyclohexane fails under similar conditions.

The high yields observed in the nitroaldol reaction of ketones promoted by bases of type **1** are due to the virtual lack of free base present at the concentrations used in these reactions. Since the corresponding nitronates are much weaker bases than the alkoxide, they are unable to deprotonate the ketones (a process that would lead to self-condensation). Once the nitronate adds to the ketone, the alkoxide thus produced

preferentially deprotonates the more acidic nitroalkane that is present in large excess. Thus ketone self-condensation is less likely to be observed under these reaction conditions.

Experimental Section

All reactions were carried under nitrogen. The carbonyl compounds were purchased from Aldrich Chemical Company and used as received. Nitroethane and nitromethane were dried over anhydrous magnesium sulfate, distilled under nitrogen and then stored over 4Å molecular sieves.

General Procedure for the Preparation of the Nitroalkanols

In a typical experiment, a small test tube containing a micro stirbar and 0.528 g (4.4 mmol) of magnesium sulfate was sealed with a septum and then evacuated to 200 millitorr. The tube was then filled with nitrogen gas followed by 1.0 mL of the nitroalkane, and then the mixture was stirred vigorously until all the magnesium sulfate was incorporated into the suspension. To this suspension was added 2.0 mmol of the carbonyl compound. The mixture was stirred for 5 min after which a solution of 60 mg of **1b** (or 43 mg of **1a** or 52 mg of **1c**, 0.20 mmol) dissolved in 1.0 mL of the nitroalkane was added. After the time periods specified in Tables 1- 5 had elapsed, any remaining nitroalkane was removed under reduced

pressure. The reaction mixture was then loaded onto a small silica gel column and eluted with 100% diethyl ether. Nitroalkanols **3e**, **3k**, **3l**, **3m**, **3n**, **3q**, **3s** (as a 1:1 mixture of diastereomers), **3t** and **3u** were obtained as pure products in excellent yields, while the others were purified as detailed below.

Purification of the dinitro product

The product mixture of the nitroalkanol and the dinitro derivative was loaded onto a silica gel column using a small amount of ether. The separation of the two compounds was then achieved by eluting with diethyl ether in pentane. The ratio of ether was increased in 5% portions from 0% to 80% in 50 mL volumes, and 20 mL fractions were collected. The nitroalkanol eluted first while the dinitro compounds followed at about 50% diethyl ether in pentane.

Ackowledgement

The authors thank the Donors of the Petroleum Research Fund administered by the American Chemical Society and the Iowa State Center for Advanced Technology Development for grant support of this work.

References

1. (a) Rosini, G. In *Comprehensive Organic Synthesis*, Vol. 2, Trost, B. M. Ed.: Pergamon, New York, **1991**, 321-340. (b) For recent publications on the utility of the Henry Reaction see: Iseki, K.; Oishi, S.; Sasai, H.: Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9081. Barco, A.; Benetti, S.; Risi, C.: Polloni, G. *ibid.* **1996**, *37*, 7599. Sasai, H.; Hiroi, M.; Yamada, Y.: Shibasaki, M. *ibid.* **1997**, *38*, 6031; Shibasaki, M.; Sasai, H.: Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236.
2. Brittain, R.; Jack, D.; Ritchie, A., *Adv. Drug Res.* **1970**, 5.
3. Williams, T. M.; Mosher, S. H. *Tetrahedron Lett.* **1985**, *26*, 6269.
4. (a) Ballini, R.; Bosica, G. *J. Org. Chem.* **1994**, *59*, 5466. (b) Ballini, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1419. (c) Ballini, R.: Bosica, H. *J. Chem. Res.; Synop.* **1993**, 371.
5. Mikite, G.; Jakucs, K.; Darvas, F.; Lopata A. *Pestic. Sci.* **1982**, *13*, 557.
6. Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261.
7. (a) Sakanaka, O.; Ohmorti, T.; Kazaki, S.; Suami, T.; Ishii, T.; Ohba, S.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1753. (b) Sasai, H.; Matsuno, K.; Suami, T. *J. Carbohydr. Chem.* **1985**, *4*, 99.
8. Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Chem. Comm.* **1990**, *12*, 894.

9. (a) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367. (b) Hwu, J. R.; Gilbert, B. A. *J. Am. Chem. Soc.* **1991**, *113*, 5917 and references cited therein. (c) For a review on the Nef reaction see: Noland, W. E. *Chem. Rev.* **1955**, *55*, 137. Pinnick, H. W. In *Organic Synthesis*, Paquette, L.A..; Ed.; John Wiley: New York, **1990**, Vol. 38, Chapter 3.

10. Simoni, D.; Invidiata, F. P.; Manfrenidi, S.: Ferroni, R.: Lampronti, I.: Roberti, M.; Pollini, G. P. *Tetrahedron Lett.* **1997**, *38*, 2749.

11. Morao, I.; Cossio, F. P. *Tetrahedron Lett.* **1997**, *38*, 6461.

12. Ballini, R.; Bosica, G.; Forconi, P. *Tetrahedron* **1996**, *52*, 1677.

13. Ballini, R.; Bosica, G. *J. Org. Chem.* **1997**, *62*, 425.

14. D'Sa, B.; Verkade, J. G. *Phosphorus, Sulfur, Silicon and the Related Elements* **1997**, *123*, 301.

15. Wroblewski, A.; Pinkas, J.; Verkade, J. G. *Main Group Chemistry* **1995**, *1*, 69.

16. (a) Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75. (b) Laramay, M. A. H.; Verkade, J. G. *Z. Anorg. aAlg. Chem.* **1991**, *605*, 163.

17. Tang, J.-S.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 341.

18. (a) D'Sa, B.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3691. (b) Kisanga, P.; McLeod, D. G.; D'Sa, B.; Verkade, J. G. submitted. (c) Kisanga, P.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 10057.

19. Tang, J.-S.; Dopke, J.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 5015.

20. Arumugam, S.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827.

21. Lehr, F.; Gonneermann, J.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 2258.

22. Seebach, D.; Beck, A. K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta* **1982**, *65*, 1101.

Table 1. Reactions of ketones with nitromethane in the presence of 10 mole percent of **1a** and 2.2 equivalents of magnesium sulfate for three hours.

substrate	product (% yield)	substrate	product (% yield)
2a	**3a** (95)	**2d**	**3d** (88)
2b	**3b** (93)	**2e**	**3e** (60)
2c	**3c** (94)	**2f**[a]	-

[a]Only the starting material was recovered at the end of the reaction time.

Table 2. Reactions of ketones with nitromethane in the presence of 30 mole percent of **1a** and 2.2 equivalents of magnesium sulfate 18 hours.

substrate	product (% yield)	product (% yield)
2a	**3a** (75)	**4a** (21)
2b	**3b** (59)	**4b** (15)
2c	**3c** (83)	**4c** (13)
2d	**3d** (61)	**4d** (27)
2e	**3e** (43)	**4e** (23)
2f[a]	-	-
2g	**3g** (38)	**4g** (0)
2h[a]	-	-

[a]Only starting material was recovered at the end of the reaction time.

Table 3. The reaction of carbonyl compounds with nitroalkanes in the presence of **1b** and 2.2 equivalents of magnesium sulfate.[a]

substrate	product (% yield)	substrate	product (% yield)
2a	**3a** (70)[b]	**2m**	**3m** (98)[c]
2a	**3a** (96)	**2n**	**3n** (96)[c]
2b	**3b** (93)	**2o**	**3o** (92)[c]
2c	**3c** (91)	**2p**	**3p** (88)[c]
2d	**3d** (85)	**2q**	**3q** (99)[c]
2e	**3e** (67)	**2a**	**3r** (82)[e]
2f	**3f** (0)	**2m**	**3s** (98)[c,e]
2g	**3g** (40)	**2a**	**3t** (93)[f,g]
2h	**3h** (0)	**2n**	**3u** (97)[f,h]
2i	**3i** (0)	**2q**	**3v** (99)[f,i]
2j	**3j** (94)[c]	**2q**	**3w** (99)[j,k]
2k	**3k** (99)[d]	**2n**	**3x** (95)[j,l]
2l	**3l** (98)[c]		

[a]The amount of **1b** used was 10 mole percent and the reaction time was 3 hours unless stated otherwise. [b]The reaction was performed at 40 °C for 2 hours in the presence of 1% $MgSO_4$ and 30 mole percent of of **1b**. [c]The reaction time was 40 minutes and the amount of **1b** used was 10 mole percent. [d]The reaction time was 5 minutes. [e]The nitroalkane used was nitroethane. [f]The nitroalkane used was 1-nitropropane. [g]The amount of **1b**

Table 3 (continued)

used was 0.3 equiv and the reaction time was 7 h. [h]The amount of **1b** used was 0.2 equiv and the reaction time was 2.25 h. [i]The reaction time was 1.25 h. [j]The nitroalkane used was 2-nitropropane. [k]The reaction time was 1.5 h. [l]The reaction time was 4 h.

Table 4. The reaction of ketones with nitromethane in the presence of 40 mole percent of **1b** and 2.2 equivalents of magnesium sulfate.[a]

substrate	product (% yield)	product (% yield)
2a	**3a** (79)	**4a** (15)
2b	**3b** (59)	**4b** (9)
2c	**3c** (85)	**4c** (13)
2d	**3d** (64)	**4d** (21)
2e	**3e** (40)	**4e** (20)
2f[b]	-	-

[a]The reaction time was 3 hours. [b]Only starting material was recovered.

Table 5. Comparison of the reaction of ketones with **1b** and **1c** in the presence of 2.2 equivalents of magnesium sulfate.

substrate	yield with 10 mol % **1b**[a]	yield with 30 mol % **1b**[a]	yield with 10 mol % **1c**[a]	yield with 30 mol % **1c**[a]	yield with 40 mol % **1c**[b]
2a	95	97	95	96	97
2b	91	93	91	92	92

[a]The reaction time was 3 hours. [b]The reaction time was 18 hours.

Supporting Information

^{1}H NMR and ^{13}C NMR Data with peak Assignments

3a: These NMR spectra compared favorably with that reported in *Helv. Chim. Acta* **1979**, 2258.

3b: These NMR spectra compared favorably with that reported in *Helv. Chim. Acta* **1979**, 2258.

3c: These NMR spectra compared favorably with that reported in *Synth. Commun.* **1993**, 3037.

3d: ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 3H), 1.22 (s, 3H), 1.54 (q, 2H), 2.77 (bs, 1H), 4.35 (dd, 2H). ^{13}C NMR ($CDCl_3$): δ 8.1 (s, $\underline{C}H_3$-CH_2), 24.0 (s, $\underline{C}H_3$-CH), 32.7 ($\underline{C}H_2$-CH_3), 72.1 (s, $\underline{C}$-OH), 84.1 (s, $\underline{C}H_2$-NO_2).

3e: ^{1}H NMR ($CDCl_3$): δ 0.88 (t, 6H), 1.52 (q, 4H), 2.65 (bs, 1H), 4.39 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 7.8 (s, $\underline{C}H_3$-CH_2), 29.2 (s, $\underline{C}H_2$-CH_3), 74.6 (s, $\underline{C}$-OH), 82.5 (s, $\underline{C}H_2$-NO_2).

3g: Isolated as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$): δ 0.87-0.97 (dd, 3H), 1.18-1.43 overlapping region (9H), 1.49-1.66 three broad singlets (1H), 4.29-4.57 (dd, 2H). ^{13}C NMR ($CDCl_3$): δ 15.0 & 15.3 (Me), cyclohexyl ring 21.3, 23.2, 25.3, 28.2, 30.2, 30.8, 34.6, 36.5, 38.5, 42.6; 72.6, & 73.9 (s, $\underline{C}$-OH), 84.8 (s, $\underline{C}H_2$-NO_2).

3i: ^{1}H NMR ($CDCl_3$): δ 3.23 (s, 1H), 3.77 (s, 3H), 4.39-4.58 (m, 2H), 5.32 (dd, 2H), 6.88 (d, 2H), 7.26 (d, 2H). ^{13}C NMR ($CDCl_3$): δ 55.4 (s, Me), 70.7 (s, C-OH), 81.3 (s, CH_2-NO_2), 114.4, 127.4, 130.5, 156.0.

3j: ^{1}H NMR ($CDCl_3$): δ 3.31 (s, 3H), 4.50 (m, 2H), 5.55 (dd, 1H), 7.56 (d, 2H), 8.16 (d, 2H). ^{13}C NMR ($CDCl_3$): δ 70.1 (s, C-OH), 80.8 (s, CH_2-NO_2). 124.3, 127.2, 145.3, 148.2.

3k: These NMR spectra compared favorably with those reported in *J. Org. Chem.* **1967**, 4134.

3l: ^{1}H NMR ($CDCl_3$): δ 0.91 (t, 6H), 1.68 -1.77 (m, 1H), 2.56 & 2.57 (bs, 1H), 4.00-4.06 (m, 1H), 4.31-4.49 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 17.6 & 18.6 (Me), 32.0 (s, $CH(Me)_2$), 73.6 (s, C-OH), 79.5 (s, CH_2-NO_2).

3n: The ^{1}H NMR compared favborably with that reported in *J. Org. Chem.* **1997**, *62*, 425. ^{13}C NMR Compared favorably with that reported in *Tetrahedron Lett.* **1995**, *36*, 6531.

3o: ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 6H), 2.70 (bs, 1H), 4.33-4.51 (m, 2H), 5.58 (dd, 1H), 7.02 (s, 2H), 7.27 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 18.6 (s, Me), 21.2 (s, Me), 68.1 (s, C-OH), 80.5 (s, CH_2-NO_2), 126.4, 129.6, 131.0, 131.4, 136.1, 136.6. Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found C, 61.78; H, 6.77, N, 7.02; M.P..: 72 °C.

3p: Isolated as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$): δ 1.33-1.40 (d, 3H), 2.42, 2.76 (bs, 1H), 2.80-2.92 (m, 1H). 4.20-4.37 (m, 2H), 3.39-4.50 (m, 1H), 7.26. ^{13}C NMR ($CDCl_3$): δ 17.4 & 17.6 (s, Me), 43.6 & 43.9 (S, $\underline{C}$H-Ph), 72.6 & 73.5 (s, $\underline{C}$-OH), 79.5 & 79.6 (s, $\underline{C}H_2$-NO_2),127.6, 127.6, 128.2, 129.0, 129.2, 142.1, 142.2. Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.53: H, 6.71: N, 7.17. Found C, 61.46; H, 6.69, N, 7.27; p.b.: 241 °C.

3q: ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 3H), 1.17-1.44 (m, 10H), 3.14 (bs, 1H), 4.31-4.62 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 14.0 (s, Me), 22.6 (s, C-7), 25.2 (s, C-6), 29.0 (s, C-5), 31.7 (s, C-4), 33.8 (s, C-3), 68.9 (s, $\underline{C}$-OH), 80.8 (s, $\underline{C}H_2$-NO_2,).

3r: Isolated as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$): δ 0.83-1.83 overlapping region (13H), 2.27 (t, 2H), 2.40 (bs, 1H), 4.27-4.53 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.7 (s, Me), 21.3, 25.1, 25.4, 27.2, 33.2, 35.1, 42.1, 71.7 (s, $\underline{C}$-OH), 91.2 (s, $\underline{C}H_2$-NO_2).

3s: Isolated as a mixture of diastereomers. ^{1}H NMR ($CDCl_3$): Compared favorably with that reported in *J. Chem. Soc., Perkins Trans 2* **1982**, 867. ^{13}C NMR ($CDCl_3$): 11.8, 15.0, 16.2, 18.4, 18.7, 19.7, 29.5, 30.8, 77.1 & 77.4 (s, $\underline{C}$-OH), 84.6 & 86.5 (s, $\underline{C}H_2$-NO_2).

3t: The ^{1}H NMR compared favorbaly with that reported in *Helv. Chim. Acta* **1979**, *62*, 2258. ^{13}C NMR ($CDCl_3$): δ 98.6, 71.7, 42.0, 35.2, 33.7, 27.0, 25.0, 21.5, 21.3, 21.0, 10.6.

3u: The ^{1}H NMR compared favorably with that reported in *Helv. Chim. Acta* **1982**, *65*, 1101.

3v: The ^{1}H NMR compared favorably with that reported in *Tetrahedron* **1996**, *52*, 1677. ^{13}C NMR ($CDCl_3$): δ 94.6, 94.1, 72.4, 72.0, 33.5, 33.3, 31.7, 29.1, 29.1, 25.6, 25.2, 23.8, 22.6, 21.7, 10.5, 10.2.

3w: ^{1}H NMR ($CDCl_3$): δ 3.99 (t, 1H), 2.64 (two b s, 1H), 1.56 (s, 3H), 1.54 (s, 3H), 1.22 - 1.5 (m, 10H), 0.89 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 92.3, 76.0, 31.8, 31.5, 29.1, 26.4, 23.6, 22.6, 20.3, 14.1. b. p. 176-178 °C.

3x: ^{1}H NMR ($CDCl_3$): δ 7.34-7.37 (overlapping region, 5H), 5.26 (d, 1H), 2.70 (bs, 1H), 1.55 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 138.2, 128.7, 128.3, 127.5, 92.2, 78.0, 24.4, 19.0. m.p. 62-63 °C.

4a: The M.P. compared favorably to that reported in *J. Chem. Soc.* **1947**, 1517. ^{1}H NMR ($CDCl_3$): δ 1.45-1.55 overlapping region (10H), 4.62 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 21.0, 25.2, 31.6, 41.9 [s, $\underline{C}(CH_2\text{-}NO_2)_2$], 79.1 (s, $\underline{C}H_2\text{-}NO_2$).

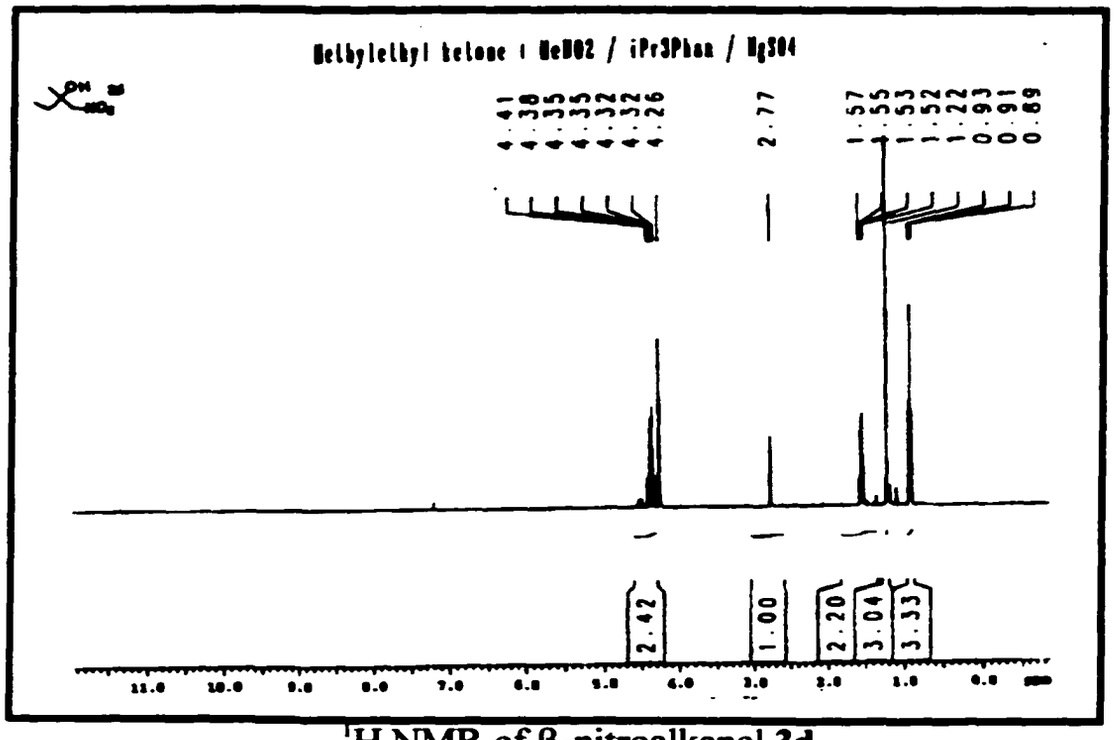
4b: ^{1}H NMR ($CDCl_3$): δ 1.63-1.66 overlapping region (4H), 1.74 (m, 4H), 4.57 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 24.4 (s, $\underline{C}H_2CH_2$), 34.7 (s, $\underline{C}H_2C$), 46.3

[s, $\underline{C}$ (CH_2-NO_2)$_2$], 79.3 (s, $\underline{C}H_2$-NO_2). Anal. Calcd. for $C_7H_{12}N_2O_4$: C, 44.68; H, 6.43; N, 14.89. Found C, 44.83; H, 6.42, N, 14.71.

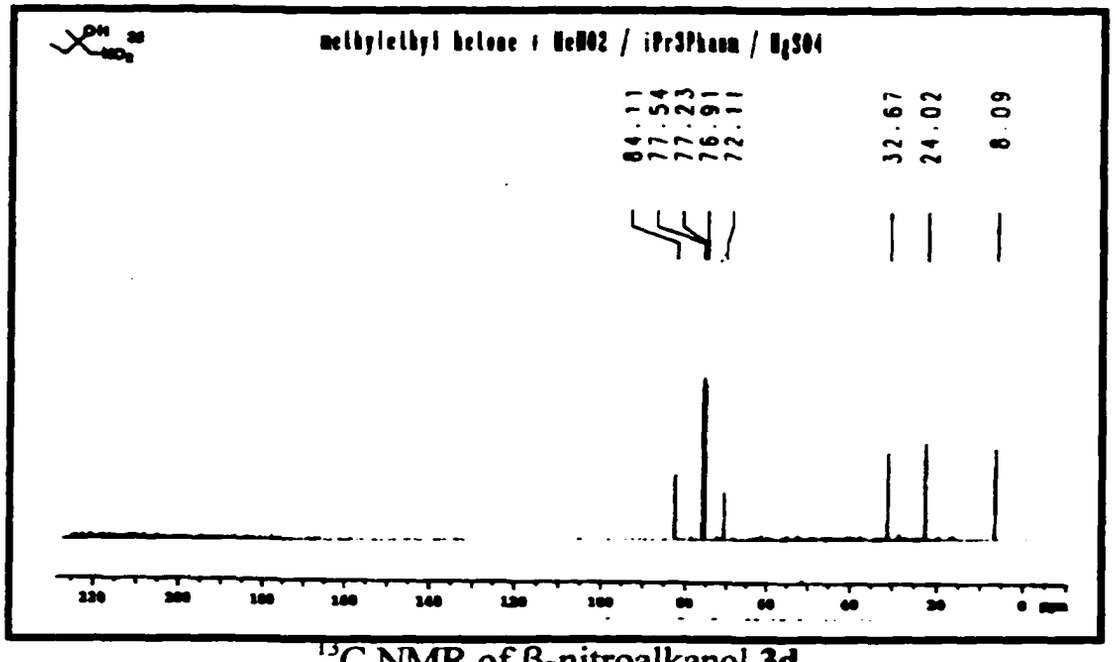
4c: The B.P. compared favorably to that reported in *J. Chem. Soc.* **1947**, 1517. ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 6H), 4.49 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 23.7 (s, Me), 36.3 [s, $\underline{C}$ (CH_2-NO_2)$_2$], 81.9 (s, $\underline{C}H_2$-NO_2).

4d: The B.P. compared favorably to that reported in *J. Chem. Soc.* **1947**, 1517. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3H), 1.09 (s, 3H), 1.39 (q, 2H), 4.52 (dd, 4H). ^{13}C NMR ($CDCl_3$): δ 7.6 (s, $\underline{C}H_3CH_2$), 20.3 (s, $\underline{C}H_3C$), 38.9 [s, $\underline{C}$ (CH_2-NO_2)$_2$], 80.1 (s, $\underline{C}H_2$-NO_2).

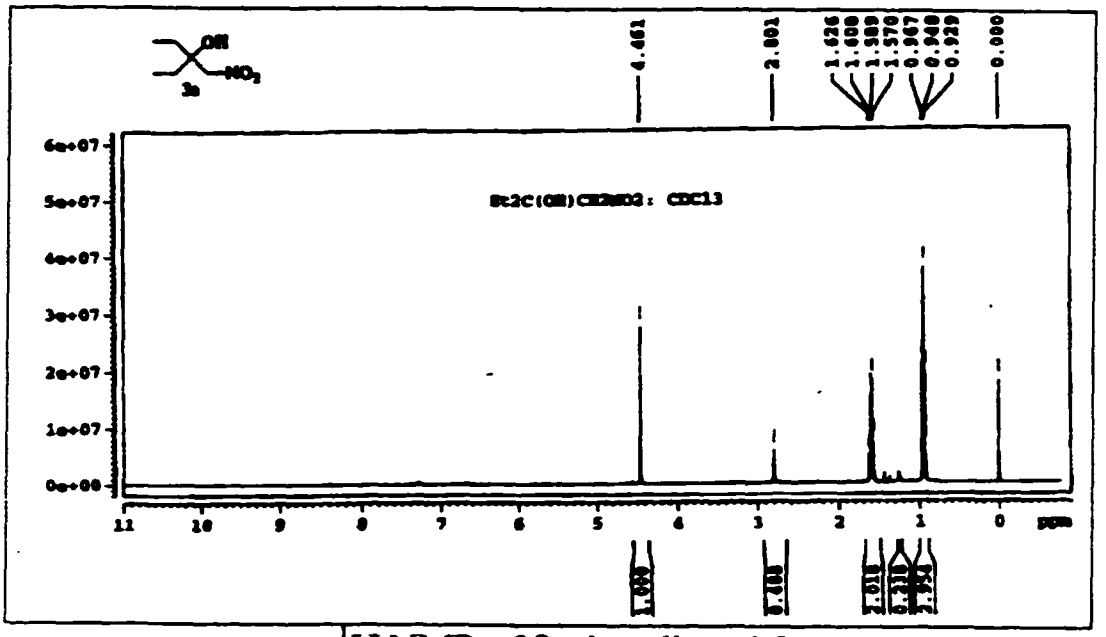
4e: The M.P. compared favorably to that reported in *J. Chem. Eng. Data* **1966**, 617. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 6H), 1.43 (q, 4H), 4.55 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 7.1 (s, $\underline{C}H_3CH_2$), 24.5 (s, $\underline{C}H_2C$), 41.9 [s, $\underline{C}$ (CH_2-NO_2)$_2$], 77.9 (s, $\underline{C}H_2$-NO_2).



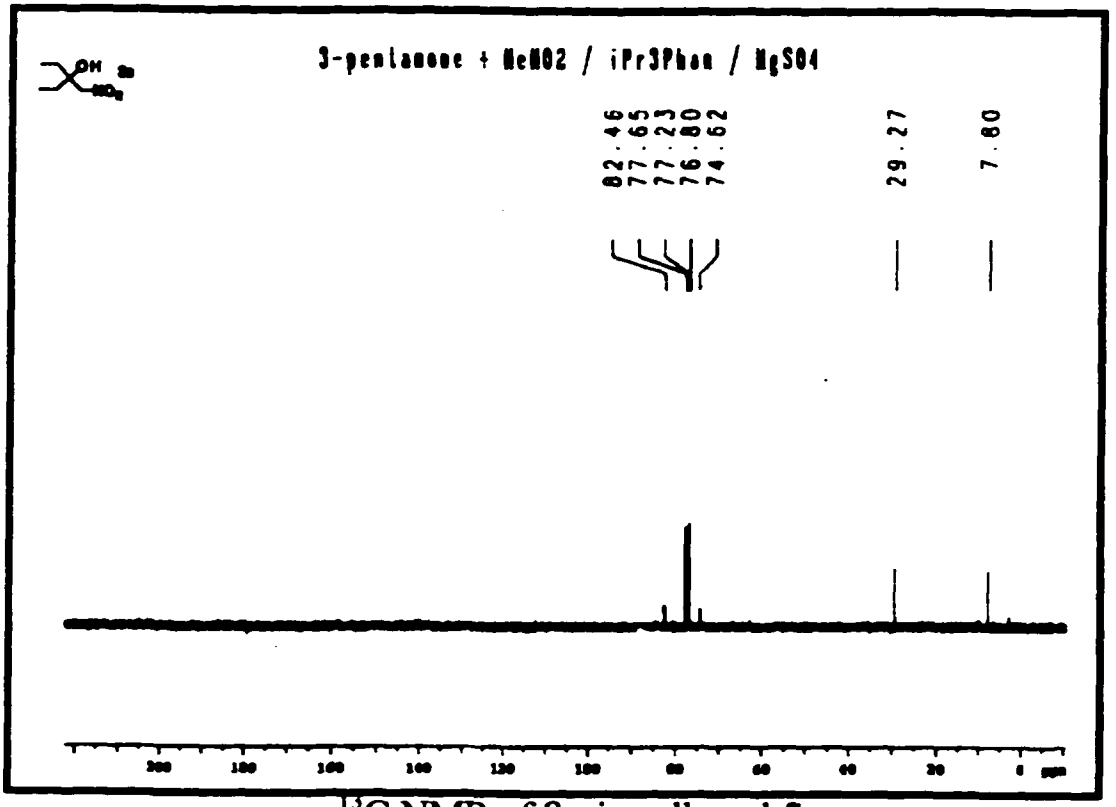
^{1}H NMR of β-nitroalkanol **3d**



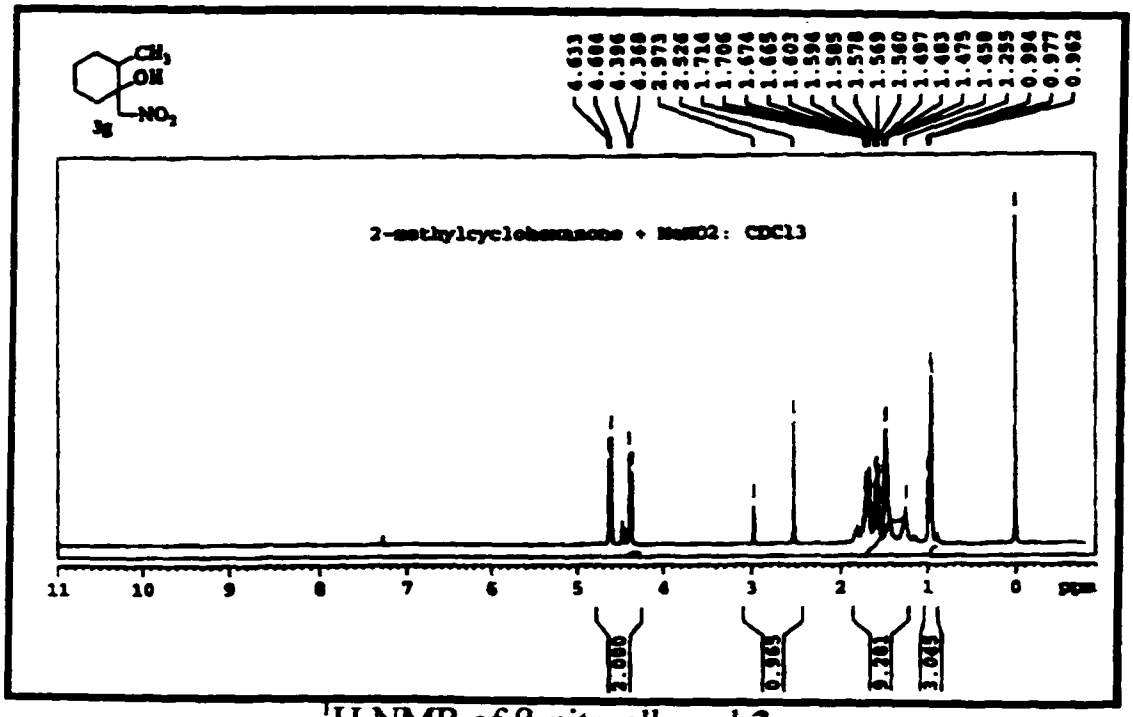
^{13}C NMR of β-nitroalkanol **3d**



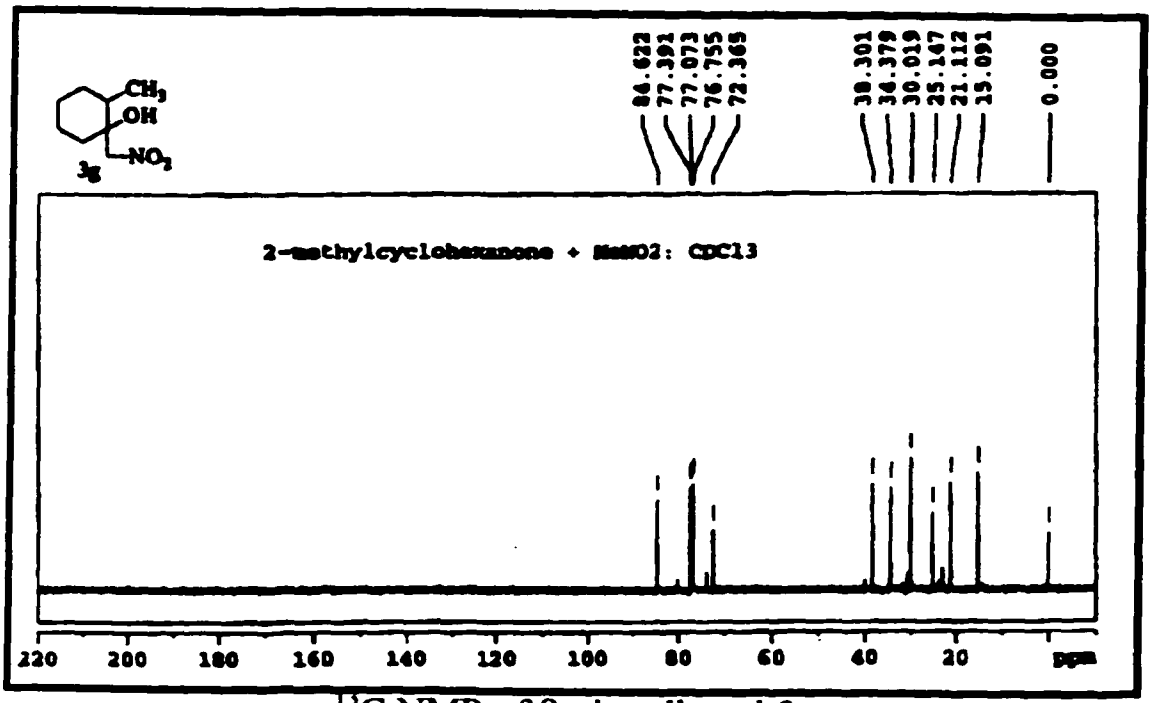
^{1}H NMR of β-nitroalkanol **3e**



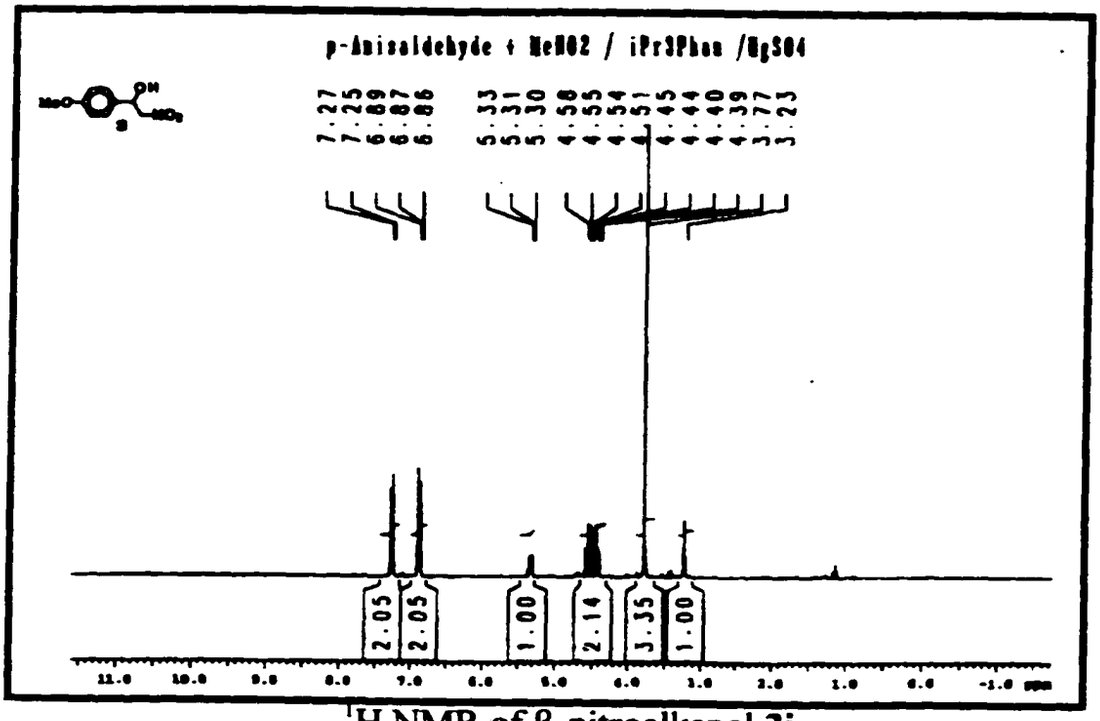
^{13}C NMR of β-nitroalkanol **5e**



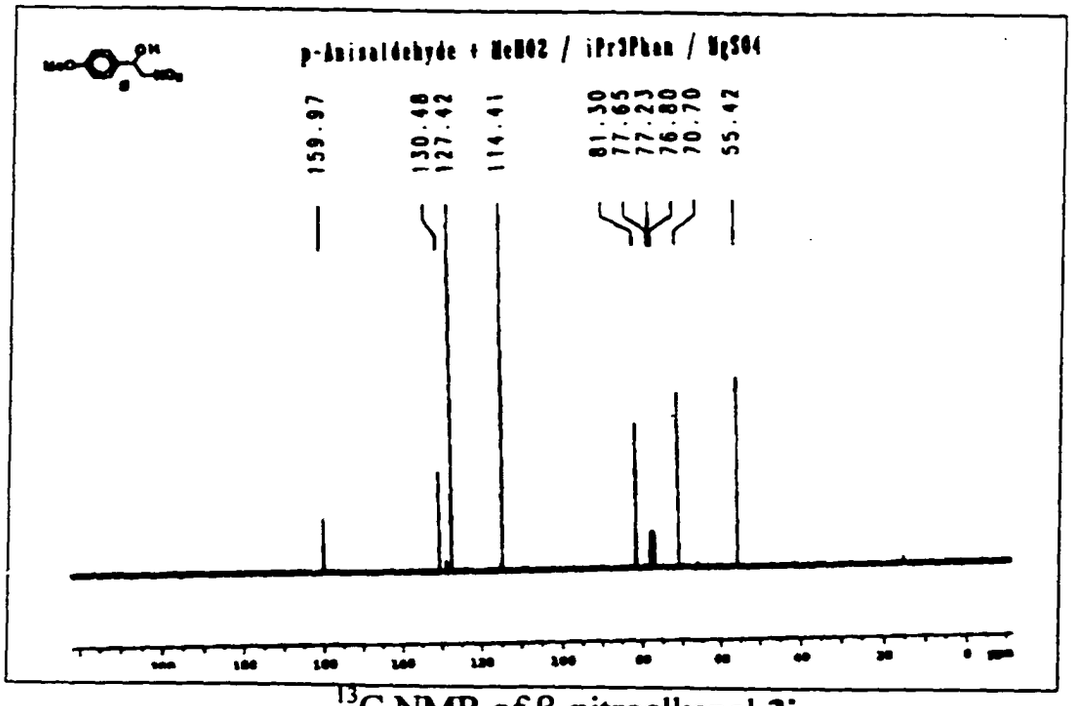
^{1}H NMR of β-nitroalkanol 3g



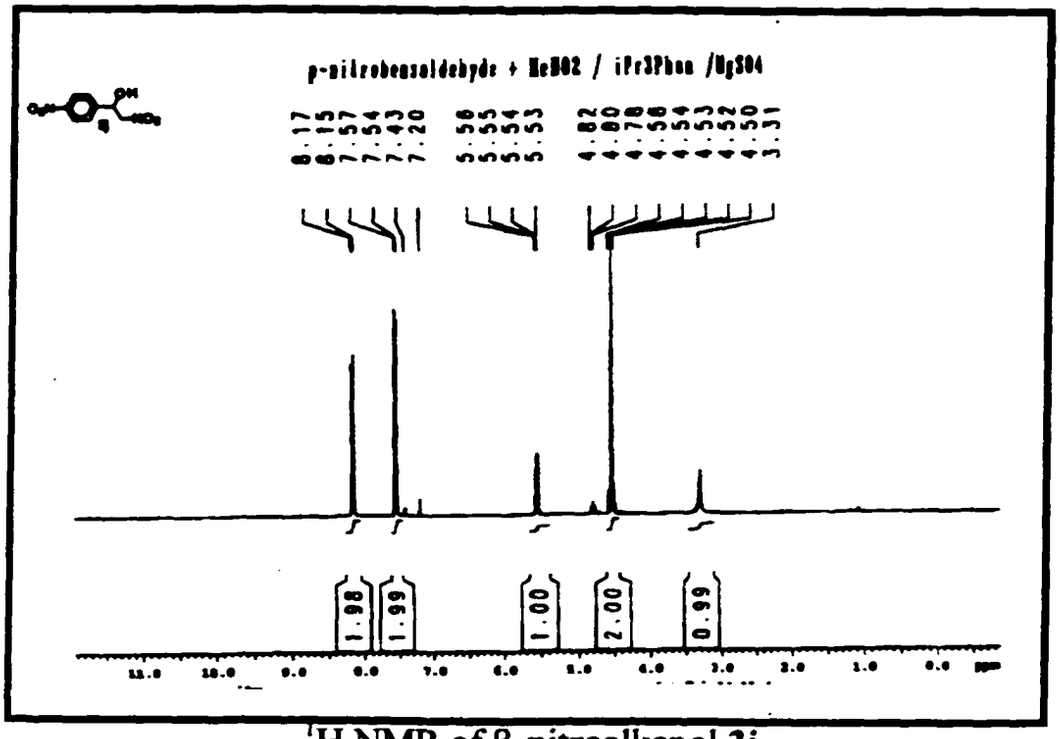
^{13}C NMR of β-nitroalkanol 3g



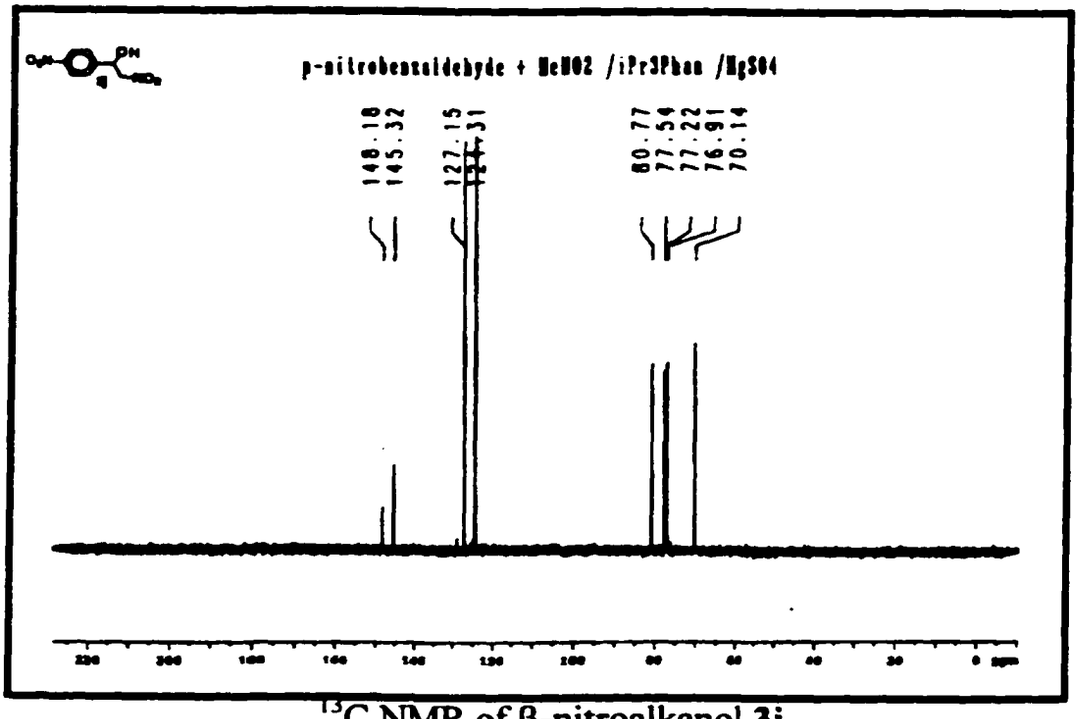
^{1}H NMR of β-nitroalkanol **3i**



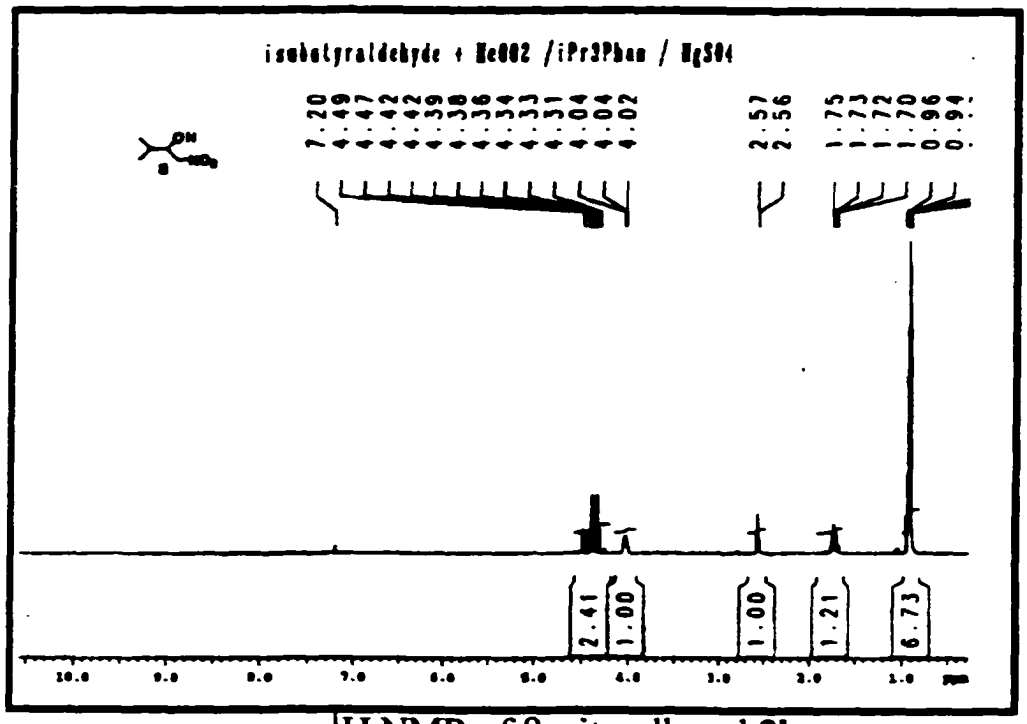
^{13}C NMR of β-nitroalkanol **3i**



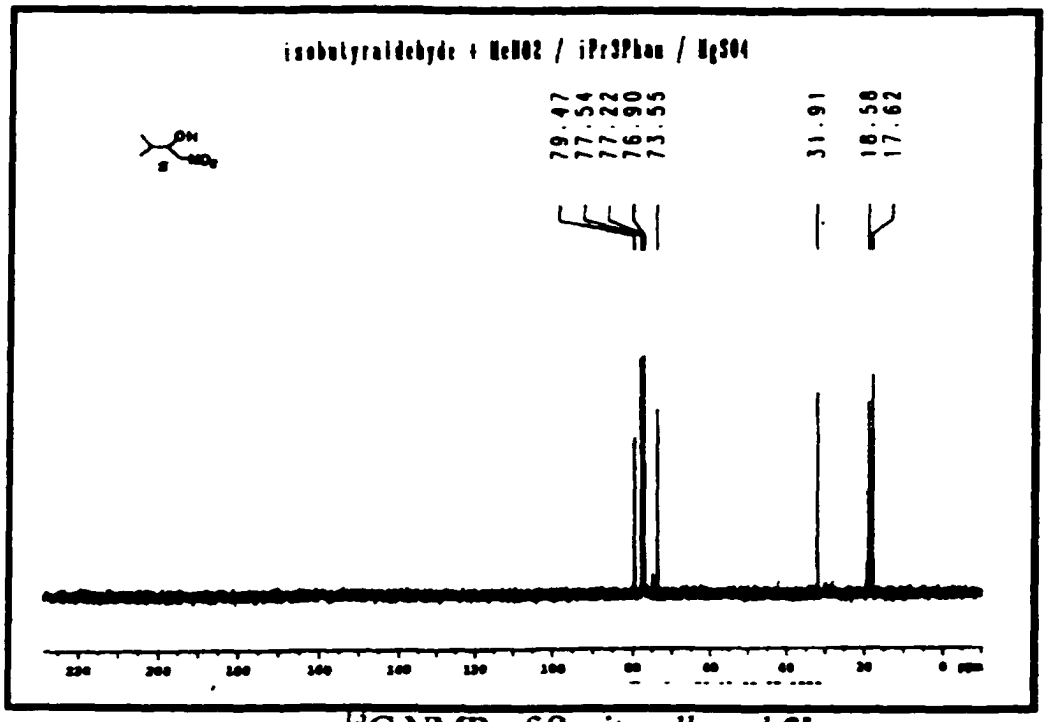
^{1}H NMR of β-nitroalkanol **3j**



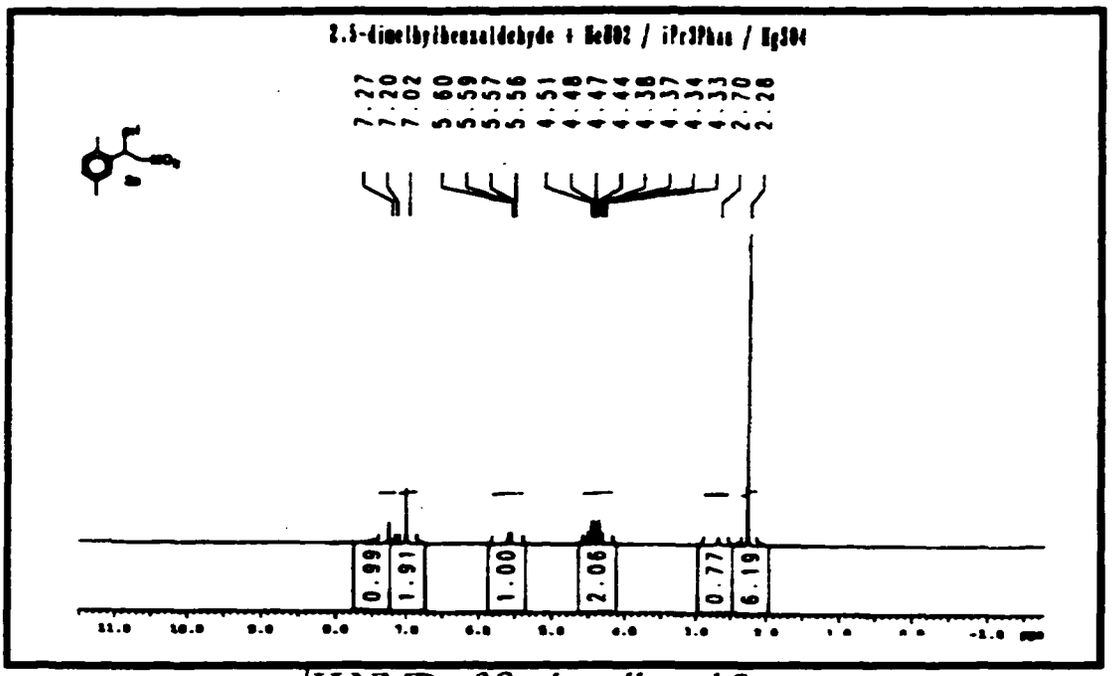
^{13}C NMR of β-nitroalkanol **3j**



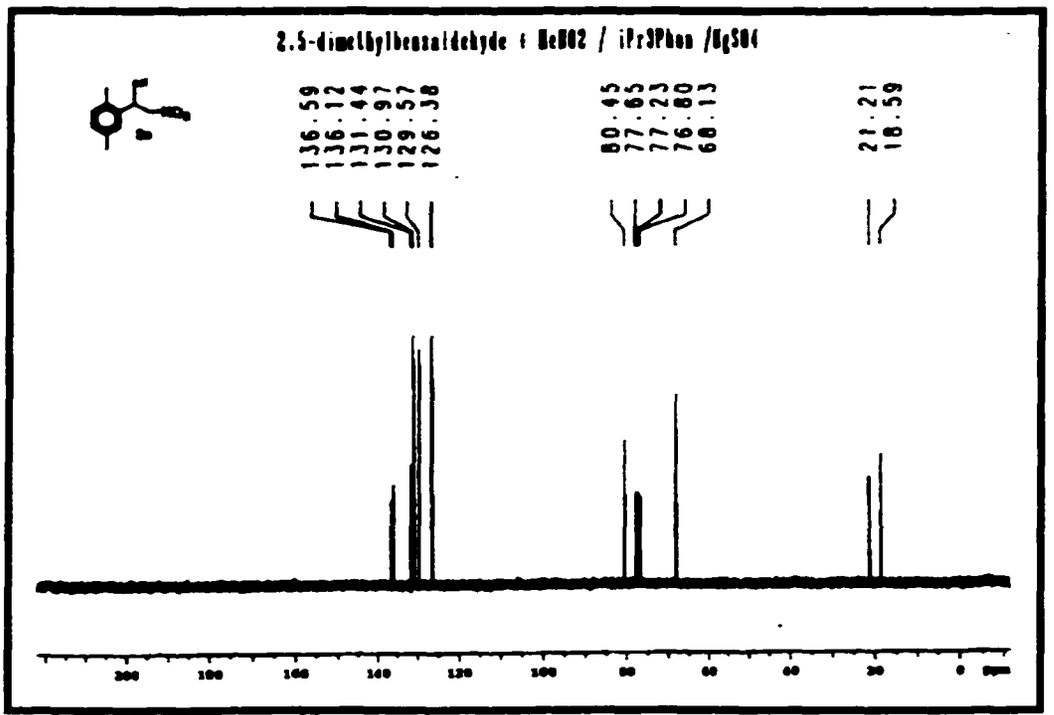
^{1}H NMR of β-nitroalkanol **3l**



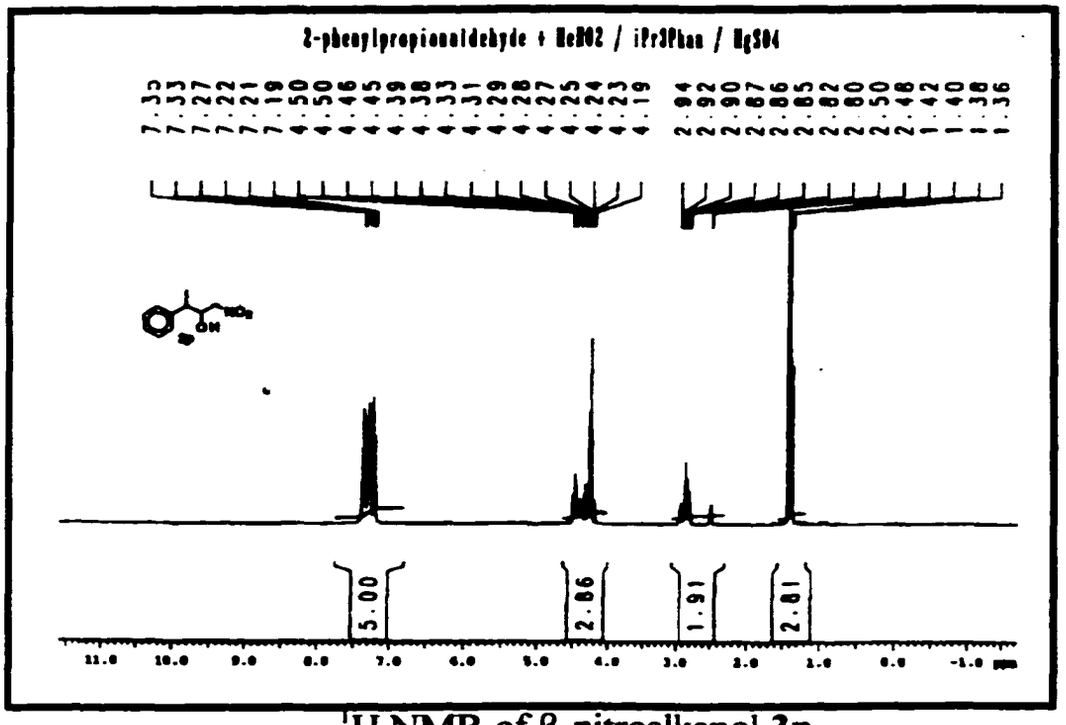
^{13}C NMR of β-nitroalkanol **3l**



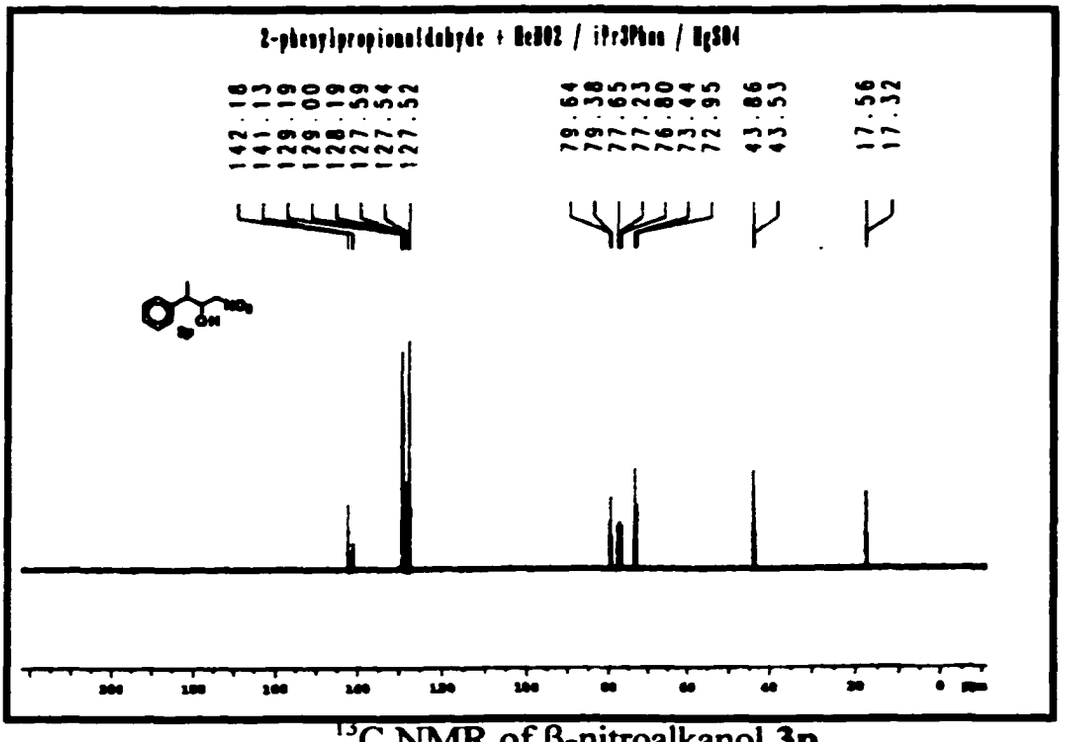
^{1}H NMR of β-nitroalkanol **3o**.



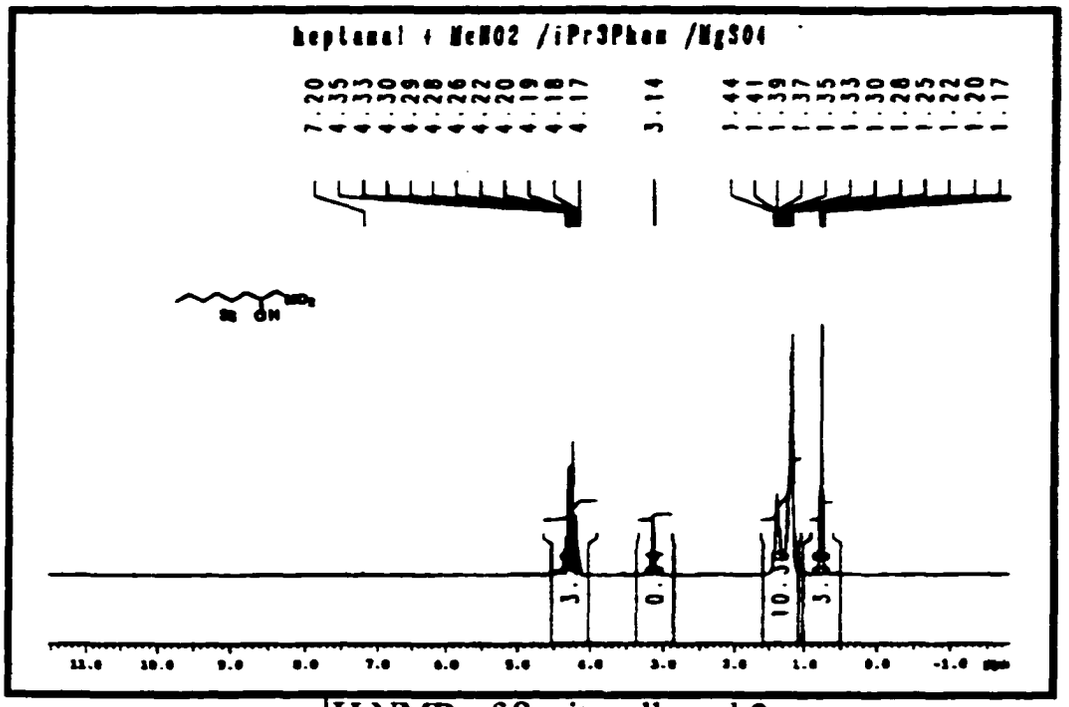
^{13}C NMR of β-nitroalkanol **3o**



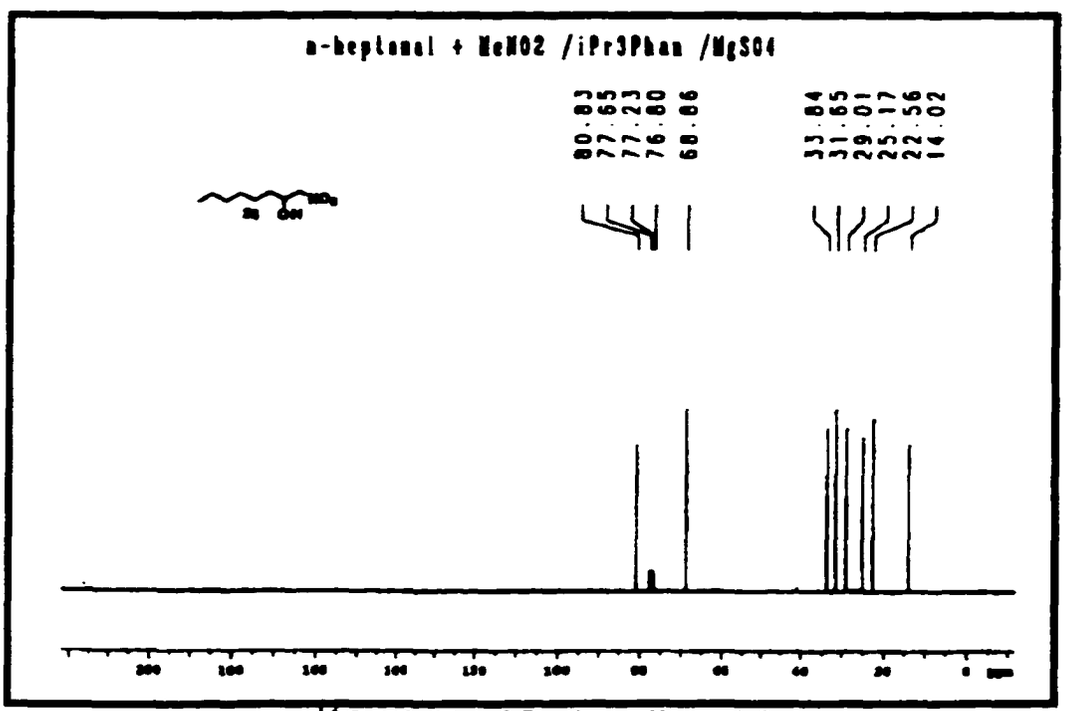
^{1}H NMR of β-nitroalkanol **3p**



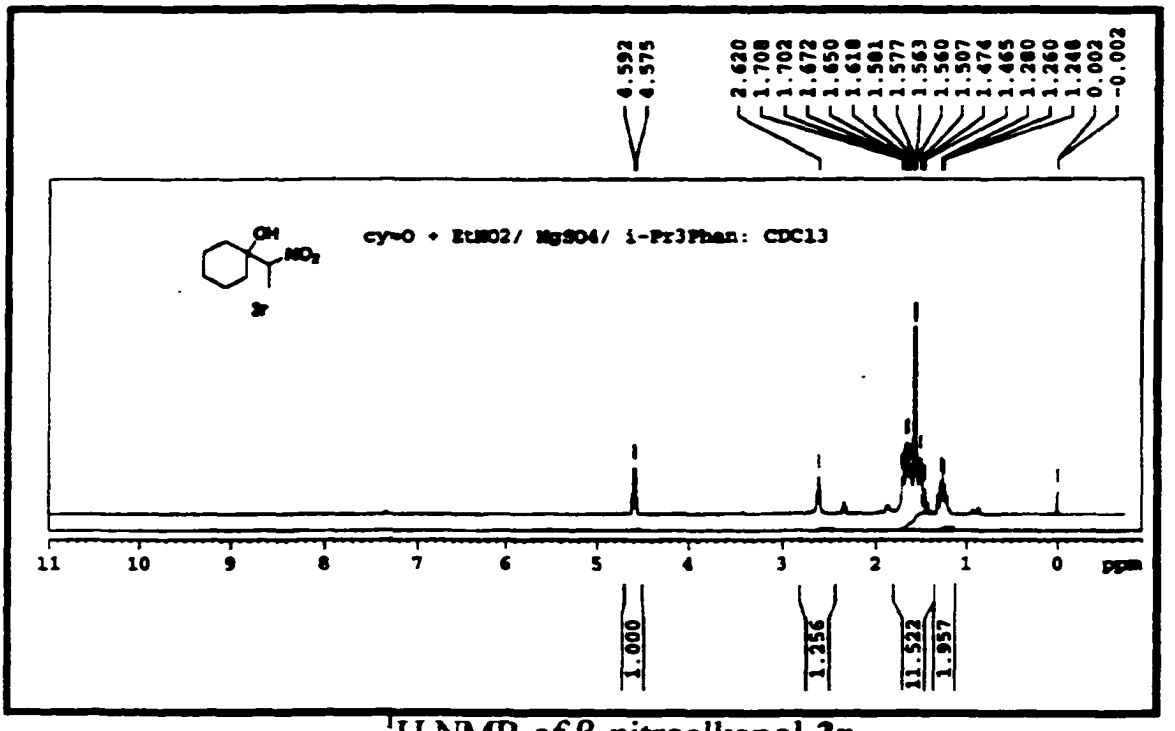
^{13}C NMR of β-nitroalkanol **3p**



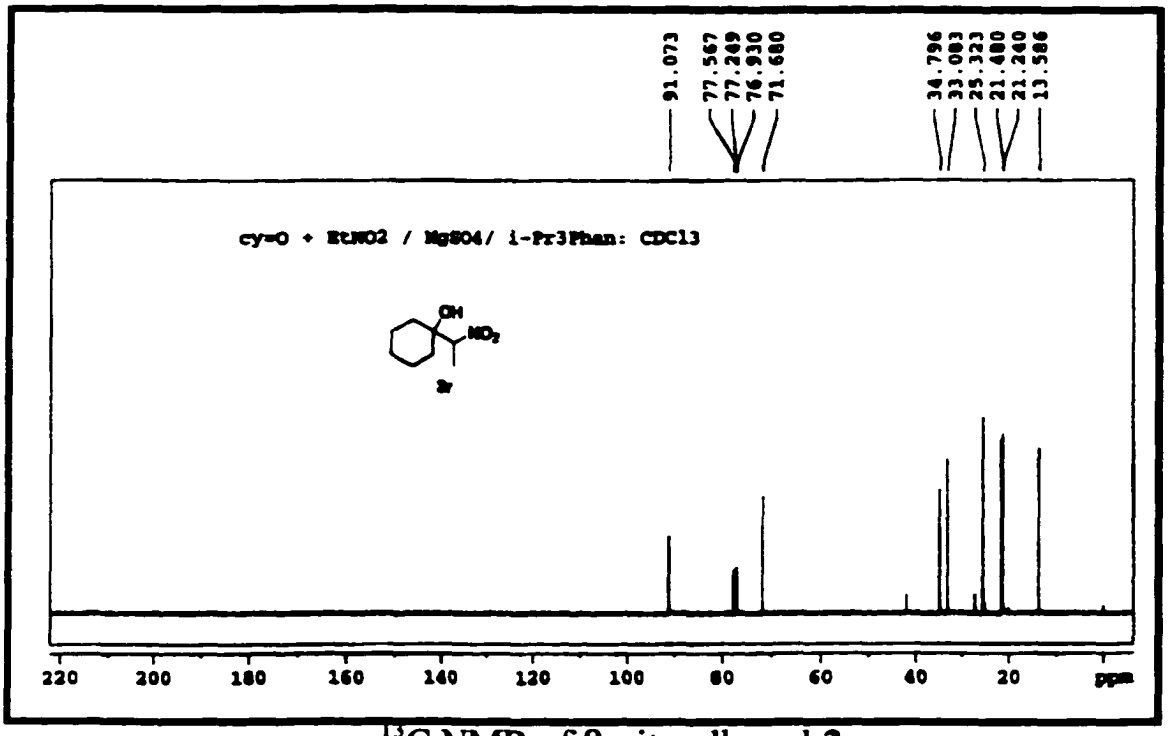
^{1}H NMR of β-nitroalkanol **3q**.



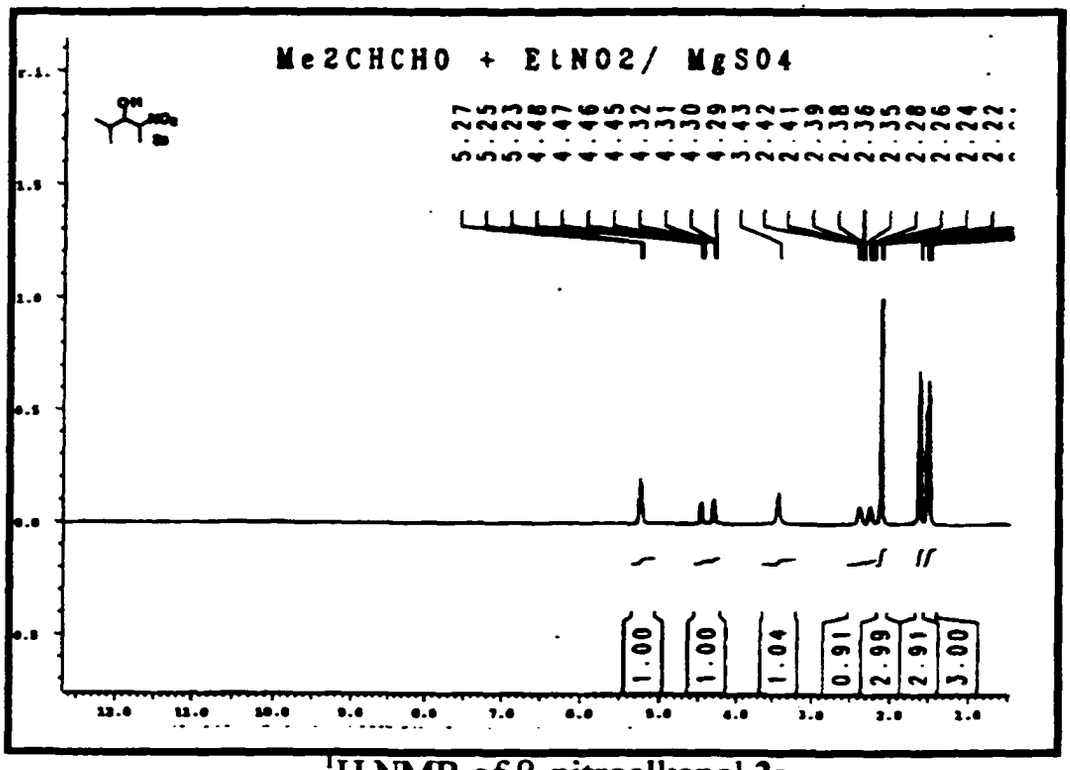
^{13}C NMR of β-nitroalkanol **3q**



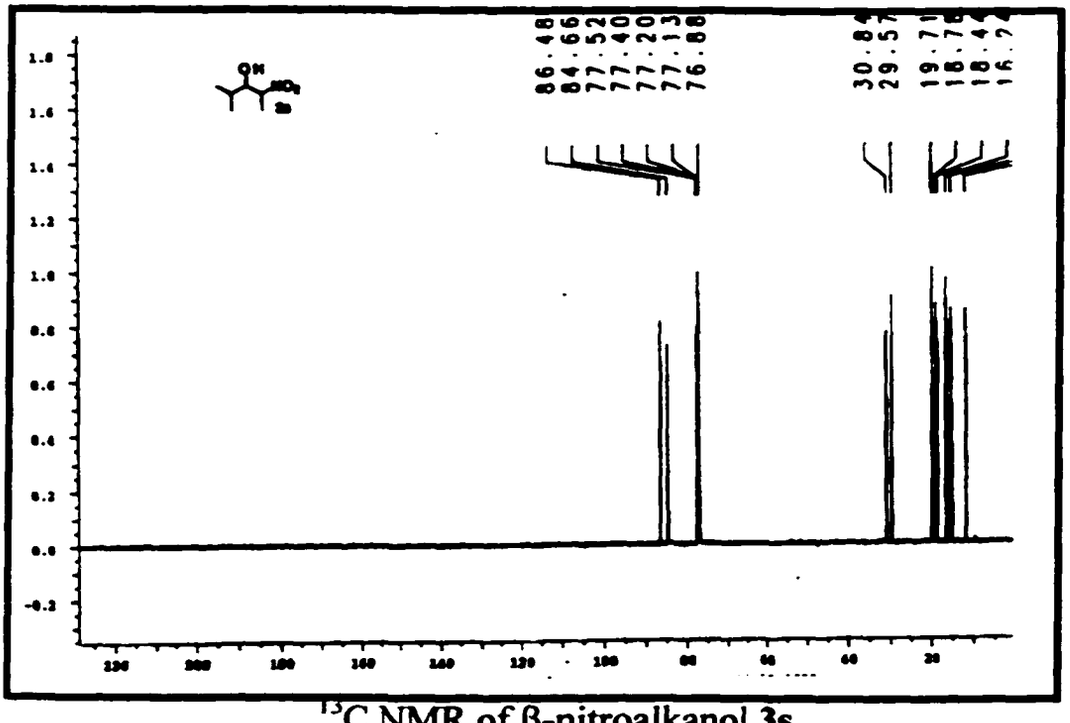
^{1}H NMR of β-nitroalkanol **3r**



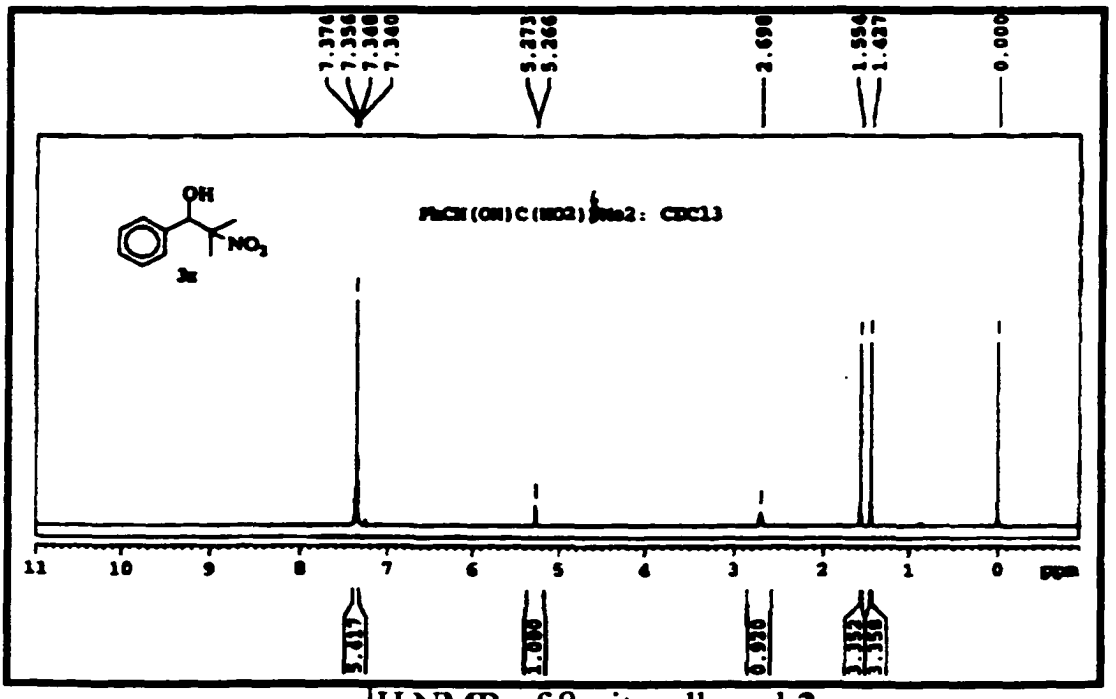
^{13}C NMR of β-nitroalkanol **3r**



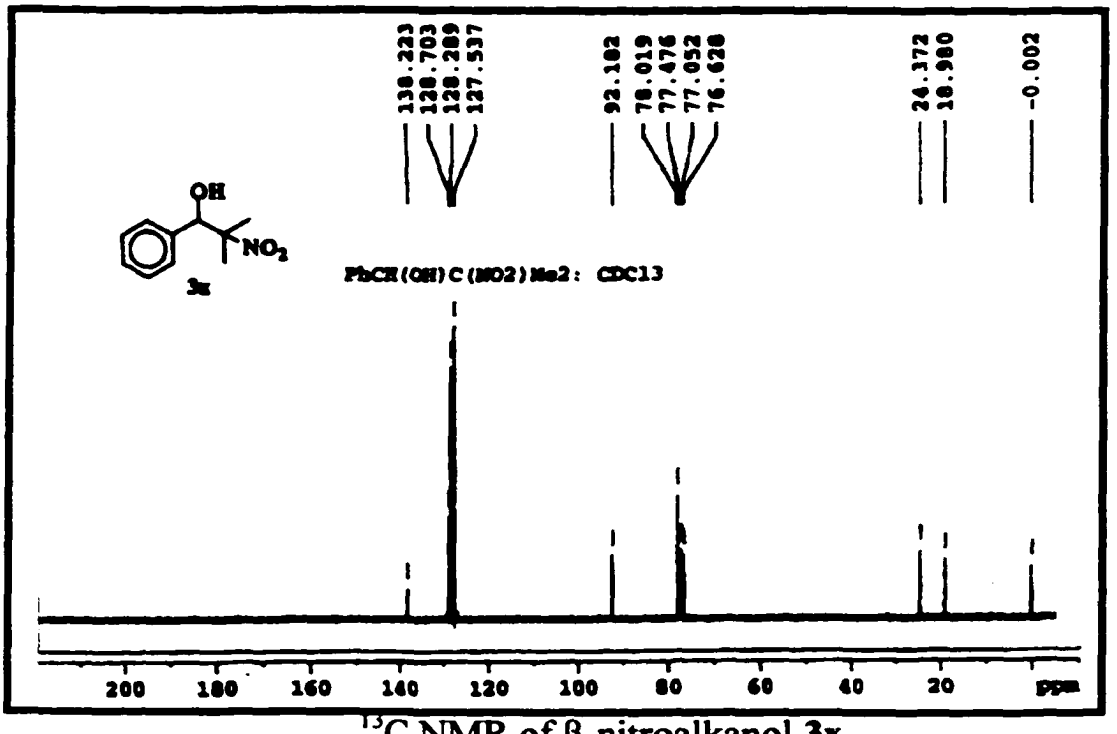
^{1}H NMR of β-nitroalkanol **3s**



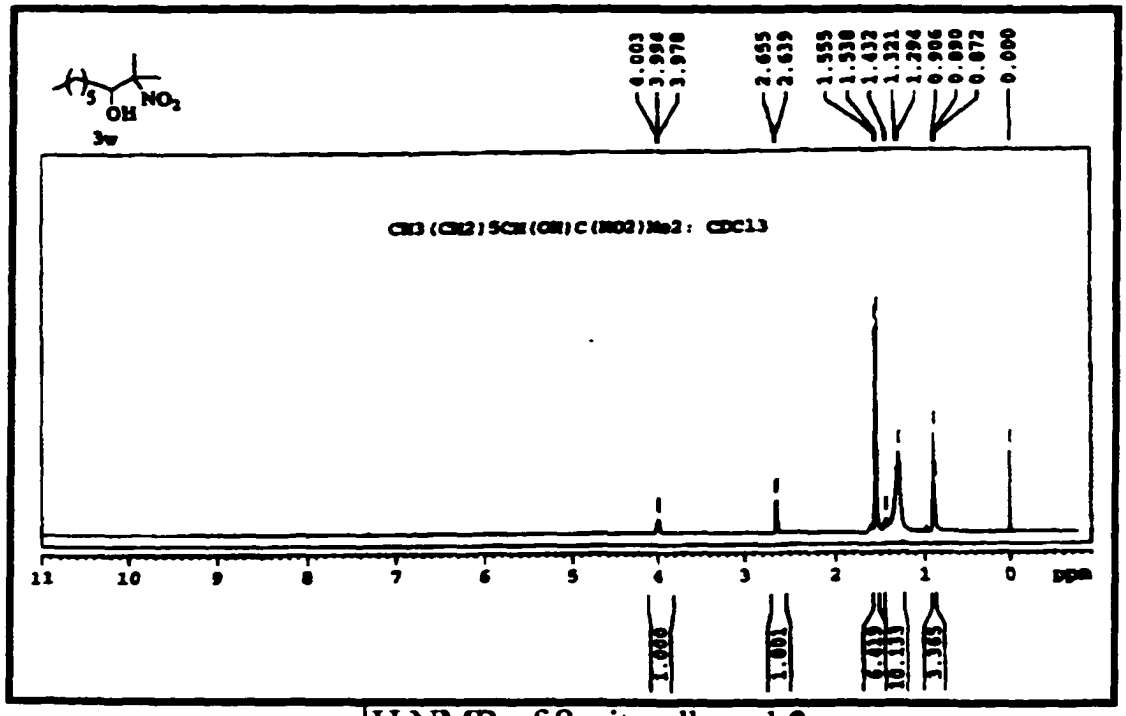
^{13}C NMR of β-nitroalkanol **3s**



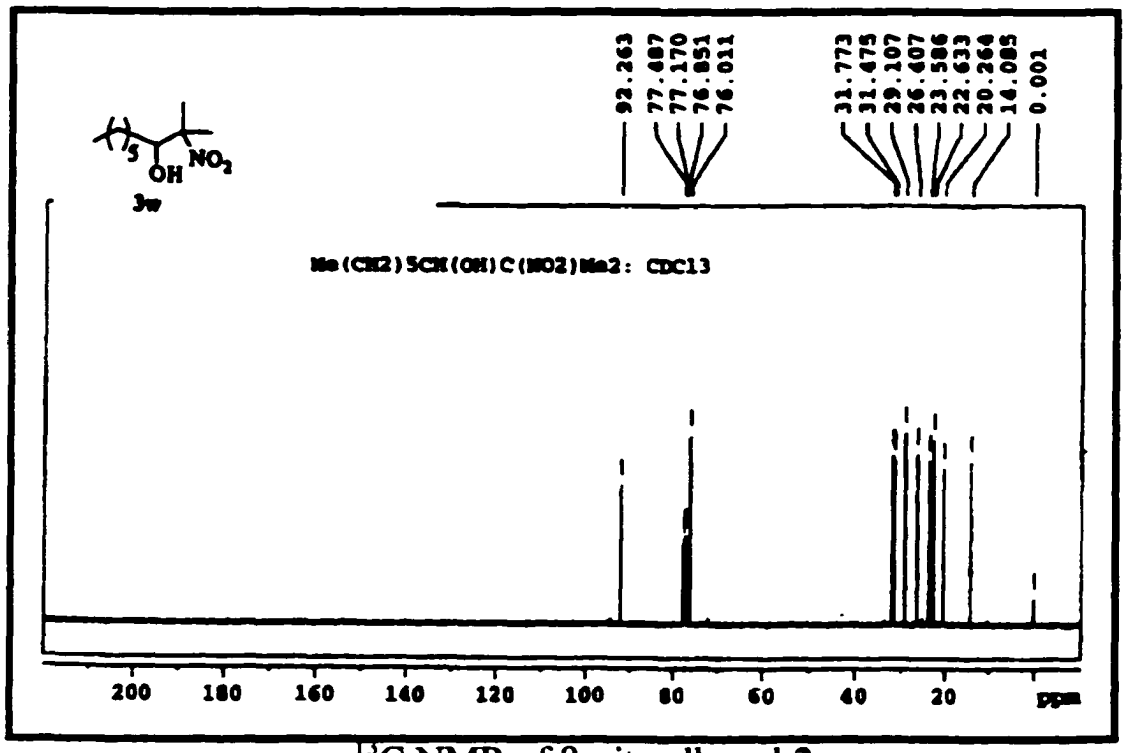
^{1}H NMR of β-nitroalkanol **3x**



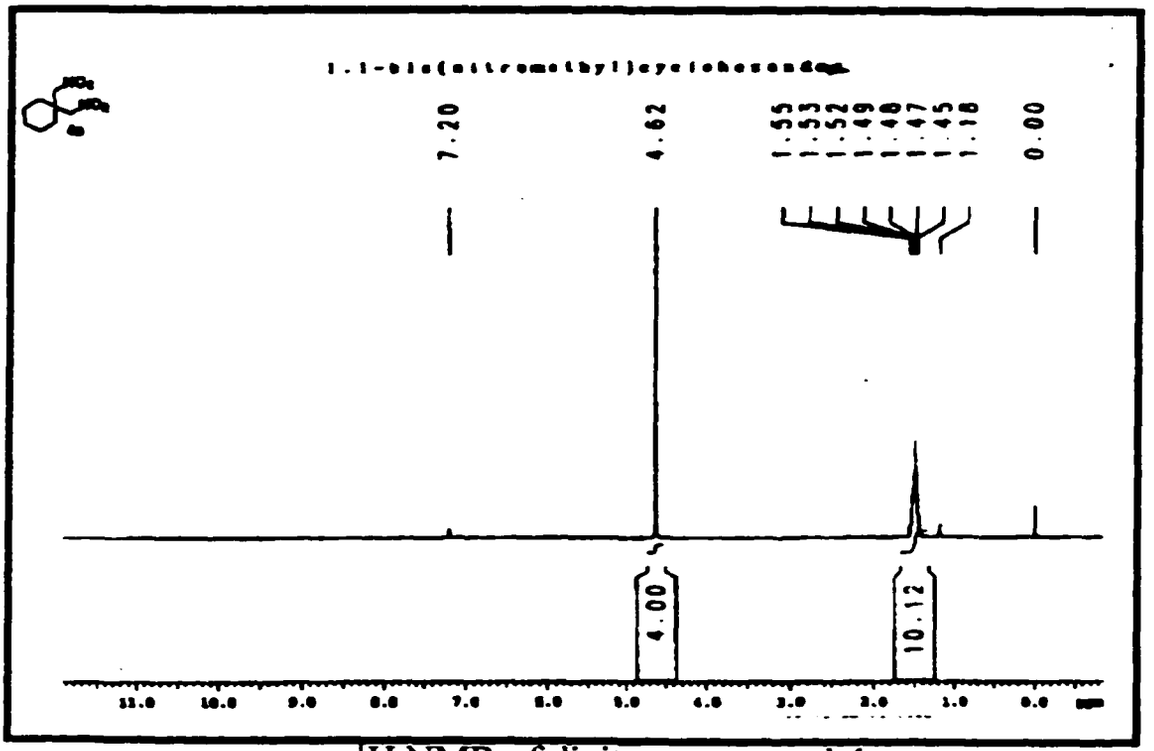
^{13}C NMR of β-nitroalkanol **3x**



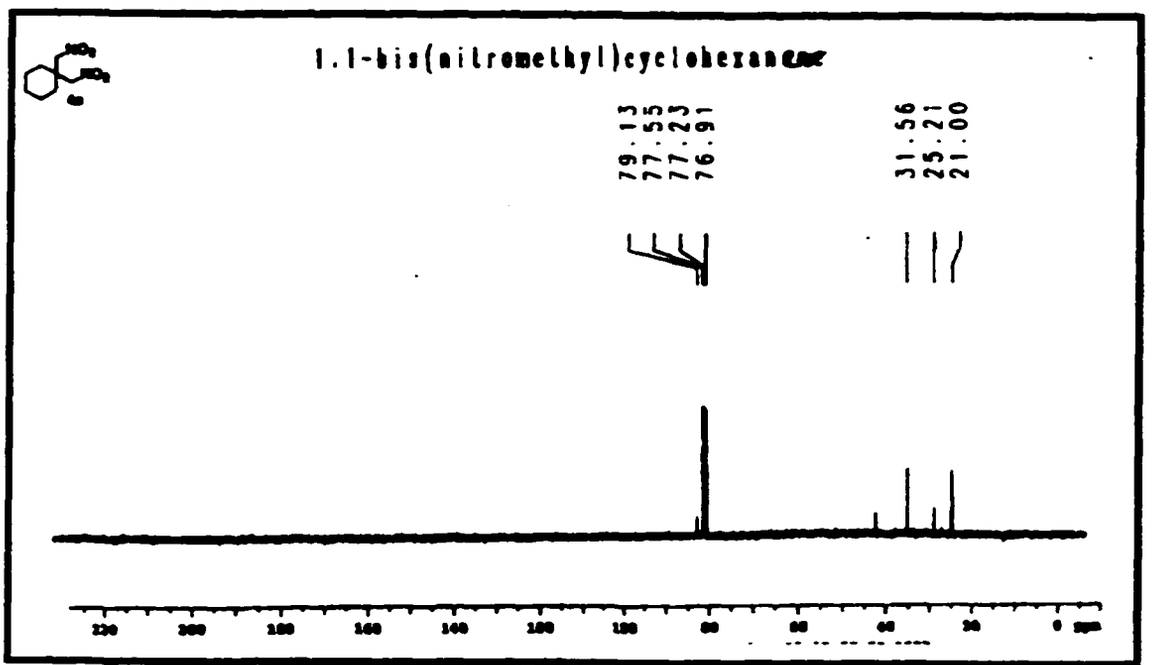
^{1}H NMR of β-nitroalkanol **3w**



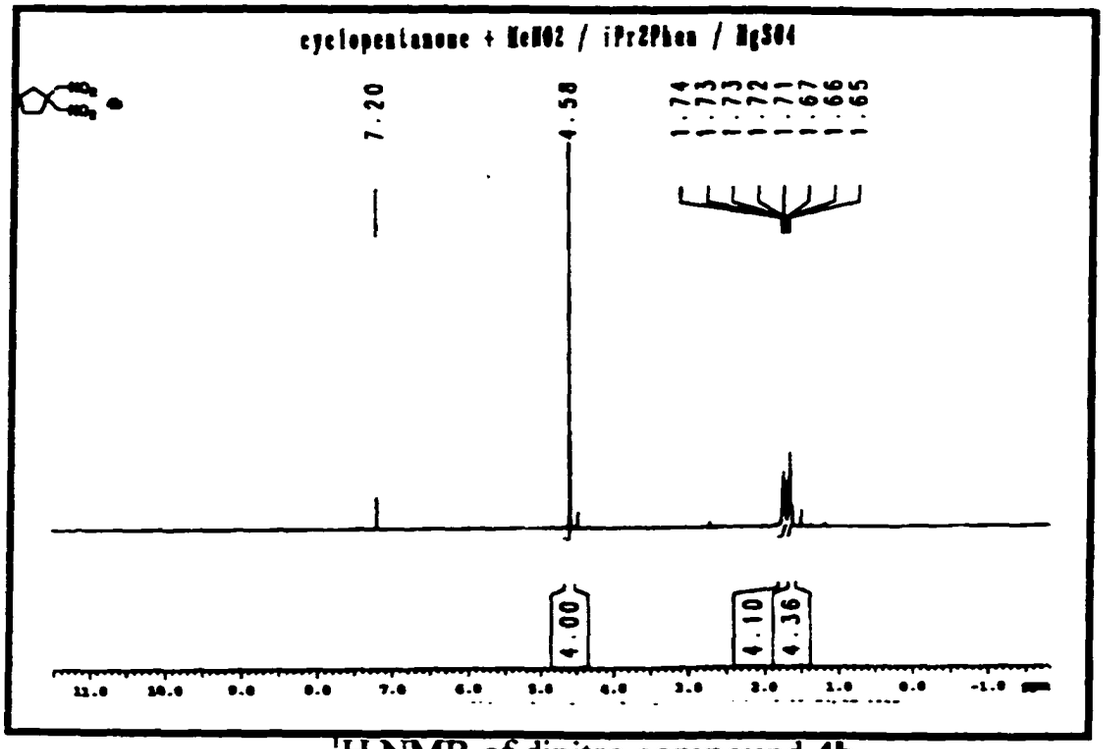
^{13}C NMR of β-nitroalkanol **3w**



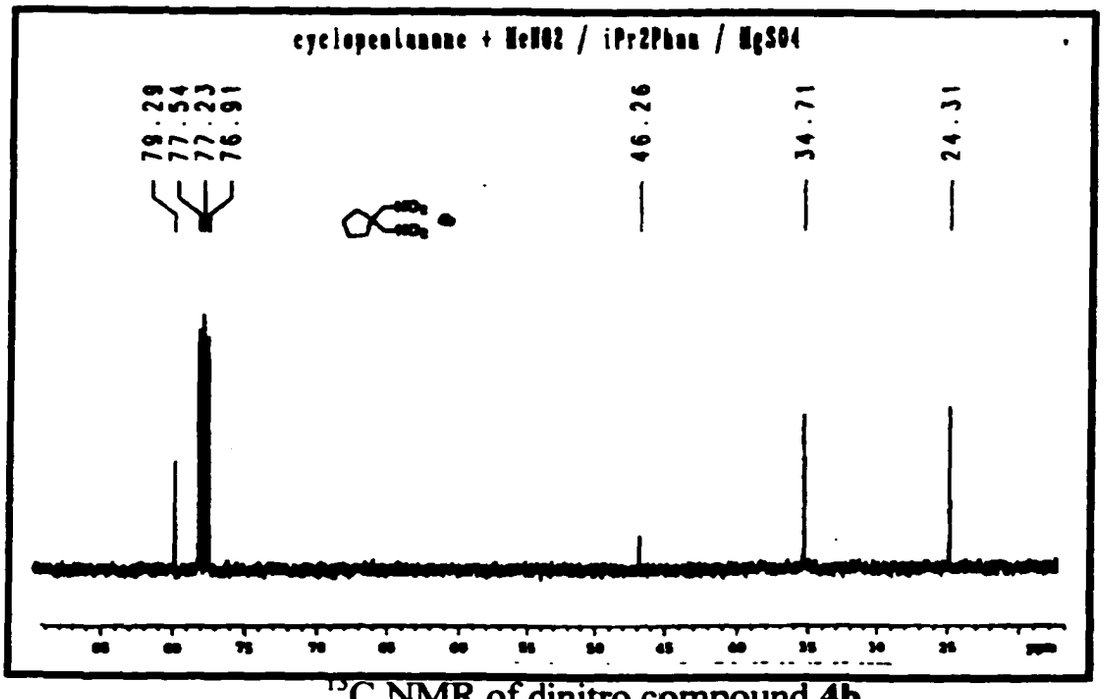
^{1}H NMR of dinitro compound **4a**



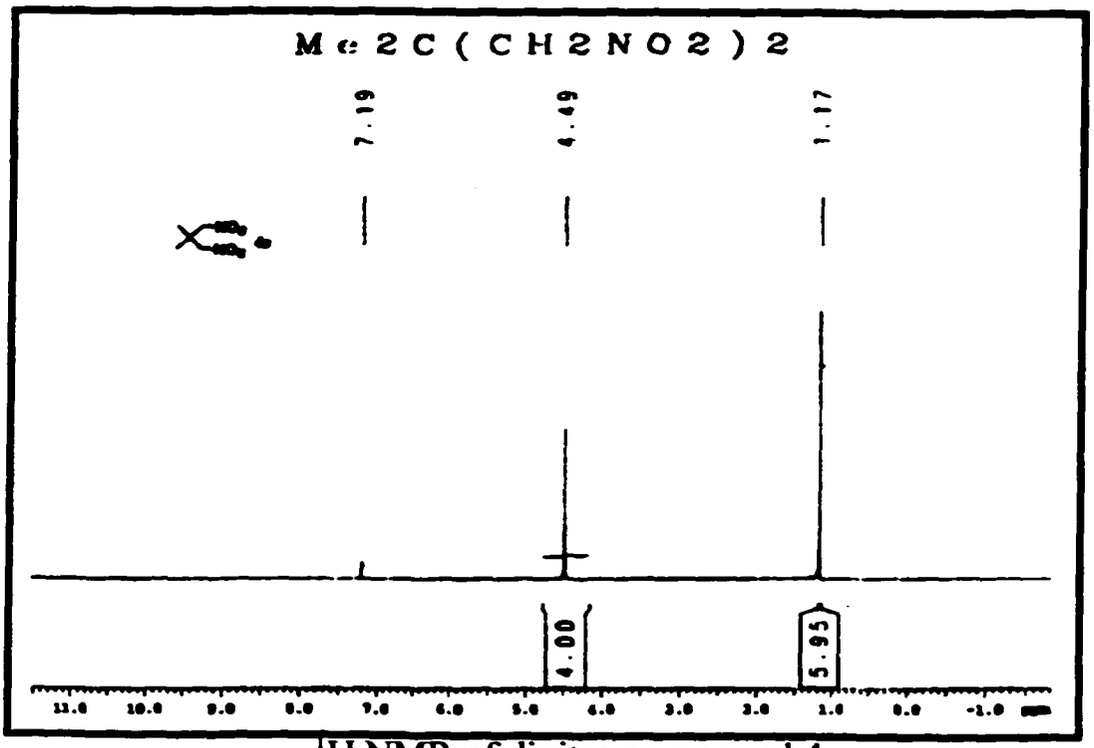
^{13}C NMR of dinitro compound **4a**



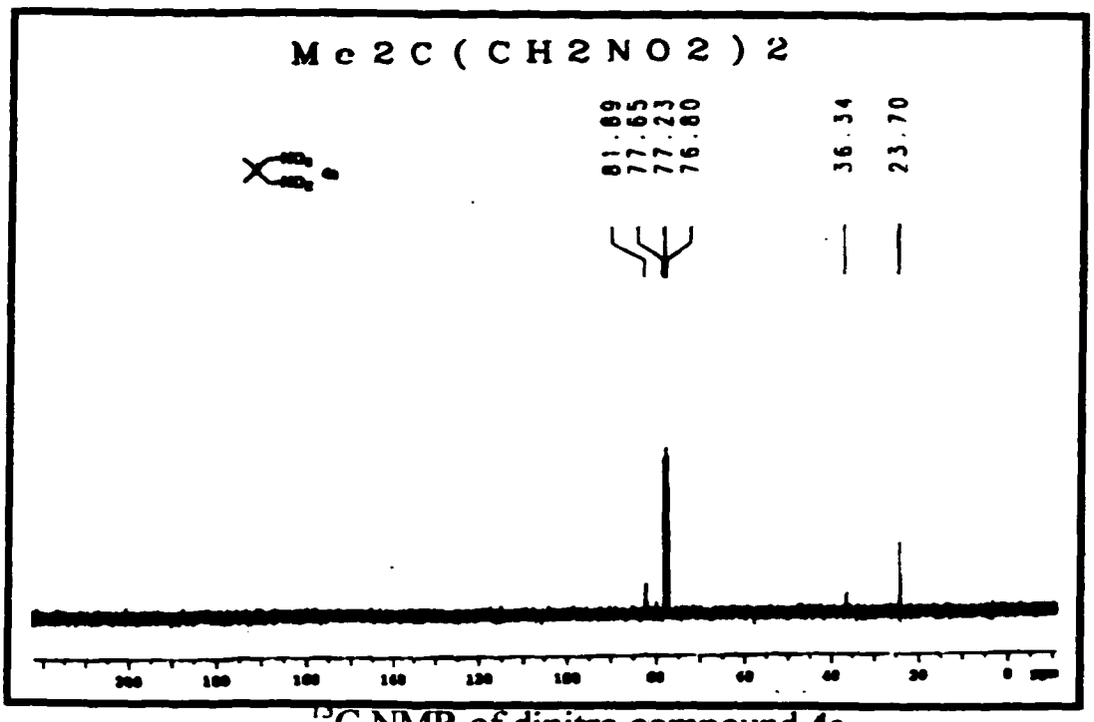
^{1}H NMR of dinitro compound **4b**



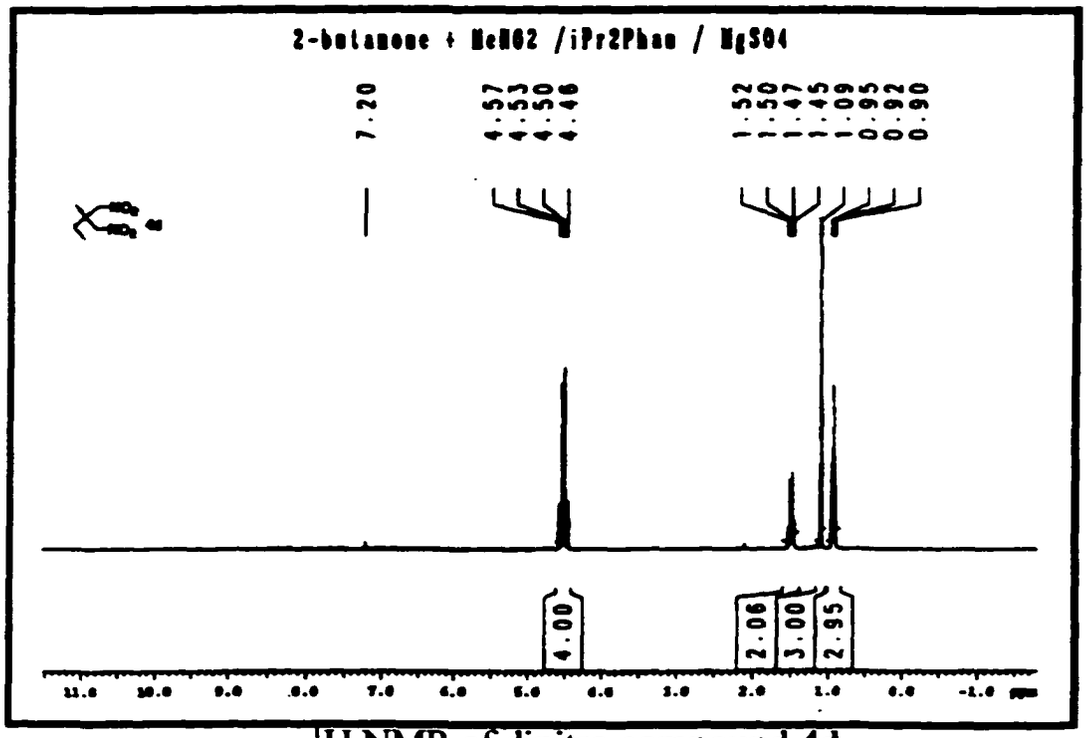
^{13}C NMR of dinitro compound **4b**



^{1}H NMR of dinitro compound **4c**



^{13}C NMR of dinitro compound **4c**



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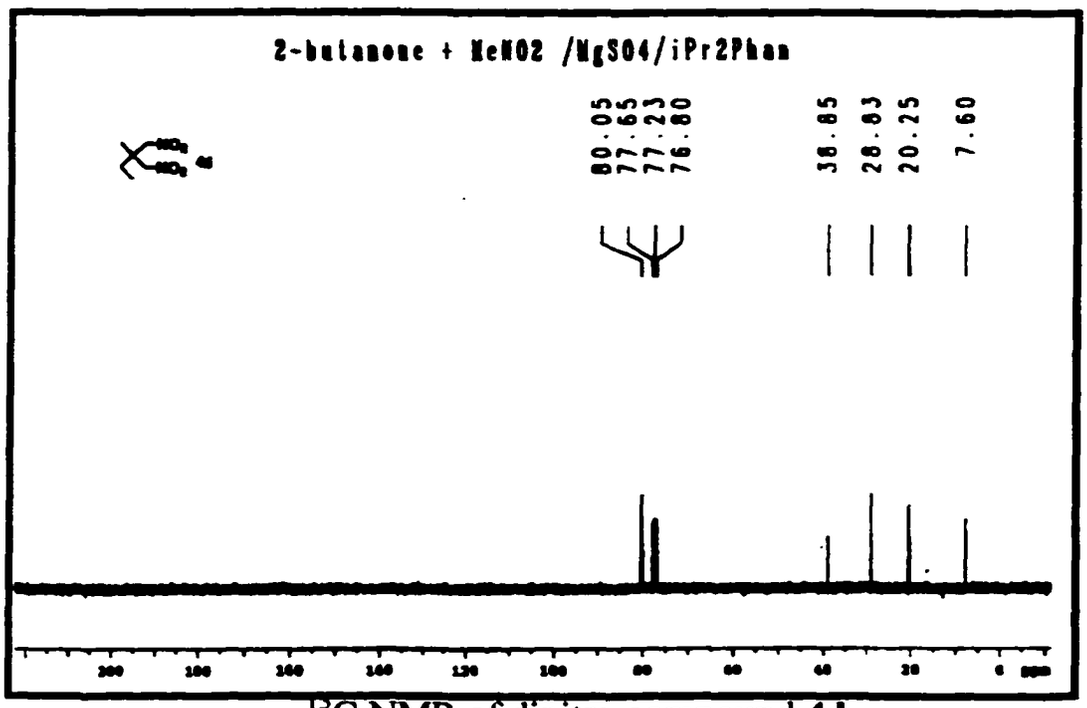
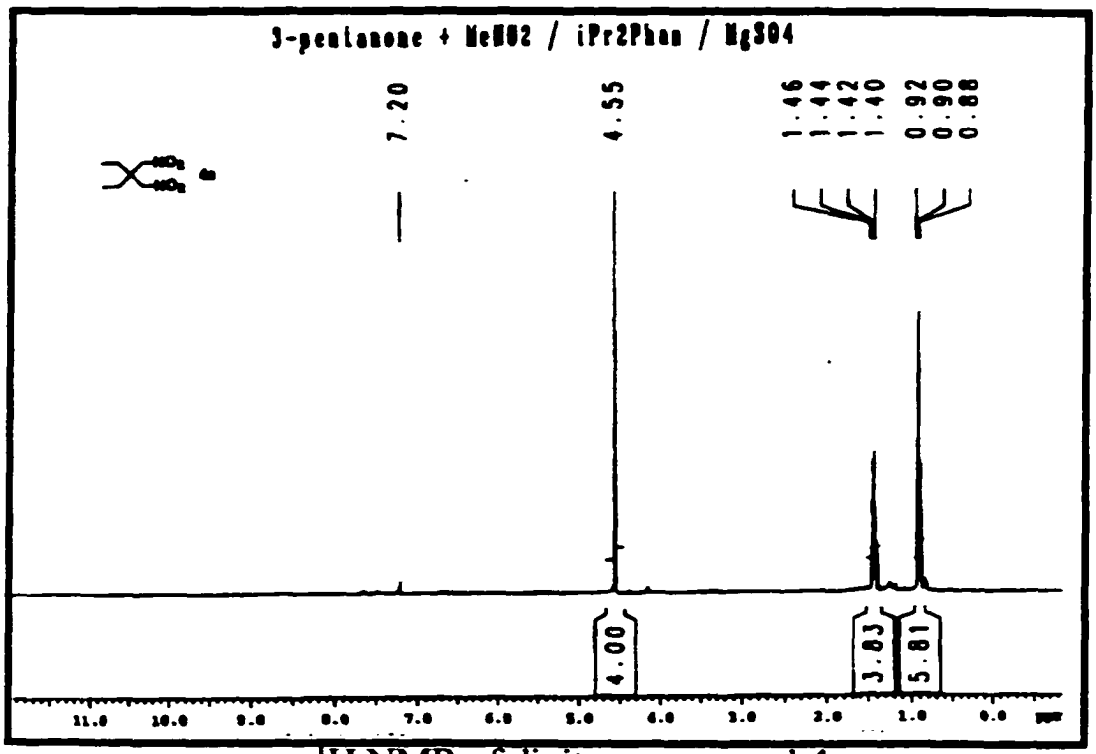
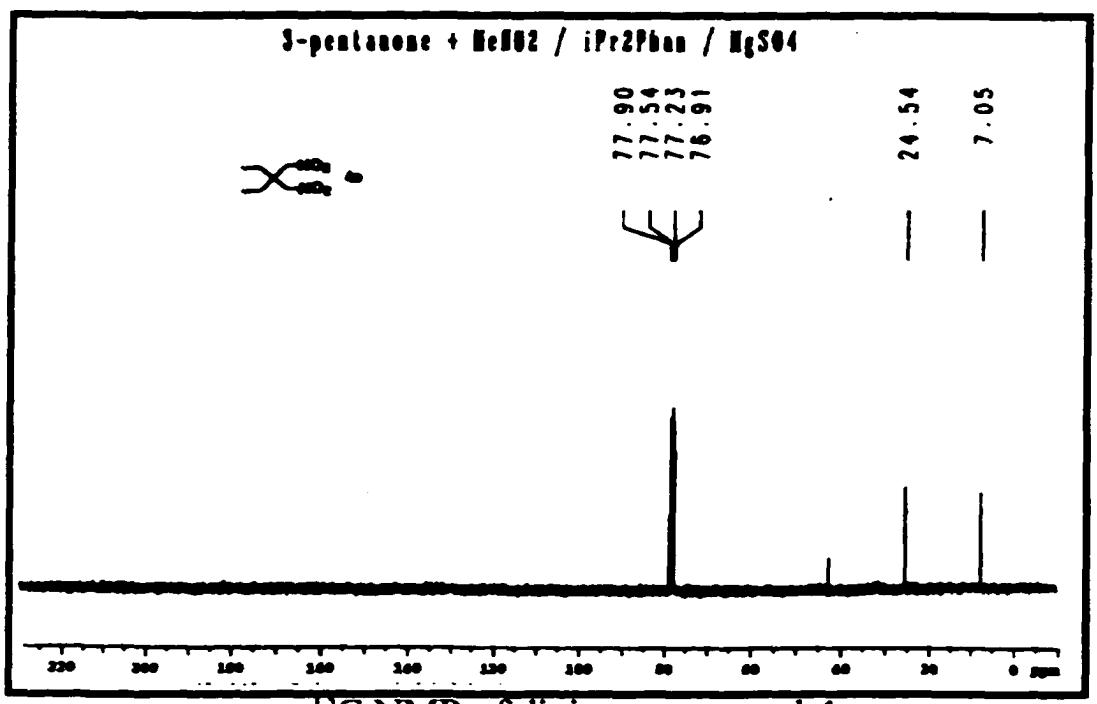


^{13}C NMR of dinitro compound **4d**



^{1}H NMR of dinitro compound **4e**



^{13}C NMR of dinitro compound **4e**

CHAPTER 7

$P(RNCH_2CH_2)_3N$: AN EFFICIENT PROMOTER FOR THE DIRECT SYNTHESIS of *E*-α,β-UNSATURATED ESTERS AND THE SYNTHESIS OF 3-SUBSTITUTED COUMARINS

A paper submitted to the Journal of Organic Chemistry[a]

Philip Kisanga,[b,c] Bosco D'Sa,[d] Xiangshu Fei[e] and John Verkade[b,f]

Abstract

Upon reacting ethyl acetate or methyl propionate with a variety of aromatic aldehydes in the presence of 1.06-1.2 equiv of the pro-azaphosphatranes, $P(MeNCH_2CH_2)_3N$, $P(i\text{-}PrNCH_2CH_2)_3N$ or $[P(i\text{-}PrNCH_2CH_2)_2(NHCH_2CH_2)N$ at 40-50 °C for 2-6 hours in isobutyronitrile, the corresponding α,β-unsaturated esters were formed as the only products. Ethyl acetate reacts with aldehydes to form exclusively *E*-isomers while the higher homologue methyl propionate gives rise to a mixture of *E* and *Z* isomers with the former as the major product. When used as the solvent, methyl propionate

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[b] Graduate student and University Professor, respectively, Department of Chemistry, Iowa State University.
[c] Primary researcher and author.
[d] Schering-Plough Research Institute, 1011 Morris Avenue, Union, NJ 07083.
[e] Postdoctoral research associate, Department of Chemistry, Iowa State University.
[f] Author for correspondence.

selectively forms the *E*-α,β-unsaturated ester. The reaction is not as successful for the preparation of α,β-unsaturated ketones. The efficacy of this methodology in the synthesis of coumarins is also demonstrated.

Introduction

The most commonly used strategy for the preparation of α,β-unsaturated esters is the Wittig reaction and its modifications devised by Horner, Wadsworth and Emmons.[1] Although these reactions are widely used, their major drawback is the need for the preparation of intermediates of the type $[Ph_3PCH_2R]^+X^-$ and $(EtO)_2P(O)CH_2CO_2R$ from the corresponding halogenated reagents. These intermediates are then deprotonated by means of an ionic base, such as NaH,[2,3] LDA[3], *t*-BuOK,[2] *n*-BuLi[2] or potassium carbonate,[4] or a nonionic base, such as an amine,[5] to form the corresponding ylids. These two-step procedures produce substantial amounts of chemical waste in the preparation of a simple unsaturated ester, and also involve the cost and time required to prepare these intermediates. Several organometallic catalysts, such as $RuCl_2(PPh_3)_3$[6], $ReOCl_3(PPh_3)_3$[7,8], $Sn(OSO_2CF_3)_2$[5], and Bu_3Sb,[9] have also been employed to convert aldehydes into α,β-unsaturated esters. However, the use of heavy metal catalysts introduces environmental concerns. Moreover, these procedures rarely produce a single isomer.[5-9] The Ru, Re and Sb compounds require the

use of ethyl diazoacetate which is explosive, and trialkylstibenes are pyrophoric.[6] Other variations of the Wittig approach that have been employed include the reaction of ylids on silica gel under microwave conditions,[10] the use of pentacoordinate spirophosphoranes,[2] and taking advantage of activated alumina[11] to promote coupling between the Wittig reagent and the aldehyde, to name but a few. These approaches proceed with moderate to high yields, require prior preparation of the intermediates and rarely produce a single isomer.

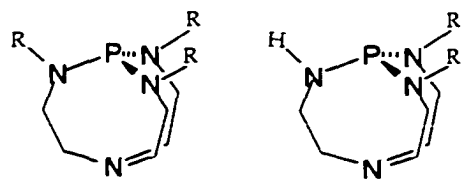
Peterson olefination[12] has also been used for the synthesis of disubstituted *E*-α,β-unsaturated esters. However, most of the variations of this reaction require elevated temperatures and they provide only modest yields.[13] Although the Wittig reaction and its Peterson and Julia-Lithgoe[14] modifications are very useful for preparing disubstituted *E*-α,β-unsaturated esters, their general failure in inducing good stereoselectivity in the preparation of trisubstituted α,β-unsaturated esters has remained a major draw-back.[15] The Julia-Lythgoe reaction has been less frequently used because it employs toxic sodium/mercury amalgam in the reductive cleavage step, although alternatives such as samarium iodide-mediated reductive cleavage have recently been introduced.[14b] 1-Alkoxycarbonylalkylidenetriphenylarsoranes[16] have been

employed to address the stereoselectivity problem in the formation of trisubstituted *E*-α,β-unsaturated esters. Although this strategy is successful in producing the *E*-tribustituted α,β-unsaturated esters in 64-95% yields, the toxicity of arsenic compounds makes this methodology less attractive.

In recent years, several transition metal compounds have been used in the preparation of *E*-α,β-trisubstituted unsaturated esters. These include the reaction of phenyl iodide with methyl methacrylate in the presence of $NaHCO_3$, $PdCl_2$, and PEG-800 in DMF at 120 °C for 6 h to afford the *E*-esters in moderate yields;[17] a Pd-catalyzed Heck[18] reaction and the use of alkenyl and aryl boronic acids in a Pd-catalyzed transformation.[19] The toxicity of DMF and the high temperature required in the PEG-800 reaction is disadvantageous, however. The aforementioned Pd-catalyzed reactions also lead to mixtures of products and require long reaction times (up to 24 hours). A reported process using aryl iodides and acrylates also requires a relatively high temperature (130 °C), the presence of platinum complexes and a reaction time of 24 hours to afford moderate conversions (26-90%) and selectivities (40-95%).[20]

Since our first report of the pro-azaphosphatrane **1a**,[21] the efficacy of this compound as a catalyst or promoter for a variety of reactions has been demonstrated in a series of reports from our laboratories.[22-31] Catalysts of type **1**

have been employed in the synthesis of α,β-unsaturated nitriles,[26] glutaronitriles,[27] β-hydroxy nitriles,[28] β-nitroalkanols,[29] homoallylic alcohols,[25a] conjugated dienes from methylene-interrupted double bond systems,[25b] Michael addition reactions[25c] and silyl ethers,[30] and also in the acylation and transesterification of alcohols.[31] The more basic analogues **1b**[23] and **1c**[24] have been shown to be even more effective in some of our more recent studies[26-28] as well as in the present one. On the other hand, **1b** has proven to be advantageous in reactions requiring longer reaction times, such as the synthesis of homoallylic alcohols via the alkylation of aldehydes,[25a] wherein both **1a** and **1c** failed to effect better conversions.



1a, R = Me
1b, R = *i*-Pr

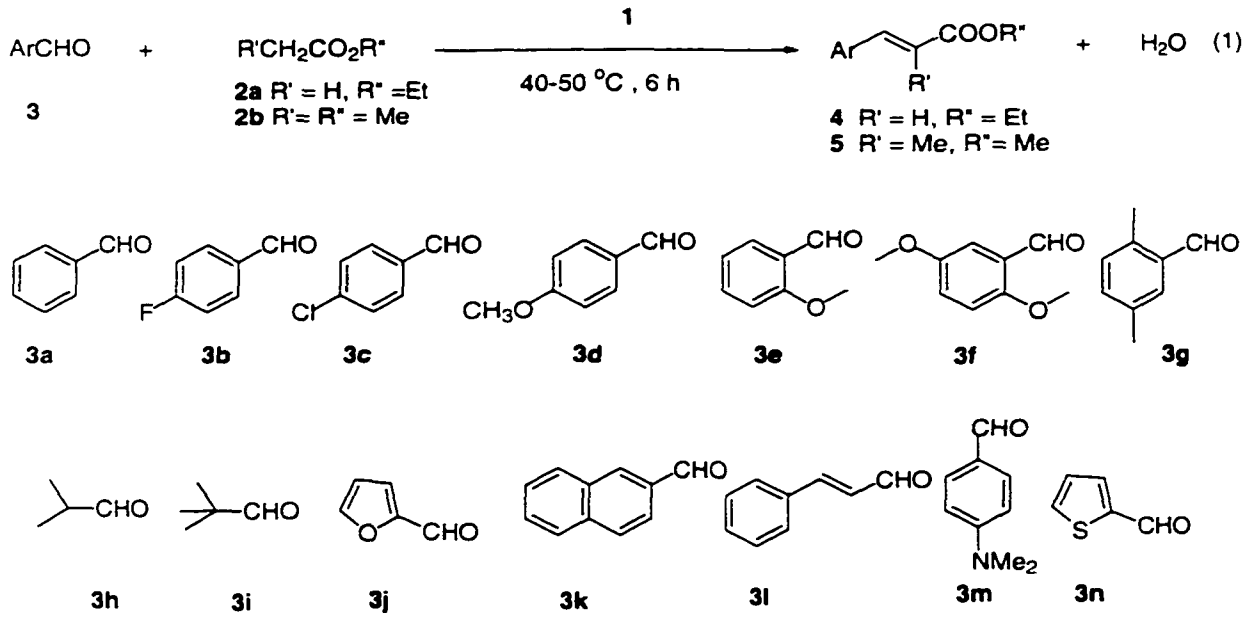
1c

We report here that bases of type **1** also efficiently deprotonate ethyl acetate to afford enolates that add to aldehydes to produce the corresponding *E*-α,β-unsaturated esters. We also report the promotion by **1b** of the direct condensation of aromatic aldehydes and methyl propionate to form the trisubstituted *E*-methyl acrylate as the sole product. To our knowledge, this is the first report in which important transformations of this type have been

effected directly or in which they have been induced by a nonionic base. We also report here the use of this methodology for the synthesis of coumarins.

Results and Discussion

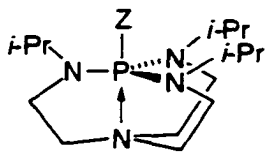
Because of the broad range of reactions catalyzed by compounds of type **1**,[21-31] we believed that such bases might be capable of deprotonating ethyl acetate (**2a**) and that the resulting enolate would add to aldehydes to produce β-hydroxy esters that would then undergo dehydration to afford the corresponding α,β-unsaturated esters (equation 1). We were disappointed, however, when only the starting aldehyde **3a** was recovered in reactions in which benzaldehyde



(**3a**) was reacted with ethyl acetate (**2g**) at 30-40 °C using 20 mol % of **1b** in the presence of THF for 6 hours. Reactions in ether, benzene, and pentane gave

similar results (Table 1). Although the reaction in ethyl acetate (**2a**) was encouraging (28% conversion to the desired product), we were disappointed to observe an overall 56% conversion to a 1:1 mixture of the desired product and the intermediate β-hydroxy ester. Upon extending the reaction time to 12 hours, the product mixture consisted of 37% of the desired product and 13% of the intermediate alcohol. By contrast, a reaction monitored by ^{31}P NMR spectroscopy indicated that the base (**1b**) was completely converted to **1b**H^+ after 4 hours at 40 °C. Since the α-methyl group in ethyl acetate is more acidic than the hydrogens in acetonitrile by about three-fold,[32] we thought that perhaps the preferential deprotonation of the ester in acetonitrile might favor α,β-unsaturated ester formation. Experimentally, however, the reaction of **3a** with **2a** in acetonitrile in the presence of **1b** gave the β-hydroxy nitrile (66% conversion) as the major product (Table 1), while showing only a 20% conversion to the desired α,β-unsaturated ester as estimated by ^1H NMR integration. Therefore, we elected to try isobutyronitrile (also a polar nitrile) as the solvent, since its addition to aldehydes would be less favored (see later) because of its greater steric hindrance. At the same time, we expected to maintain the strong basicity of the pro-azaphosphatranes[23,33] (pK_a ~33.6 for **1a** in acetonitrile[33c]) by using a nitrile solvent. A perhaps more convincing reason

to use a nitrile solvent was our observation that the protonation of **1b** is not detectable by ^{31}P NMR analysis in neat dry methyl ethyl ketone or in dry acid-free ethyl acetate. Furthermore, protonation of **1b** by either dry acid-free ethyl acetate or methyl ethyl ketone was not detected in dry C_6D_6 at temperatures up to 40 °C for 1 h. On the other hand a solution of 60 mg of **1b** in 0.75 mL of a 1:1 mixture of dry CD_3CN and methyl ethyl ketone instantaneously formed



	Z
1bH$^+$	H
1bD$^+$	D

1b, **1b**H$^+$, and **1b**D$^+$ in a ratio of 76:7:17 as shown by ^1H NMR spectroscopy. A comparable ratio (81:5:14) was observed under similar conditions for a 1:1 mixture of dry CD_3CN and ethyl acetate. These observations are consistent with a higher basicity of **1b** in acetonitrile, and/or prior deprotonation of acetonitrile by **1b** with subsequent deprotonation of the ester or ketone by the $^-CH_2CN$ ion that is produced. In a similar way, we found that a solution of **1b** in a 1:1 mixture of isobutyronitrile and ethyl acetate led to the formation of **1b** and **1b**H$^+$ in a ratio of 84:16 in about 20 minutes. These experiments indicate either a stronger basicity of **1b** in this mixed solvent medium than in neat ethyl acetate, or that a proton transfer equilibrium is reached more rapidly via the

$^{-}CH_2CN$ or $^{-}CMe_2CN$ ion. In a competitive study, we found that only addition of $^{-}CH_2CN$ to **3a** occurred in a 1:1 mixture of acetonitrile and isobutyronitrile. In contrast, less than 10% addition of isobutyronitrile to benzaldehyde (**3a**) occurs over 6 hours under identical conditions to form the correspoding β-hydroxy nitrile.

The reaction of **3a** with ethyl acetate in the presence of isobutyronitrile and 20 mol % of **1b** resulted in only a 22% conversion as estimated by ^1H NMR integration, and we attributed this to the stoichiometric nature of the reaction imposed by the inability of both OH^- and the secondary β-alkoxy anion to deprotonate the azaphosphatrane cation **1bH**$^+$ appreciably.[22] When the reaction of benzaldehyde (**3a**) with ethyl acetate was repeated in the presence of 1.06 equiv of **1b**, a 96% yield of ethyl *E*-cinnamate as the only product was obtained (Table 2). The reaction of *p*-anisaldehyde (**3d**) proceeded in 73% yield (84% conversion) while *p*-dimethylaminobenzaldehyde (**3m**) did not react under these conditions (Table 2). Although the relatively lower yield of product from **3d** is attributable to strong resonance stabilization induced by the *p*-methoxy group, the product yield is in the same range as those previously reported for this substrate for a variety of reactions.[2,11,27] The inability of *p*-dimethylamino-benzaldehyde to react under our conditions is in accord with our previous

experience with this substrate in the attempted synthesis of its corresponding β-hydroxy nitrile.[27] The reaction of *p*-chlorobenzaldehyde (**3c**) on the other hand produced the corresponding α,β-unsaturated ester in excellent yield (Table 2). The reaction of methyl propionate (**2b**) was found to be less stereoselective, although the major product was the *E*-isomer (Table 2). Table 2 also shows that both **1b** and **1c** are efficient bases for the preparation of unsaturated esters, but that probably because of its somewhat lower basicity,[23] **1a** is less efficient.

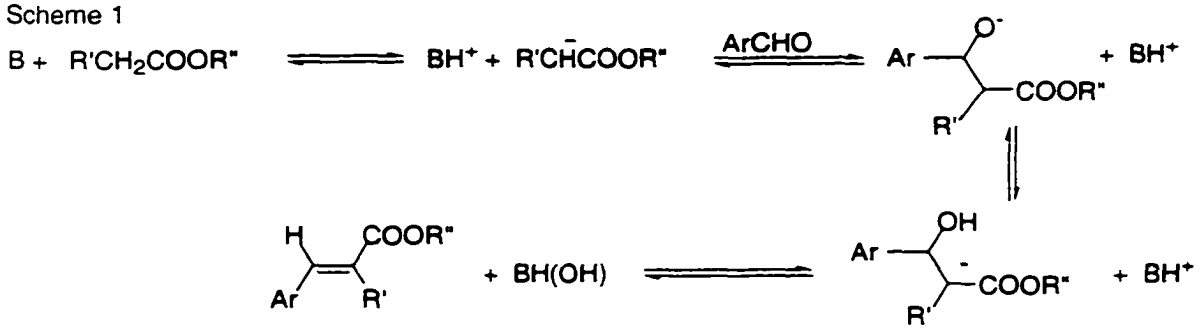
The production of some *Z*-olefin from **3d** and the low conversion of **3l** (although comparable with recently reported results[5-8]) was rather disappointing, spurring us to seek alternative conditions under which higher selectivities could be realized. We subsequently observed that the use of ethyl acetate as the solvent, although producing a mixture of the corresponding *E*-α,β-unsaturated ester and β-hydroxy ester (Table 1), failed to produce detectable amounts of the *Z*-isomer. When an acid-free sample of ethyl acetate was used as the solvent, the conversions using 0.2 and 0.5 mole equiv of **1b** in separate reactions were found to be 30% and 79%, respectively, in 6 h at 50 °C (Table 3). With 1.2 equiv of **1b**, however, the conversion was quantitative over 6 h at 50 °C (Table 3). This table also shows that neither **1a** nor **1c** efficiently promote the preparation of the *E*-α,β-unsaturated esters in ethyl acetate. Lower

yields with **1c** are attributed to the requirement of elevated temperatures at which this base is relatively unstable with respect to oligomerization[24] compared with **1b**, while lower yields with **1a** are attributable to its lower basicity. The efficacy of our methodology is demonstrated by the superior yields and selectivities compared with those reported by Kayser *et al.*[34] (36-95% yields, 100:0 to 70:30 *E:Z* ratios), Fujimura *et al.* (85-92% yields, >99:1 to 90:10 *E:Z* ratios)[6] and Sano *et* al.[5] (29-100% yields, 100:0 to 6:94 *E:Z* ratios). The reactions of the aliphatic aldehydes **3i** and **3h** produced none of the expected unsaturated ester, and no starting material is either recovered or observed in a ^{1}H NMR-monitored reaction after 4 h. The unpredictable reactivity of **3h** is not surprising and is in accord with our previous findings,[26,27] but the inability of **3i** to afford the desired unsaturated ester is unexpected. However, in another study, we found that γ-alkyl and γ,γ-dialkyl substituted α,β-unsaturated nitriles are able to dimerize and oligomerize in the presence of bases of type **1**.[27] We have recently found that some enones (e.g., 2-cyclohexenone, 4-hexen-3-one, methyl vinyl ketone and mesityl oxide) and γ-alkyl-α,β-unsaturated esters (e.g., ethyl *E*-crotonate) exhibit similar dimerization or oligomerization behavior.[25c] In the reactions of the two substrates **3h** and **3i**, we observed that like ethyl *E*-crotonate,[25c] they

oligomerize in the presence of **1b**. Perhaps, the corresponding α,β-unsaturated ester produced oligomerizes upon formation. Although **3f** is somewhat sterically hindered and also experiences reduced reactivity because of possible resonance with the *o*-methoxy group, the desired unsaturated ester is produced in 82% yield.

Motivated by these results, we explored the selectivity of reaction 1 for the synthesis of trisubstituted α,β-unsaturated esters. In the presence of 1.06 equiv of **1b** at 50 °C, benzaldehyde (**3a**) reacted with **2b** in 6 h to provide a 95% conversion to the corresponding trisubstituted α,β-unsaturated ester as the sole product as shown by TLC, ^{1}H and ^{13}C NMR analyses. In the presence of 1.2 equiv of **1b** the reaction was quantitative. The reactions of of 4-fluorobenzaldehyde (**3b**) or 4-chlorobenzaldehyde (**3c**) with methyl propionate (**2b**) at 50 ^{0}C for 6 hours were quantitative and afforded single products as well. Comparison of the ^{1}H NMR spectra of these products to those reported in the literature[35] showed that we obtained the *E*-isomer[35b] of the expected esters with excellent selectivity. We therefore repeated the reaction for a variety of aldehydes and the results of these experiments are shown in Table 4. This table shows that in addition to excellent selectivity, the isolated yields range from very good to excellent with the exception of *p*-anisaldehyde (**3d**) which gave a

Scheme 1



moderate yield, and *p*-dimethyaminobenzaldehyde (**3m**) which does not react under our conditions. The use of molecular sieves in these reactions proved fruitless. The superiority of our methodology is also evident from the high conversions and isolated yields obtained in the reaction of **2b** with the sterically hindered aldehydes **3e** and **3g** to form the corresponding new trisubstituted *E*-α,β-unsaturated esters.

The proposed pathway of this reaction shown in Scheme 1 is initiated with a pre-equilibrium that lies far to the left. This assumption is substantiated by the aforementioned experiments in which no detectable protonation of **1b** is observed in neat ethyl acetate or methyl ethyl ketone. Indirect support for this assumption lies in our observation that the addition of **1b** to dry CD_3OD, a more acidic solvent, for up to 6 h leads to only 8-10% deuteration. The unfavorable pre-equilibrium in the first step of Scheme 1

therefore requires a comparatively large amount of the base in order to accelerate the reaction. In Scheme 1, both the secondary β-alkoxide and the hydroxide anion are relatively weak bases that are unable to deprotonate the protonated base appreciably.[22]

Since the α-protons of ketones are more acidic than those of esters,[30] we expected bases of type **1** to catalyze a cross-aldol condensation between ketones and aldehydes. Because of the sterically hindered nature of the pro-azaphosphatranes, we believed they would be able to regioselectively deprotonate the less hindered methyl protons in methyl ethyl ketone. However, in the presence of Me_2CHCN, ether or THF as the solvent, the reaction mixture showed no upfield signals in the ^1H NMR spectra that could be attributed to the expected product (PhCH:CHCOEt) although all of the aldehyde was consumed. We attribute this to the strong basicity of **1b** which may induce self-condensation of the ketone. When the amount of the base was decreased to 0.2 equiv, the same reaction pattern was observed with both **1a** and **1b**. However in benzene, a 31% conversion to the olefin was observed with **1a** in about 30 minutes. This product was isolated by column chromatography to afford a 23% yield of (*E*)-PhCH:CHCOEt. Reaction mixtures produced by **1b** under similar conditions were complicated and revealed that all the aldehyde was

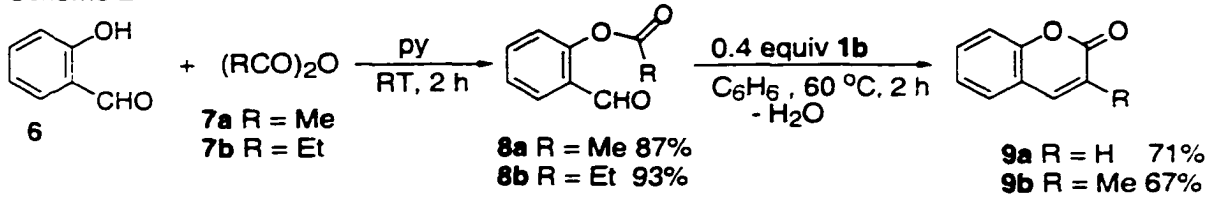
consumed. Attempts at increasing the time of the reaction utilizing **1a** to over 1 h led to the formation of unidentifiable materials which gave a continuum of spots on TLC analysis. Increasing the amount of **1a** to more than 20% led to an instantaneous disappearance of the aldehyde but no detectable amounts of α,β-unsaturated ketones. The foregoing argument implying a possible oligomerization of $Me_3CCHCHCOOEt$ does not seem to apply here because of our observation that PhCH=CHCOMe is stable in the presence of bases of type **1**. The consumption of the aldehyde without the formation of the expected unsaturated ketone was observed even when the reaction was attempted at -78 °C. This reaction is under further investigation in our laboratories.

Synthesis of coumarins

With the success of the methodology shown in equation 1, we attempted to apply an intramolecular version of this reaction to the synthesis of coumarins. This class of compounds has recently been prepared by Cartwright *et al.* by flush vacuum pyrolysis[36] in an attempt to circumvent the variable yields and inconvenient workups encountered in Wittig olefination-cyclizations.[37] More recently, a rhodium-catalyzed process[38] has been introduced that produces a mixture of coumarins and benzofurans in variable yields.

The required salicyladehyde 2-carboxylates were prepared according to a published method[39] as shown in step one of Scheme 2. Crude **8a** and **8b** were then used in an intramolecular olefination using **1b** as a promoter.

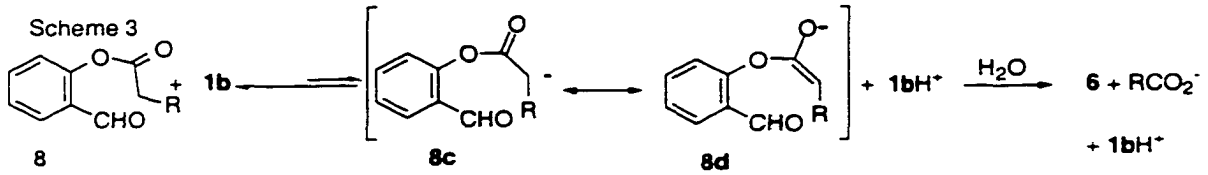
Scheme 2



When **8a** was reacted with 1.2 equiv of **1b** at 40 °C for 3 h, a 50:50 mixture of **6** and **9a** was observed in the reaction mixture. A similar product mixture was obtained with **8b**. Decreasing the amount of **1b** to 0.5 or 0.4 equiv gave an identical product mixture. Further reduction in the amount of **1b** to 0.3 equiv resulted in an incomplete reaction. Therefore, we assumed that 0.4 equiv of **1b** was an optimum amount of **1b** required for the reaction. When we attempted to increase the reaction temperature to 60 °C or to use magnesium sulfate[28,29] (a Lewis acid we have found to be compatible with bases of type **1**), over 70% deacylation to **6** was observed. When 4 Å molecular sieves were added in a repetition of the reaction at 40 °C for 3 h in the presence of 0.4 equiv of **1b**, 71% and 67% of the coumarins **9a** and **9b**, respectively, were isolated, while the remaining starting material in each case (**8a** and **8b**, respectively) was deacylated to **6**. The deacylation of **8** is assumed to proceed through the

pathway shown in Scheme 3. Such reactions have recently been studied in our laboratories in a different context.[31] Although the isolated yields of the coumarins synthesized herein are not superior to those reported by Cartwright,[36]

Scheme 3

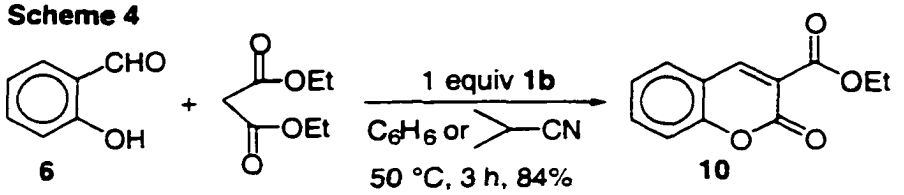


the methodology represents a more simple and convenient alternative to pyrolysis or Wittig olefination-cyclization.

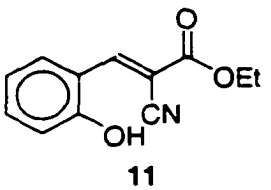
The Knoevenagel condensation has often been used to prepare 3-substituted coumarins. Highly efficient reactions have recently been reported involving the condensation of salicylaldehydes with malonates in the presence of piperidine under microwave conditions,[40a] and the use of montmorillonite KSF.[40b] Both strategies produced this class of compounds in yields up to 94%[40] and 92%, respectively. However, the temperature at the end of the 10-minute microwave reaction is 120 °C[40a] and the montmorillonite process requires reaction at 100 °C for 24 h.[40b] When we attempted the reaction of salicylaldehyde with diethyl malonate in the presence of 1.0 equiv of **1b** in benzene or isobutyronitrile, the isolated yield of **10** was 84% (Scheme 4). Increasing the amount of **1b** to 1.5 equiv and the quantity of diethyl malonate to 1.2 equiv led to the isolation of 94% of the desired product **10**. Although this

result is more favorable than that reported in the literature[40] owing to the lower temperature we employ (50 °C), the relatively large amount of **1b** (1.5 equiv) required coupled with the inability of ethyl cyanoacetate to afford a

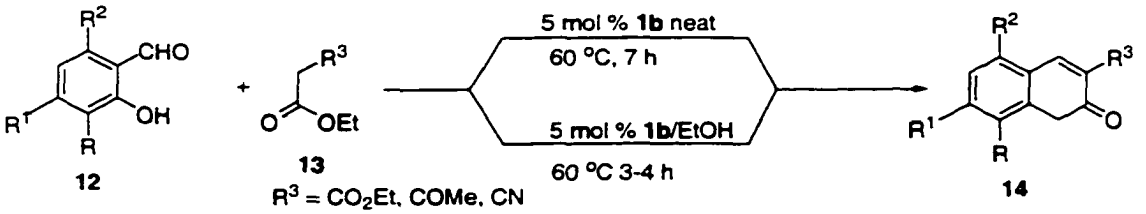
Scheme 4



high conversion to the corresponding coumarin (~20%) as determined by ^{1}H NMR integration were disappointing. The latter result may be associated with the configuration of the solvated intermediate Knoevenagel product (**11**) in isobutyronitrile, whose geometry could be unfavorable for the formation of



Scheme 5



the desired coumarin. A solution to this apparent problem was realized by employing either a neat reaction or using ethanol as the solvent. Under these conditions, a catalytic reaction occurred in the presence of 10 mol % of **1a** or

1b to afford the desired coumarins as the only products in high yields (Scheme 5 and Table 5).

It should be mentioned that the reaction of either **6** or its substituted analogues **12** with ethyl acetate or methyl propionate under the conditions in Scheme 5 did not afford detectable amounts of the desired coumarins **9a** or **9b**, respectively. While the yields in Table 5 are competitive with those reported in the literature,[40] the mild conditions and the shorter reaction times in our methodology constitutes a more practical alternate route to coumarins.

Conclusion

We have shown that the pro-azaphosphatrane **1b** is an efficient base for the direct synthesis of α,β-unsaturated esters from the corresponding aldehydes and esters in excellent *E*-stereoselectivity. This reaction can be carried out in isobutyronitrile as a solvent or in the presence of excess dry acid-free ester as the reactant and solvent. The reaction of methyl propionate with aldehydes gives the corresponding trisubstituted α,β-unsaturated esters with excellent *E*-selectivity. Since the base can be efficiently recovered for recycling (see Experimental Section) the only waste product in reaction 1 is water. Compounds **1a** and **1b** can also be used as a promoters for the synthesis of coumarins in a superior manner.

Experimental Section

All reactions were carried out under nitrogen. The esters (ethyl acetate and methyl propionate) were purchased from Aldrich chemical company and were dried according to standard procedures[49] and then stored under nitrogen over 4Å molecular sieves. The bases **1a-1c** were prepared according to previously reported methods[21-23] although **1a** is commercially available (Strem).

Procedure for the preparation of α,β-Unsaturated Esters in Me_2CHCN

In a typical experiment, 2.00 mmol of the aldehyde was dissolved in isobutyronitrile (2.0 mL) in a small flask preflushed with nitrogen. A solution of 2.10 mmol of **1** (449 mg of **1a**, 636 mg of **1b** or 547 mg of **1c**) in 1.0 mL of isobutyronitrile was then prepared in another flask under nitrogen. To this solution was added 2.1 mmol of the ester (ethyl acetate or methyl propionate). This solution was then added to the solution of the aldehyde and stirring was continued while the mixture was warmed under the conditions stated in Table 2. At the end of the reaction time the reaction mixture was allowed to cool to room temperature. The crude reaction mixture was then loaded onto a small silica gel column and column filtered with 100% ether. The crude product was purified when necessary by fractionation on a silica gel column using an eluent

system consisting of hexane and ethyl acetate. The esters eluted with 30% EtOAc in hexane. The esters from **3f**, **3l**, **3n** did not separate well with the ethyl acetate/hexanes eluent system and were thus eluted with a hexanes/ethyl ether solvent system, eluting at 40% ether in hexanes.

Procedure for the Preparation of α,β-Unsaturated Esters in Ethyl Acetate

In a typical experiment 2.10 mmol of **1** (449 mg of **1a**, 636 mg of **1b** or 547 mg of **1c**) was dissolved in dry ethyl acetate (2.0 mL) in a small flask preflushed with nitrogen. The solution was warmed at 50 °C for 2 minutes. To this solution was added 2.00 mmol of the aldehyde and the mixture was stirred for 6 h at 50 °C. After cooling to room temperature, the crude product was loaded onto a small silica gel column and column filtered with 100% ethyl ether. When necessary, purification was achieved as detailed above.

Procedure for the Preparation of α,β-Unsaturated Esters in $EtCO_2Me$

In a typical experiment 2.40 mmol of **1b** (720 mg of) was dissolved in dry methyl propionate (2.0 mL) in a small flask preflushed with nitrogen. The solution was warmed at 50 °C for 2 minutes. To this solution was then added 2.00 mmol of the aldehyde and the mixture was stirred for 6 hours. The process was continued as stated above for ethyl actetate.

Procedure for the Synthesis of Coumarins 9a and 9b

In a typical experiment, 0.800 mol of **1b** (240 mg) was weighed in a small flask followed by the addition of 2.0 mL of dry isobutyronitrile or benzene. Into another flask containing activated 4Å molecular sieves under nitrogen was syringed 1.0 mL of the solvent (isobutyronitrile or benzene) followed by 2.00 mmol of the 2-salicylaldehyde alkyl carboxylate (328 mg of **8a** or 356 mg of **8b**). The second flask was warmed to 40 °C for 2 minutes followed by the addition of the contents of the first flask by means of a syringe. After stirring was continued for 3 hours, the reaction mixture was allowed to cool to room temperature and then flushed through a small silica gel column with 5% methanol in ethyl ether. Removal of the solvent under reduced pressure afforded the crude coumarins which were fractionated on a silica gel column with an eluent system made up of ethyl acetate in hexane. The ratio of ethyl acetate was increased in 5% increments and the coumarins eluted with about 25% ethyl acetate in hexanes to afford 71% of **9a** and 67% of **9b**, respectively.

General Procedure for the Preparation of Coumarins in the Presence of Catalytic Amounts of 1a or 1b

Method A. Neat Reaction

2.00 mmol of the aldehyde **12**, 2.40 mmol of the diactivated methylene compound **13** and 0.1 mmol of **1a** or **1b** were mixed under nitrogen and heated at 60 °C for 7 h with continuous stirring. The reaction mixture was then allowed to cool to room temperature. The crude products were purified by eluting on a silica gel column using a 3:1 mixture of ethyl acetate and hexanes. The coumarins **14d**, **14f**, and **14j** were purified by eluting on a silica gel column using a 3:1:1 mixture of hexane, ethylacetate and methylene chloride.

Method B. Reaction in ethanol

2.00 mmol of the aldehyde **12** and 2.40 mmol of the diactivated methylene compound **13** were mixed under nitrogen. To this mixture was added 0.1 mmol of **1a** or **1b** dissolved in 20 mL of absolute ethanol and then the reaction mixture was heated at 60 °C for 3-4 h (Table 5) with continuous stirring. At the end of this time, the reaction mixture was allowed to cool to room temperature and the solvent removed under reduced pressure. The crude products were purified as stated in Method A.

Catalyst Recovery

After the reaction times given in Tables 2-4, the solvent was removed under reduced pressure and then the mixture was dissolved in the least amount of water and extracted with 5x20 mL portions of ether. The ether extracts were dried over anhydrous potassium carbonate and the solvent was removed under reduced pressure to afford the crude ester. The aqueous layer was then treated with 5 mL of 1.0 M HCl and extracted four times with 10 mL portions of methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate followed by removal of the solvent under reduced pressure affording the protonated base in 81% yield. This base hydrochloride can be deprotonated according to our previously published methods.[21,22,23] The yields of the α,β-unsaturated esters obtained by this workup procedure are slightly lower (by about 5%) than those obtained by the column filtration method given above.

Acknowledgment

The authors thank the Iowa State Center for Advanced Technology Development for grant support of this work.

References

1. Maryanoff, B. E.; Reitz, A. B. *Chem Rev.* **1989**, *89*, 863 and references therein.
2. Kojima, S.; Takagi, R.; Akiba, K. *J. Am. Chem. Soc.* **1997**, *119*, 5970.
3. Ando, K. *J. Org. Chem.* **1997**, *62*, 1934.
4. Mouloungui, Z.; Elmestour, R.; Delmas, M.; Gaset, A. *Tetrahedron* **1992**, *48*, 2119.
5. Sano, S.; Yokoyama, K.; Fukushima, M.; Yagi, T.; Nagao, Y. *J. Chem. Soc., Chem. Commun.* **1997**, 559.
6. Fujimura, O.; Honoma, T. *Tetrahedron Lett.* **1998**, *39*, 625.
7. Ledord, B. E.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 8125.
8. Herrmann, W. A.; Wang, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1641.
9. Lao, Y.; Huang, Y. *Tetrahedron Lett.* **1990**, *31*, 5897.
10. Xu, C.; Chen, G.; Fu, C.; Huang, X. *Synth. Commun.* **1995**, *25*, 2229.
11. Dhavale, D. D.; Sindkhedkar, M. D.; Mali, R. S. *J. Chem. Res. (Synopsis)* **1995**, 414.
12. (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) Bellassoued, M.; Majidi, A. *J. Org. Chem.* **1993**, *58*, 2517 and references cited therein. (c)

For reviews, see: Ager, D. J. *Synthesis* **1984**, 384; Ager, D. J. *Org. React.* **1990**, *38*, 1.

13. Bellassoued, M.; Ozanne, N. *J. Org. Chem.* **1995**, *60*, 6582 and references therein.
14. For recent references see (a) Markó, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2089. (b) Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194. (c) For a recent review see: Breit, B. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 453 and references therein.
15. For recent references see (a) Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron* **1992**, *48*, 8801. (b) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron* **1994**, *41*, 12029. (c) Satoh, T.; Yamada, N.; Asano, T. *Tetrahedron Lett.*. **1998**, *39*, 6935.
16. Castells; J.; Lopez-Calahorra, F.; Yu, Z. *Tetrahedron* **1994**, *50*, 13765.
17. Ruhong, K.; Jianrong, H. *Huaxue Shiji*, **1997**, *19*, 308. *Chem. Abstr.* **1997**, *127*, 331257.
18. Beller, M.; Riermeier, T. *Tetrahedron Lett.* **1996**, *37*, 6535.
19. Cho, C. S.; Uemura, S. *J. Organomet. Chem.* **1994**, *465*, 85.
20. Kelkar, A. A. *Tetrahedron Lett.* **1996**, *37*, 8917.
21. Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.*

1989, *578*, 75.

22. (a) Tang, J.-S.; Verkade, J. G. U.S. Patent 5,260,436, 1993. *Chem. Abstr.* **1994**, *120*, 218836. (b) Tang, J.-S.; Verkade, J. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 896. (c) Tang, J.-S.; Verkade, J. G. U.S. Patent 5367084. *Chem . Abstr.* **1995**, *123*, 83101. (d) Tang, J.-S.; Verkade, J. G. U.S. Patent 5554746, 1996. *Chem. Abstr.* **1997**, *127*, 307251. (e) Tang, J.-S.; Verkade, J. G. *J. Org. Chem.* **1994**, *59*, 7793. (f) Arumugam, S.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827.

23. Wroblewski, A.; Pinkas, J.; Verkade, J. G. *Main Group Chemistry* **1995**, *1*, 69.

24. D'Sa, B.; Verkade, J. G. *Phosphorus Sulfur Silicon* **1997**, *123*, 301.

25. (a) Wang, Z.; Kisanga, P.; Verkade, J. *J. Org. Chem.*, accepted. (b) Yu., Z.; D'Sa, B. Wang., Z.; Kisanga, P.; Zhang.; G.; Verkade, J. G. manuscript in preparation. (c) Kisanga, P.; Ilankumaran, P.; Verkade, J. G. manuscript in preparation.

26. D'Sa, B.; Kisanga, P.; Verkade, J. *J. Org. Chem.* **1998**, *63*, 3691.

27. Kisanga, P.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1998**, *63*, 10057.

28. Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 3090.

29. Kisanga, P.; Verkade, J. *J. Org. Chem.* in press.

30. (a) D'Sa, B.; Verkade, J. G. *J. Am. Chem. Soc.* **1996**, *118*, 832. (b) D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963.

31. Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086.

32. Schwesinger, R.; Schlemper, H.; Hasenfratz, C.; Willaredt, J.; Dambacher, T.; Breuer, T.; Ottaway, C.; Fletschinger, M.; Boele, J.; Fritz, H.; Putzas, D.; Rotter, H. W.; Bordwell, F. G.; Satish, A. V.; Ji, G.-Z.; Peters, E.-M.; Peters, K.; von Schnering, H. G.; Walz, L. *Liebigs Ann.* **1996**, 1055.

33. (a)Laramay, M. A. H.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1991**, *605*, 163. (b) Arnett, E.M.; Small, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 808. (c) Kisanga, P.; Verkade, J. G. manuscript in preparation.

34. Kayser, M. M.; Zhu, J.; Hooper, D. L. *Can. J. Chem.* **1997**, *75*, 1315.

35. (a) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Synthesis* **1990**, 1123. (b) Heerdan, S.; Bezuidenhoudt, B. C. B.; Ferreira, D.; *Tetrahedron* **1996**, *52*, 12313.

36. (a) Cartwright, G. A.; McNab, H. *J. Chem. Res. (Synopsis)* **1997**, 296. (b) Black, M.; Cadogan, J. I. G.; Cartwright, G. A.; McNab, H.; MacPherson, A. D. *J. Chem. Soc., Chem. Commun.* **1993**, 959.

37. (a) Mali, R. S.; Yeola, S. N.; Kulkarni, B. K. *Indian J. Chem. Sect. B.*, **1983**, *22*, 352. (b) Turner, A. D.; Pizzo, S. V.; Rozakis, G.; Porter, N. *J. Am. Chem. Soc.* **1988**, *110*, 244.

38. Yoneda, E.; Sugioka, T.; Hirao, K.; Zhang, S. -W.; Takahashi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 447.

39. Kato, K.; Chen, C. Y.; Akita, H. *Synthesis* **1998**, 1527.

40. (a) Bogdal, D. *J. Chem. Res. (Synopsis)* **1998**, *8*, 468. (b) Bigi, F.; Chesini, L.; Maggi, R.; Santoni, G. *J. Org. Chem.* **1999**, *64*, 1033.

41. Rajayalakshimi, K.; Srinivasan, V. R. *J. Heterocycl. Chem.* **1980**, *17*, 17.

42. Horning, G. C.; Horning, M. G.; Dimming, D. A. *Org. Prep. Proc.* **1955**, *73*, 4972.

43. Krause, G. A.; Pezzanite, J. O. *J. Org. Chem.* **1979**, *44*, 2480.

44. Hoening, E. C.; Horning, M. G. *J. Am. Chem. Soc.* **1947**, *69*, 968.

45. Czerney, P. *J. Prakt. Chem.* **1982**, *324*, 21.

46. Corrie, J. E. T. *J. Chem. Soc., Perkin Tran. 1* **1994**, 2975.

47. Buckingham, J. *Dictionary of Organic Compounds*, 5th ed., Chapman and Hall: New York 1982.

48. Fadda, A. A. Zeimaty, M. T.; Gerges, M. M.; Refat, H. M.; Biehl, E. R. *Heterocycles* **1996**, *43*, 23.

49. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals, 3rd Ed.* Permagon Press: New York, 1988, p. 175.

Table 1. The Reaction of benzaldehyde with ethyl acetate in different solvents and at various temperatures for 6 h in the presence of 20 mol % of **1b**

solvent	T (°C)	% conversion[a] to ethyl cinnamate	% starting material (**3a**)[b]
isobutyronitrile	40	22	78
THF	40	0	100
benzene	40	<1	100
ether	30	0	100
ethyl acetate	40	28	43 (28)[c]
acetonitrile	40	20	13 (66)[d]
pentane	30	<1	>99
isobutyronitrile	30	15	85
isobutyronitrile	50	24	76
ethyl acetate	50	36	42 (22)[c]

[a]Based on the aldehyde as estimated by ^{1}H NMR integration. [b]The quantities in parentheses represent side products as estimated by ^{1}H NMR integration.

[c]Conversion to β-hydroxy ester as estimated by ^{1}H NMR integration.

[d]Conversion to β-hydroxy nitrile as estimated by ^{1}H NMR integration.

Table 2. The reaction of esters with aldehydes in the presence of 1.06 equiv of **1a-c**[a]

starting materials	base	T °C / time (h)	% yield[b] (E/Z)[c] of product
3a + 2a	**1b**	40 / 2	96 (100:0)
3a + 2b	**1b**	40/2	91 (10:1)
3c + 2a	**1b**	40 / 2	95(100:0)
3c + 2b	**1b**	40 / 2	93 (9:1)
3d + 2a	**1b**	40 /6	73(5:3)
3d + 2b	**1b**	50 /6	40 (1:1)
3h + 2a	**1b**	30 /2	0[d]
3i + 2a	**1b**	30 /2	0[d]
3l + 2a	**1b**	40/2	67 (100:0)
3m + 2a	**1b**	40/6	0
3a + 2a	**1a**	40/ 2	83 (100:0)
3a + 2a	**1c**	40/2	94 (100:0)
3d + 2a	**1a**	40/2	61 (2:1)
3d + 2a	**1c**	40/2	75(9:4)

[a]The reactions were carried out in isobutyronitrile as solvent. [b]Isolated yield. [c]Determined by ^{1}H NMR integration. [d]None of the starting aldehyde was observed in the reaction mixture.

Table 3. Reactions of ethyl acetate (**2a**) with aldehydes in the presence of bases **1a-c**[a]

aldehyde	base	T °C/time (h)	% yield[b] of *E*-product
3a	**1b**[c]	50/6	30
3a	**1b**[d]	50 / 6	73
3a	**1b**	50 / 6	96
3b	**1b**	50 / 6	95
3c	**1b**	50 /6	98
3d	**1b**	50 /6	60
3e	**1b**	50 /6	91
3f	**1b**	50 /6	82
3g	**1b**	50 /6	95
3h	**1b**	30/4[e]	0
3i	**1b**	30/4[e]	0
3j	**1b**	50 /6	96
3k	**1b**	50 /6	96
3l	**1b**	50/6	88
3m	**1b**	50/18	0
3n	**1b**	50/6	98
3c	**1a**	40 /12	(89)[f]
3c	**1c**	40 /12	(82)[f]
3d	**1a**	40 /12	(50)[f]
3d	**1c**	40 /12	(55)[f]

Table 3 (continued)

[a]The amount of **1** used was 1.06 equiv unless stated otherwise. [b]Isolated yield after column chromatography. [c]The amount of **1b** used was 0.2 equiv. [d]The amount of **1b** used was 0.5 equiv. [e]All the aldehyde was consumed after 4 h with no detectable formation of the expected unsaturated esters. [f]Conversion as estimated by ^{1}H NMR spectroscopy integration.

Table 4. The reaction of methyl propionate **2b** with aldehydes in the presence of 1.2 equiv of **1b**

substrate	T (^{0}C) /time (h)	% yield of *E*-product
3a	50/6	93
3b	50/6	93[a]
3c	50/6	95
3d	50/6	68
3e	50/6	87
3f	50/6	88
3g	50/6	76
3h	40/4	0
3i	40/4	0
3j	50/6	83
3k	50/6	91
3l	50/6	64[a]
3m	50/18	0
3n	50/6	98

[a]A trace amount of the *Z*-isomer was observed but was not separated from the major *E*-isomer.

Table 5. Synthesis of coumarins in the presence of 5 mol % of **1a** or **1b**

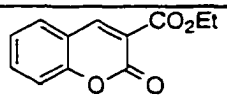
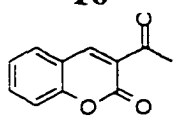
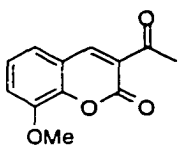
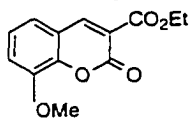
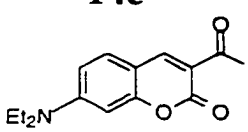
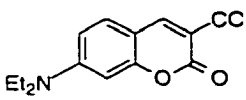
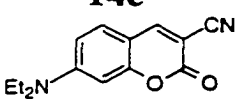
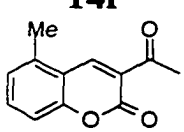
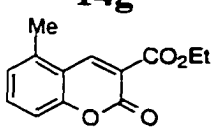
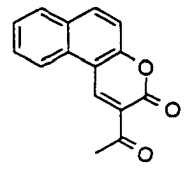
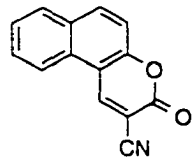
product	neat % yield[a]		% yield in EtOH[b]		mp °C (recry. solvent)	literature mp °C	literature NMR data
	1a	**1b**	**1a**	**1b**			
 **10**	81	85	95[c]	93[c]	93 (Et_2O)	93-94[42]	^1H NMR[42]
 **14a**	89	87	83	90	121-123 (EtOH)	124[41]	^1H NMR[41]
 **14b**	85	92	87	90	170-172 (EtOH)	173-174[44]	–[d]
 **14c**	92	89	90	94	90-91 (Et_2O)	88-90[44]	–[d]
 **14d**	80	77	81	76	150-152 (EtOH)	151-153[45]	^1H NMR[45]
 **14e**	83	82	78	88	75-77 (Et_2O)	77-78[46]	^{1}HNMR[46]
 **14f**	79	87	75	81	228-229 (MeCN)	229[45]	^1H NMR[45]
 **14g**	93	90	94	95	115-116 (EtOH)	115[47]	–[d]
 **14h**	88	95	94	90	120-121 (Et_2O)	122-122.5[47]	–[d]

Table 5 (continued)

 **14i**	79	87	80[c]	85[c]	187-188 (DMSO)	190[45]	^{1}H NMR[45]
 **14j**	93	90	95	96	294-296 (DMSO)	298-299[48]	^{1}H NMR[48]

[a]The reaction time was 7 h. [b]The reaction time was 3 h unless stated otherwise. [c]The reaction time was 4 h. [d]No NMR data are reported (see Supporting Information).

Supporting Information

^{1}H NMR and ^{13}C NMR spectral data with peak Assignments

4a: The ^{1}H NMR spectrum compared favorably with that reported in *Tetrahedron Lett.* **1997**, *37*, 1947. The ^{13}C NMR spectrum compared favorably to that reported in *J. Org. Chem.* **1986**, *52* , 3535.

4b: The ^{1}H NMR spectrum compared favorably to that reported in *Aust. J. Chem.* **1982**, *35*, 729. The ^{13}C NMR spectrum compared favorably to that reported in *Can. J. Chem.* **1969**, *47*, 3137.

4c: The ^{1}H NMR spectrum compared favorably to that reported in *Aus. J. Chem.* **1982**, *35*, 729. ^{13}C NMR ($CDCl_3$): δ 166.7, 143.1, 136.1, 133.0, 129.2, 129.1, 118.9, 60.6, 14.3.

4d: The ^{1}H NMR spectrum compared favorably to that reported in *Synth. Commun.* **1988**, 1349. The ^{13}C NMR compared favorably to that reported in *Acta Chem. Scand., Ser. B.* **1981**, *35*, 419.

4e: The ^{1}H NMR spectrum compared favorably to that reported in *Can. J. Chem.* **1969**, *47*, 3137. The ^{13}C NMR spectrum compared favorably to that reported in *J. Org. Chem.* **1986**, *52*, 3535.

4f: The ^{1}H NMR spectrum compared favorably to that reported in *Can. J. Chem.* **1969**, *47*, 3137. The ^{13}C NMR spectrum compared favorably to that reported in *Acta Chem. Scand., Ser. B.* **1981**, 419.

4g: The ^{1}H NMR spectrum compared favorably to that reported in *Can. J. Chem.* **1969**, *47*, 3137. The ^{13}C NMR spectrum compared favorably to that reported in *Acta Chem. Scand. Ser. B.* **1981**, *35*, 419.

4j: The ^{1}H NMR spectrum compared favorably to that reported in *J. Org. Chem.* **1995**, *60*, 8360. The ^{13}C NMR spectrum compared favorably to that reported in *Synthesis* **1988**, 534.

4k: ^{1}H NMR ($CDCl_3$): δ 7.91 (s, 1H), 7.80-7.86 (overlapping region, 4H), 7.65 (dd, 1H, J = 8.4, J = 2), 7.49 (m, 2H), 6.52 (d, 1H, J = 16), 4.29 (q, 2H), 1.353 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 167.0, 144.6, 134.2, 133.2, 131.9, 129.9, 128.6, 128.5, 127.7, 127.15, 126.6, 123.4, 118.4, 60.5, 14.3.

4l: ^{1}H NMR ($CDCl_3$): δ 7.44-7.49 (m, 3H), 7.31-7.40 (m, 3H), 6.80-7.30 (overlapping region, 2H), 5.98 (d, 1H, J = 15.3), 5.23 (q, 2H), 1.33 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 167.1, 144.6, 140.4, 136.0, 129.0, 128.8, 127.2, 126.2, 121.3, 60.4, 14.3.

4n: The ^{1}H NMR spectrum compared favorably with that reported in *Tetrahedron* **1991**, *47*, 8443. The ^{13}C NMR spectrum compared favorably with that reported in *Tetrahedron* **1989**, *45*, 4103.

5a: The ^{1}H NMR spectrum compared favorably with that reported in *Tetrahedron* **1996**, *52*, 12313. ^{13}C NMR ($CDCl_3$): δ 169.2, 139.0, 135.9, 129.7, 128.4, 128.3, 128.3, 52.1, 14.1.

5b: ^{1}H NMR ($CDCl_3$): δ 7.64 (s, 1H), 7.37 (dd, 2H, J = 5.4 Hz, J = 8.4 Hz), 7.05-7.11 (overlapping region, 2H), 3.82 (s, 3H), 2.1 (d, 3H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$): δ 169.1, 164.2, 160.0, 137.8, 131.6, 115.5 (d, J = 21 Hz), 52.1, 14.0.

5c: The ^{1}H NMR spectrum compared favorably with that reported in *J. Org. Chem.* **1974**, *40*, 3866. ^{13}C NMR ($CDCl_3$): δ 168.9, 137.6, 134.3, 134.2, 130.9, 128.9, 128.7, 52.2, 14.1.

5d: Both of these spectra compared favorably with that reported in *Indian J. Chem.* **1992**, 613.

5e: ^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.29 (AB q, 2H), 6.90-6.97 (overlapping region, 2H), 3.85 (s, 3H), 3.81 (d, 3H, J = 1.5 Hz), 2.05 (d, 3H, J = 1.5 Hz). ^{13}C NMR ($CDCl_3$): δ 169.1, 157.6, 134.9, 130.2, 129.8, 128.3, 124.8, 120.1, 110.5, 55.5, 52.0, 14.2.

5f: ^{1}H NMR ($CDCl_3$): δ 7.80 (s, 1H), 6.83-6.86 (overlapping region, 3H), 3.76-3.81 (overlapping region, 6H), 3.73 (s, 3H), 2.06 (d, 3H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$): δ 169.0, 153.0, 152.0, 134.7, 128.7, 125.6, 116.1, 114.3, 111.5, 56.0, 55.8, 52.0, 14.3. HRMS: Calcd for $C_{13}H_{16}O_4$ 236.10490, found *m/e* (M^+) 236.10509.

5g: ^{1}H NMR ($CDCl_3$): δ 7.73 (s, 1H), 7.09(d, 1H), 7.01-7.04 (overlapping region, 2H), 3.82 (s, 3H), 2.32 (s, 3H), 2.23 (s, 3H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 169.0, 138.6, 135.0, 134.9, 133.7, 130.0, 128.9,

5l: ^{1}H NMR ($CDCl_3$): δ 7.48 (d, 4H), 7.28-7.46 (overlapping region, 4H), 7.05 (t, 1H), 6.85 (d, 1H, J = 15.6 Hz). ^{13}C NMR ($CDCl_3$): δ 168.8, 139.1, 138.5, 136.6, 128.8, 128.7, 128.6, 127.1, 127.1, 123.9, 51.9, 12.9. HRMS: Calcd for $C_{15}H_{14}O_2$ 226.0994, found *m/e* (M^+) 226.0992 Anal. Calcd for $C_{15}H_{14}O_2$ C, 79.61; H, 6.24. Found: C, 79.59: H, 6.24.

5n: ^{1}H NMR ($CDCl_3$): δ 7.86 (s, 1H), 7.48 (d, 1H), 7.27 (d, 1H), 7.11 (dd, 1H), 3.81 (s, 3H), 2.21 (d, 3H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$): δ 169.0, 139.2, 131.7, 129.2, 127.3, 124.6, 52.1, 14.3.

9a: The ^{1}H and ^{13}C NMR spectra compared favorably to those reported in *J. Chem. Res. (Synopsis)* **1997**, 296.

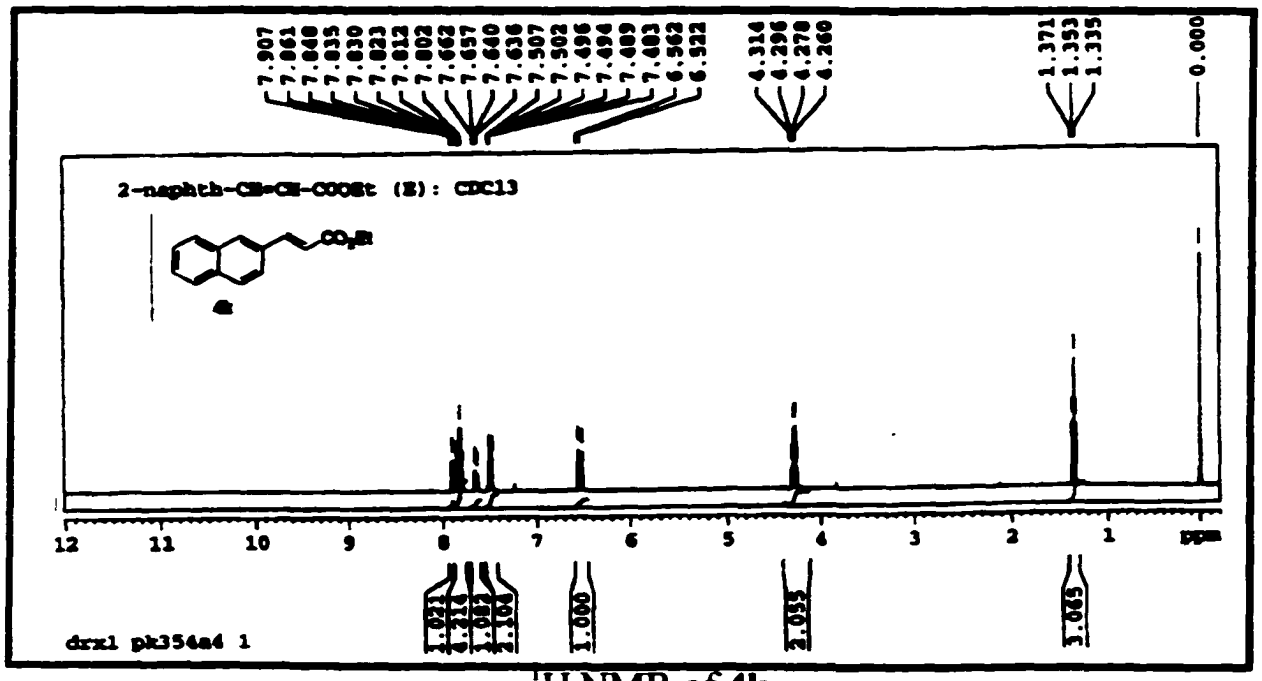
9b: The ^{1}H and ^{13}C NMR spectra compared favorably to those reported in *J. Chem. Res. (Synopsis)* **1997**, 296.

14b: ^{1}H NMR (DMSO-d_6): δ 8.48 (s, 1H), 7.17-7.30 (overlapping area, 3H), 3.99 (s, 3H), 2.73 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 195.7, 159.1, 153.3, 147.5, 136.0, 134.8, 130.7, 124.8, 118.4, 116.4, 30.6, 20.7.

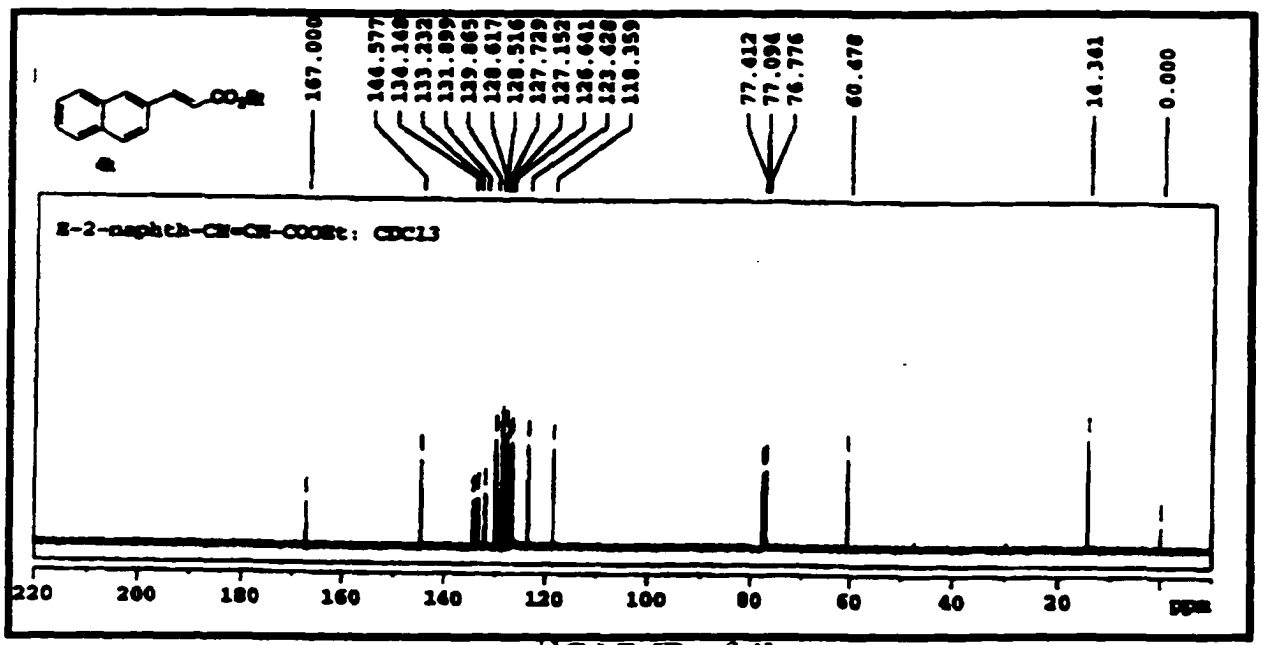
14c: ^{1}H NMR ($CDCl_3$): δ 8.50 (s, 1H), 7.16-7.29 (overlapping region, 3H), 4.41 (q, 2H), 3.97 (s, 3H), 1.408 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 165.2, 163.5, 157.6, 157.2, 149.0, 130.8, 114.2, 113.7, 111.7, 100.4, 61.8, 56.1, 14.4.

14f: ^{1}H NMR (DMSO-d_6): δ 8.46 (s, 1H), 7.43-7.48 (overlapping region, 2H), 7.26 (dd, 1H), 2.73 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 195.7, 159.1, 153.3, 147.5, 135.0, 134.8, 130.7, 124.9, 118.4, 116.4, 30.6, 20.7.

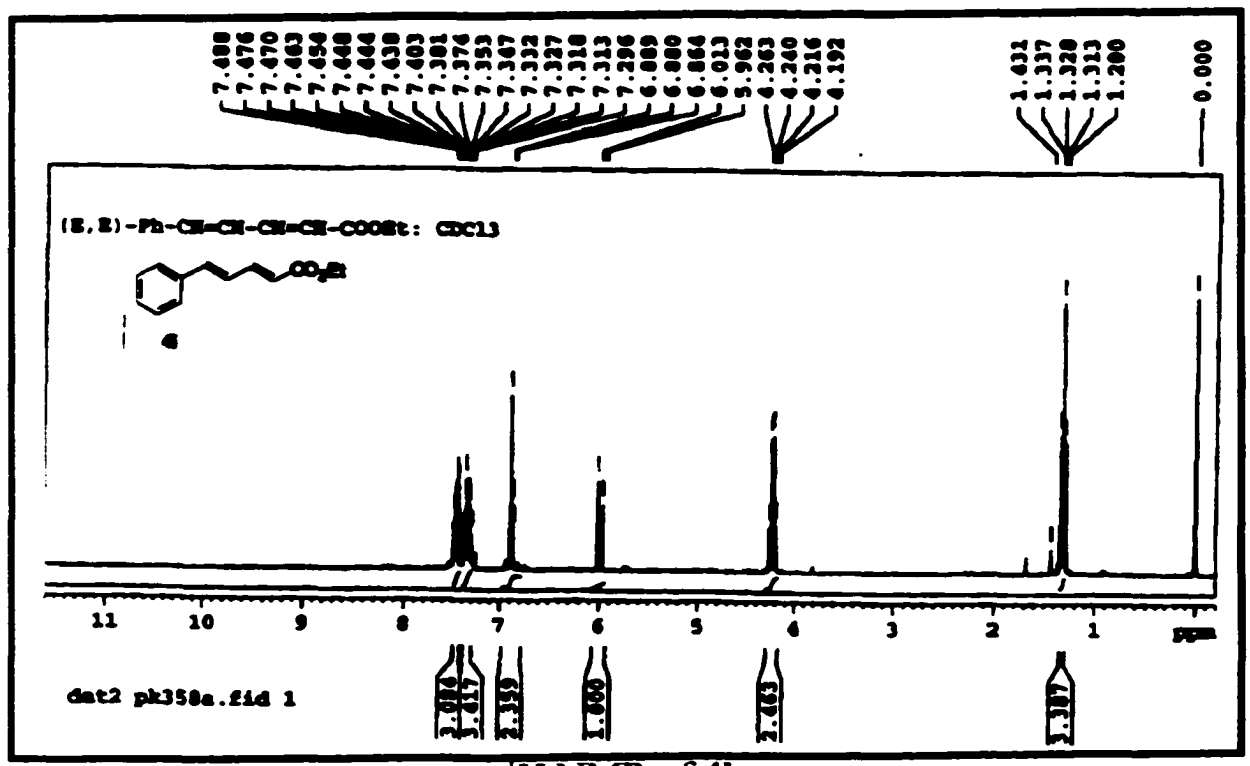
14h: ^{1}H NMR ($CDCl_3$): δ 8.48 (s, 1H), 7.39-7.46 (overlapping region, 2H), 7.44 (d, 1H), 4.41 (q, 2H), 2.43 (s, 3H), 1.41 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 163.2, 157.0, 153.4, 148.7, 135.6, 134.7, 129.2, 118.1, 117.7, 116.5, 61.9, 20.7, 14.3.



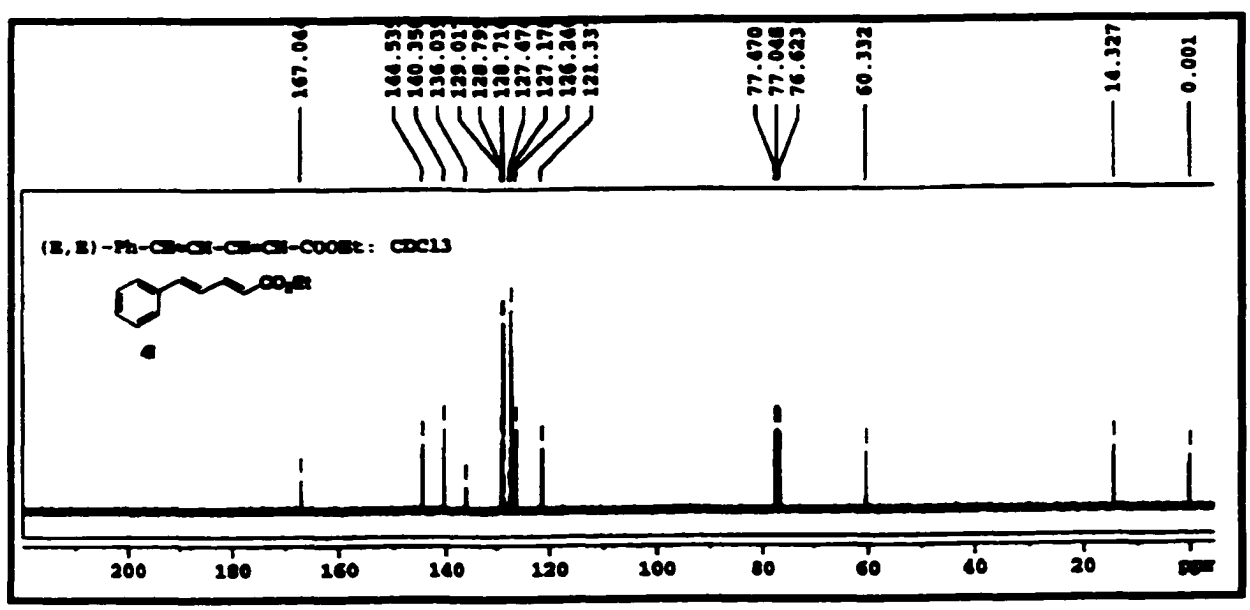
^{1}H NMR of 4k



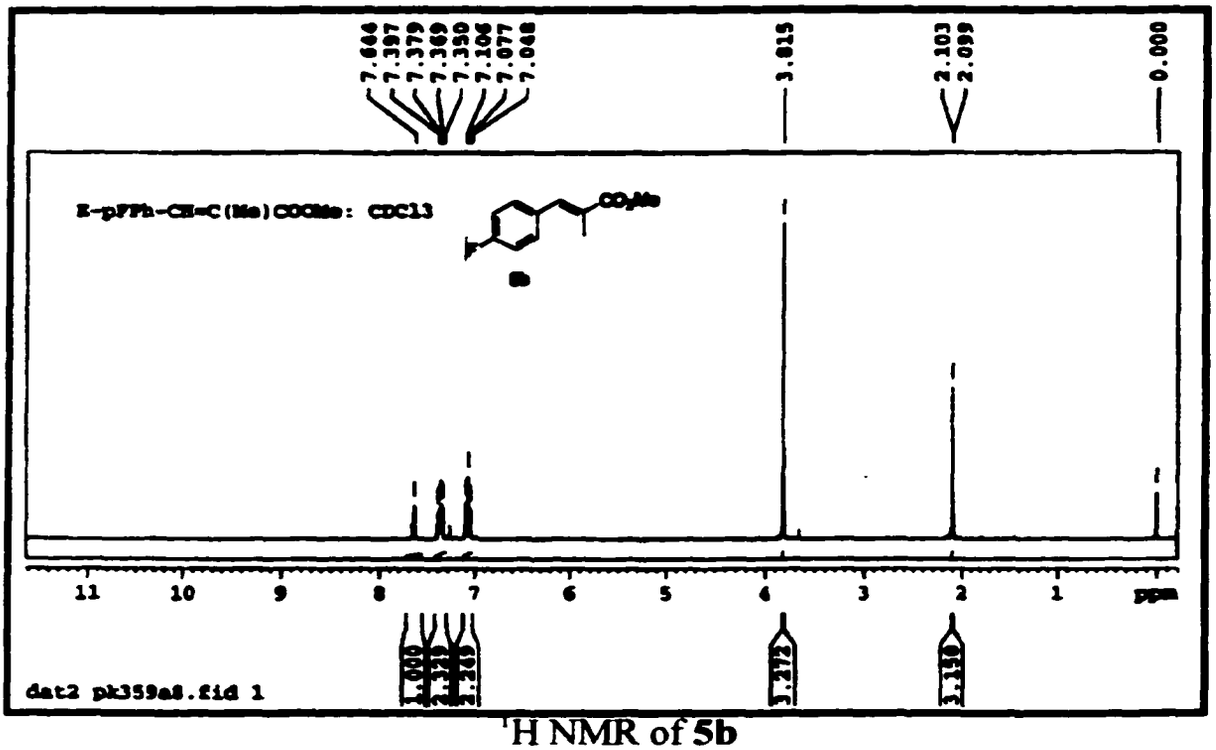
^{13}C NMR of 4k



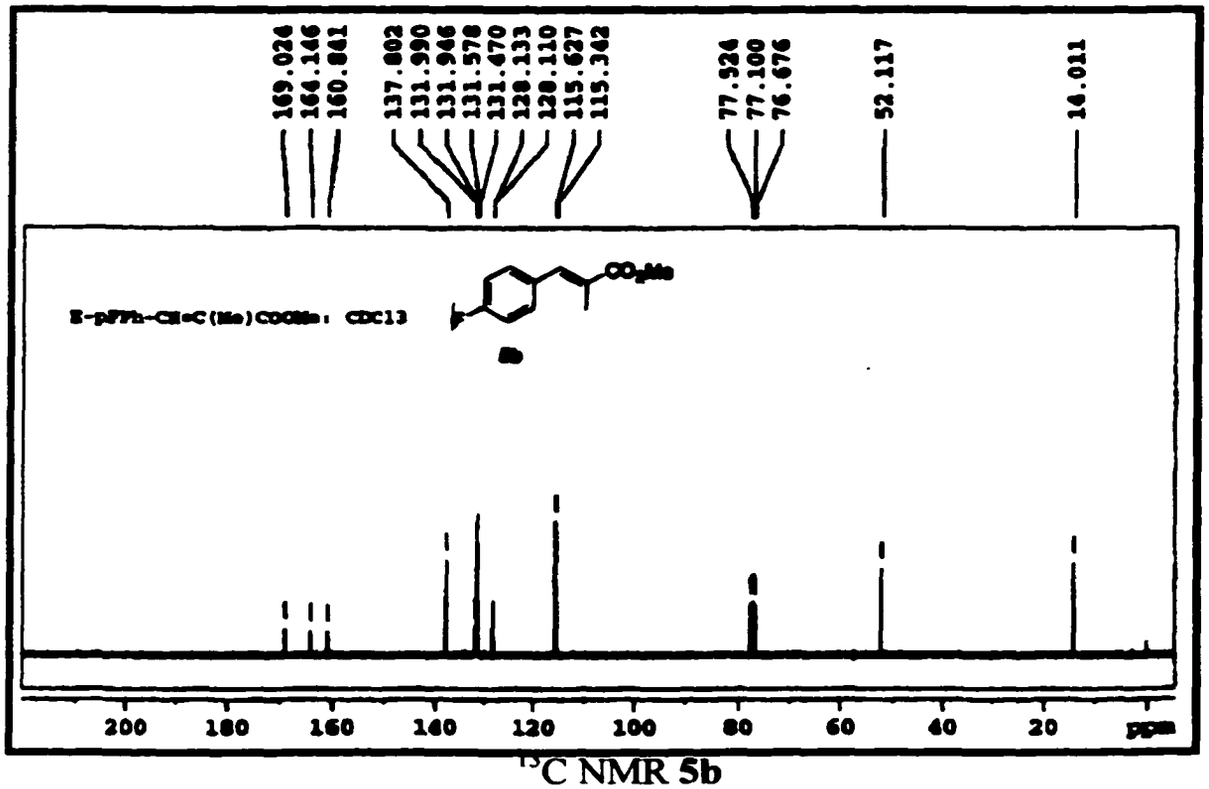
^{1}H NMR of **4l**



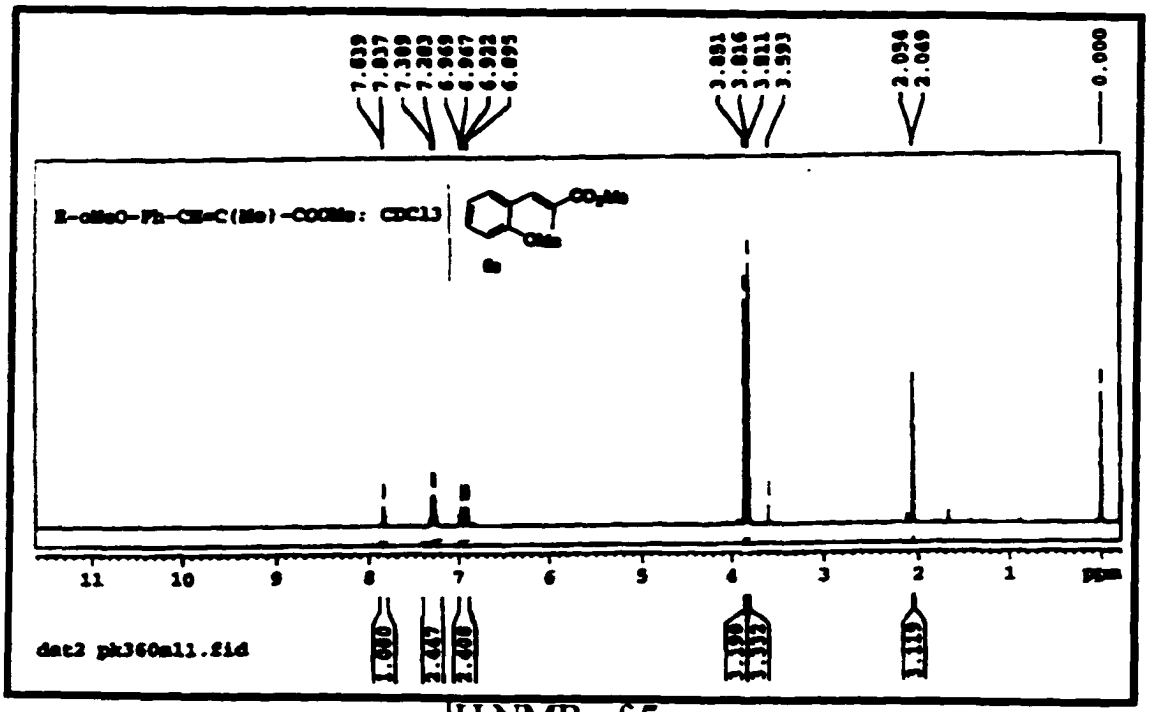
^{13}C NMR of **4l**



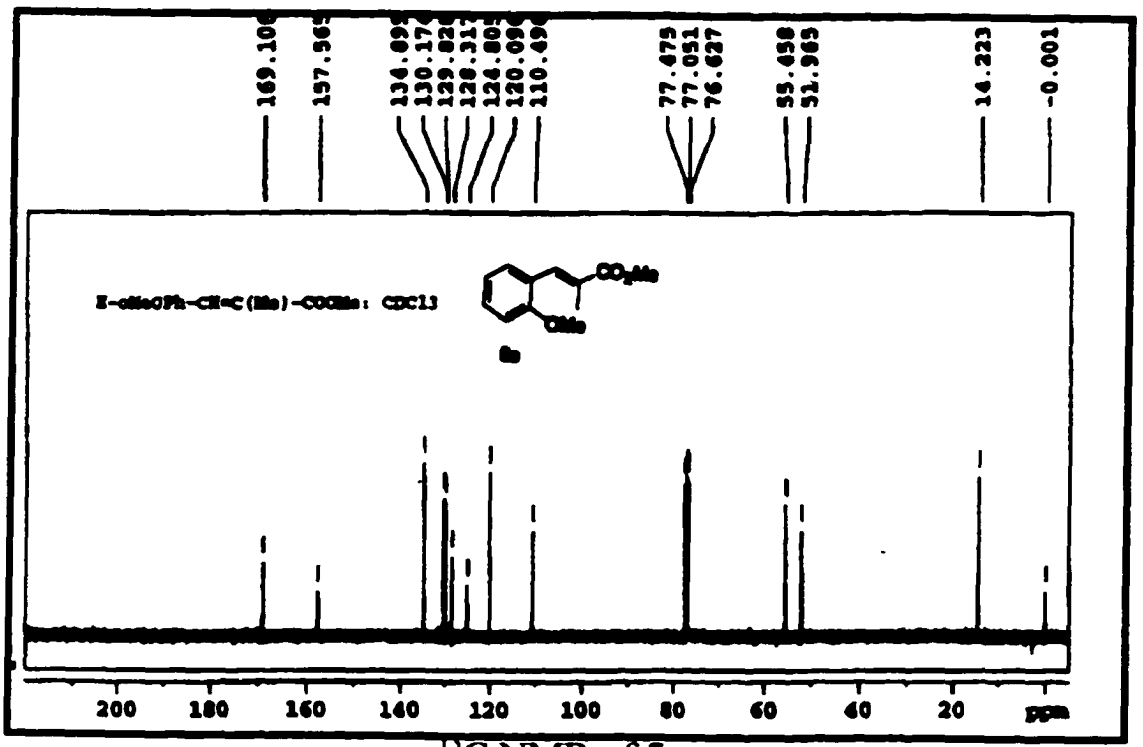
^{1}H NMR of **5b**



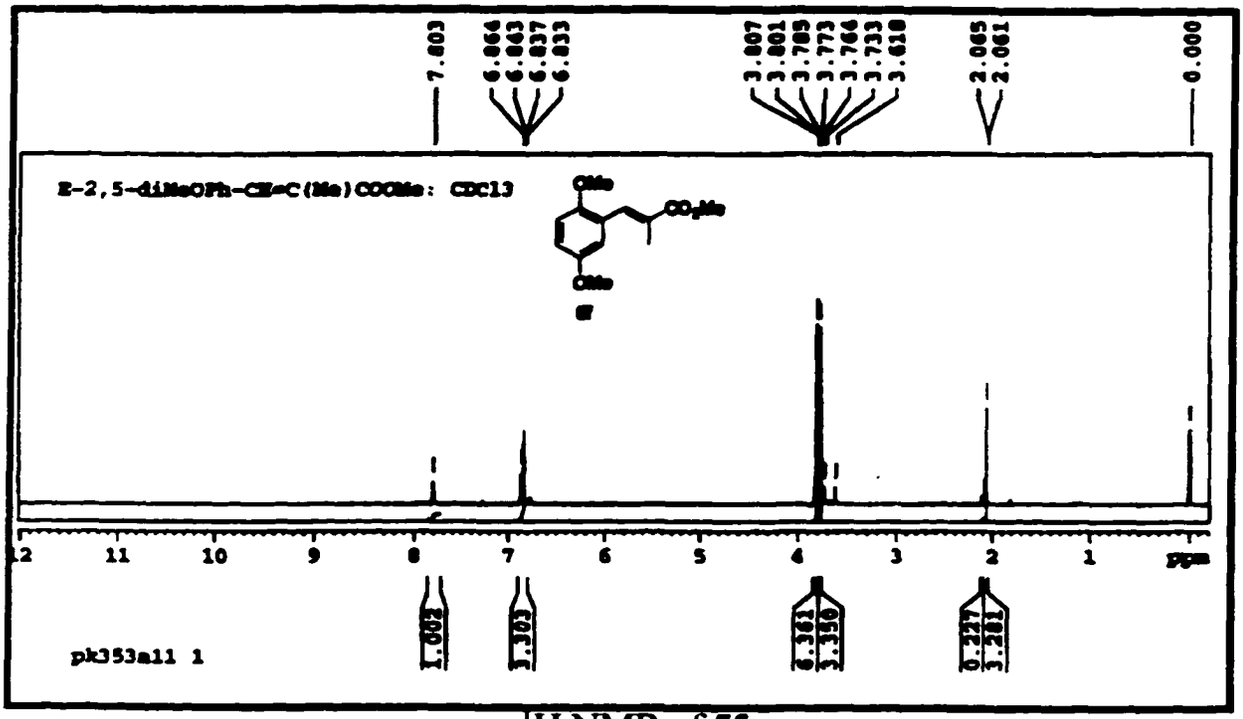
^{13}C NMR **5b**



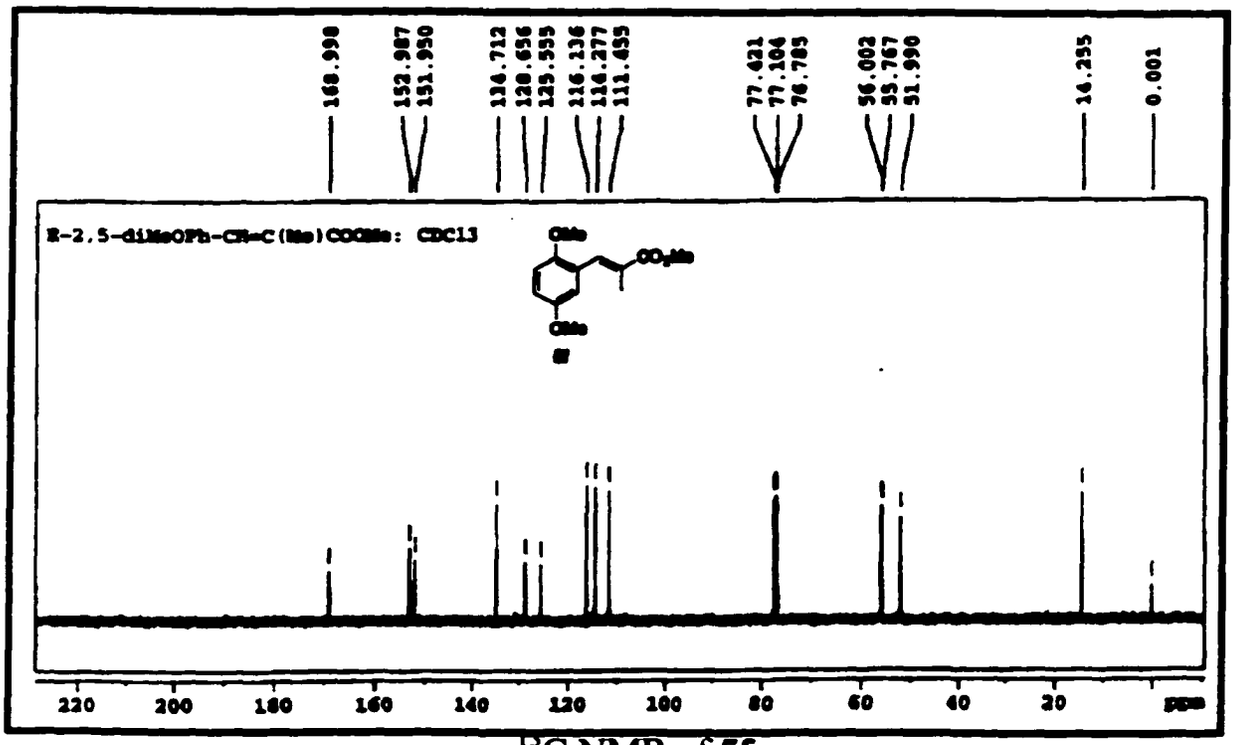
^{1}H NMR of 5e



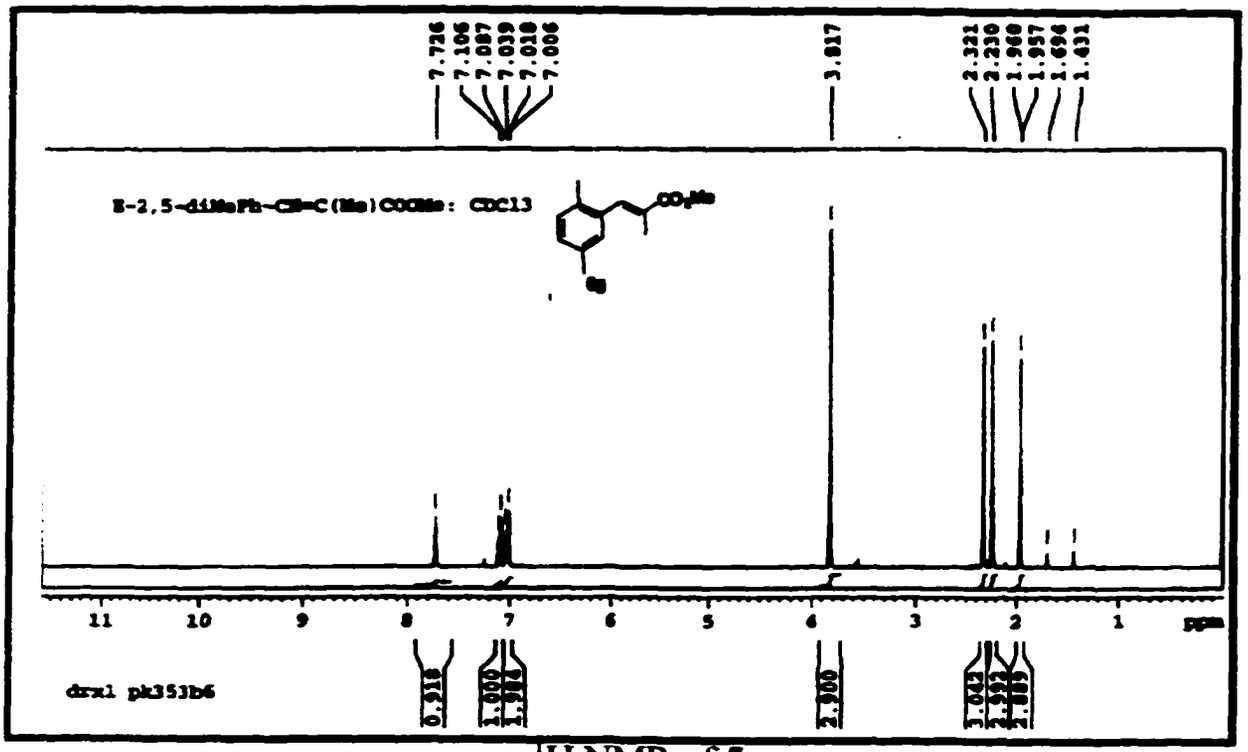
^{13}C NMR of 5e



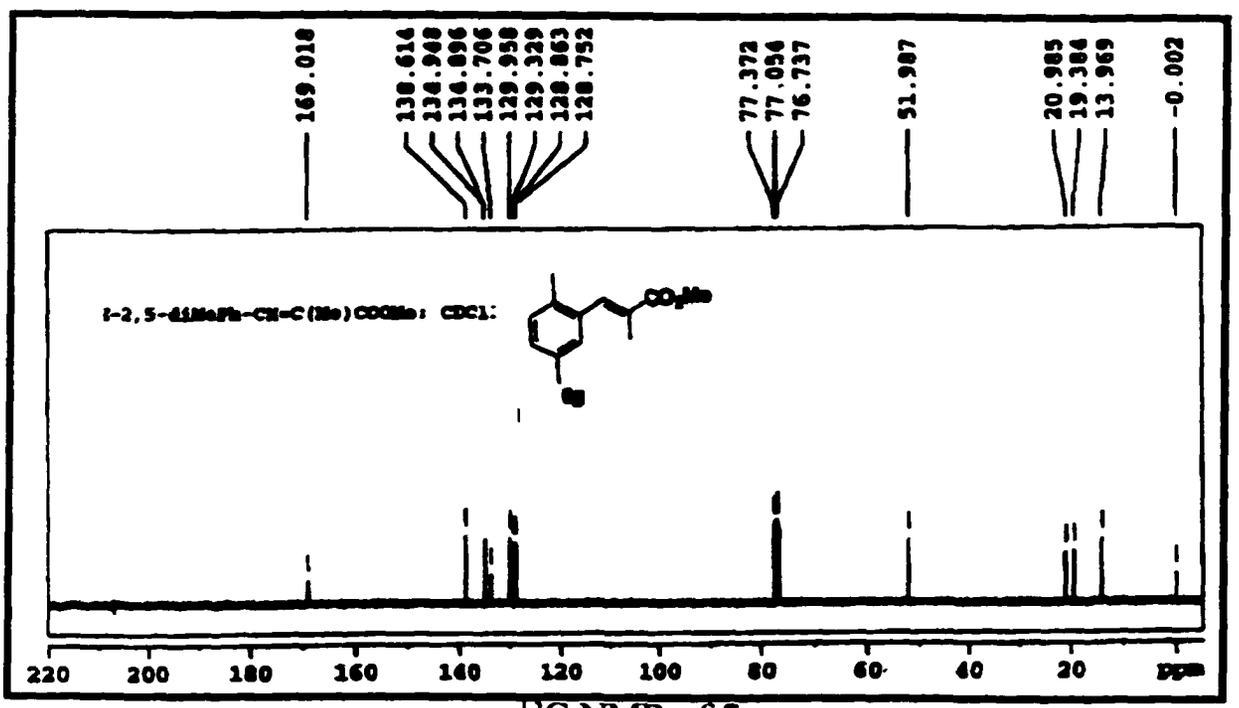
^{1}H NMR of **5f**



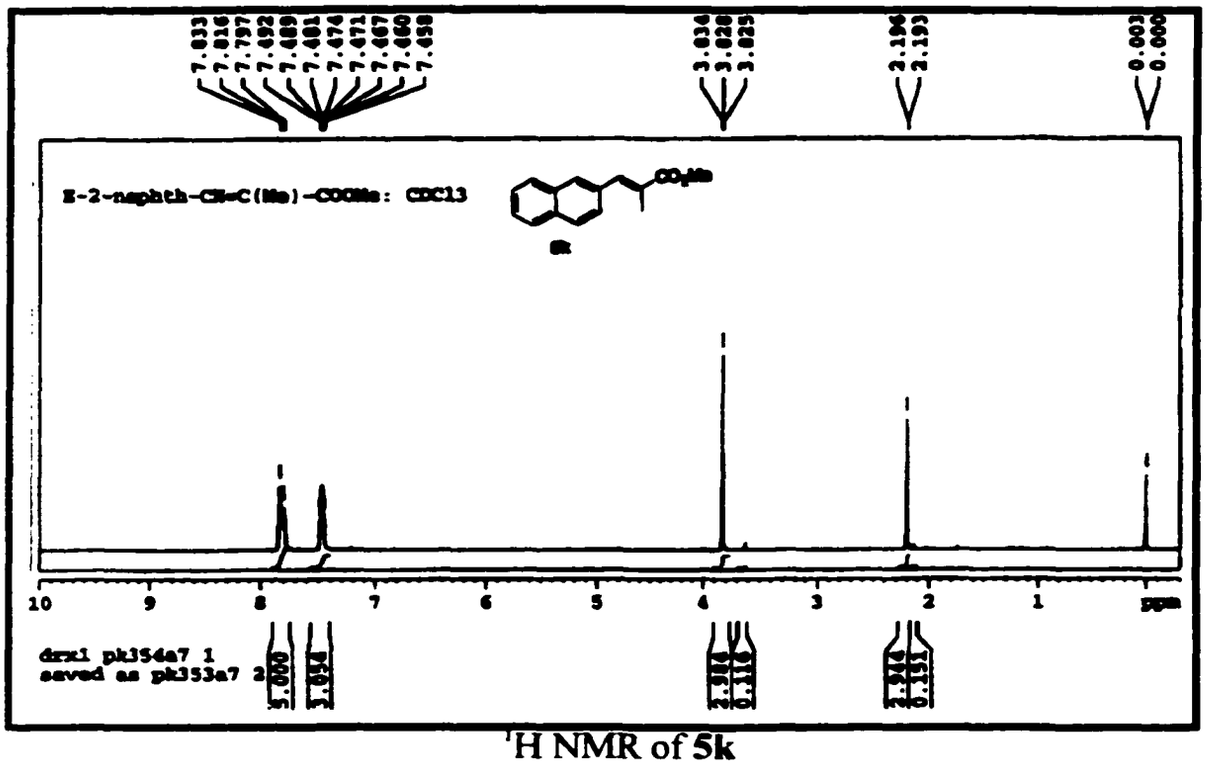
^{13}C NMR of **5f**



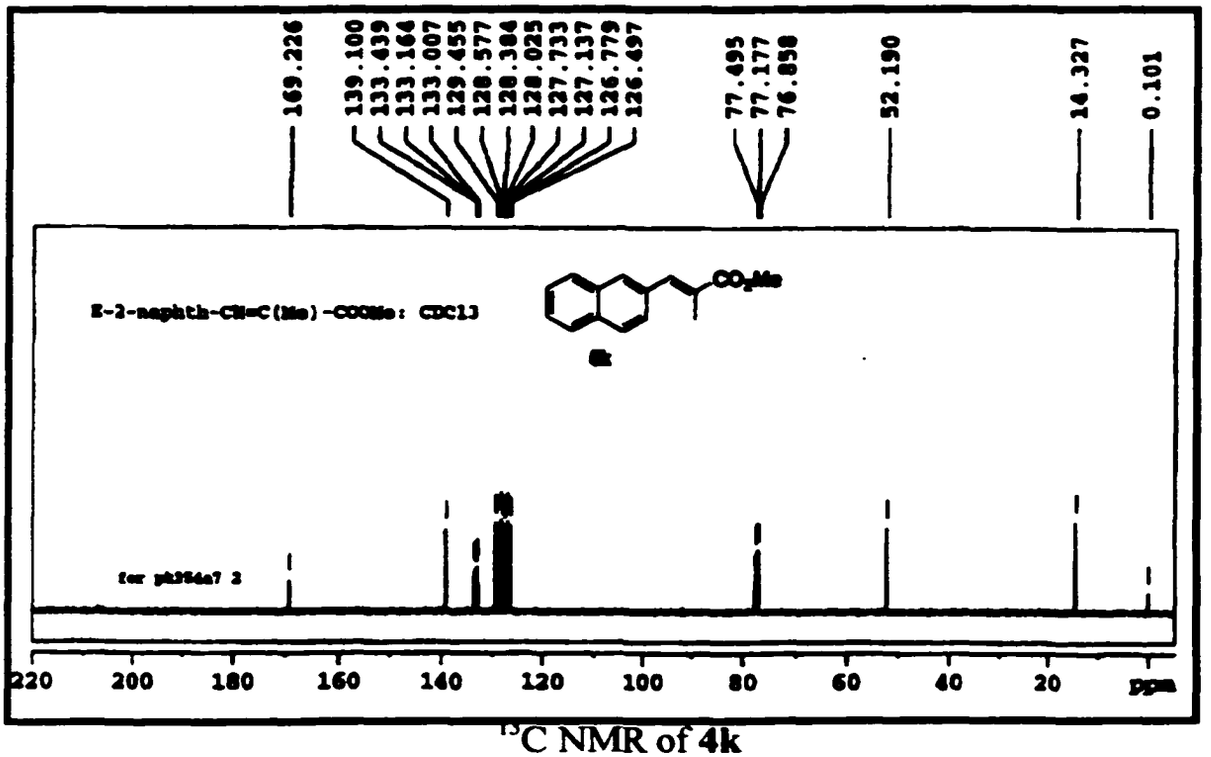
^{1}H NMR of 5g



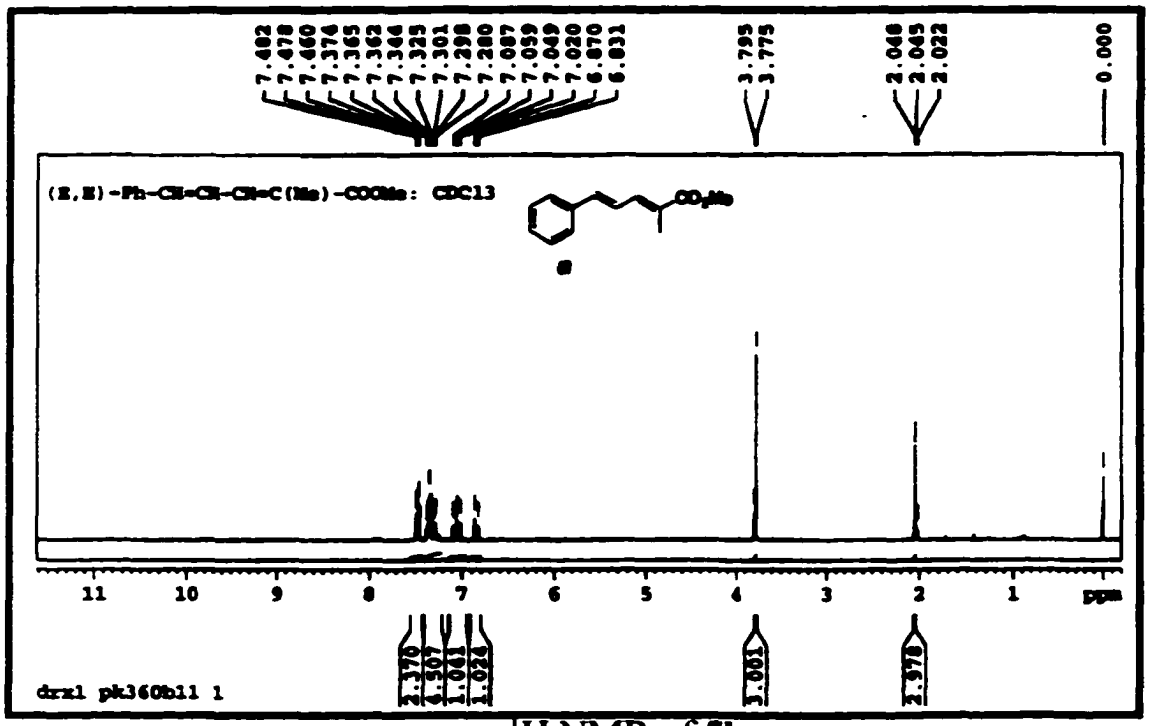
^{13}C NMR of 5g



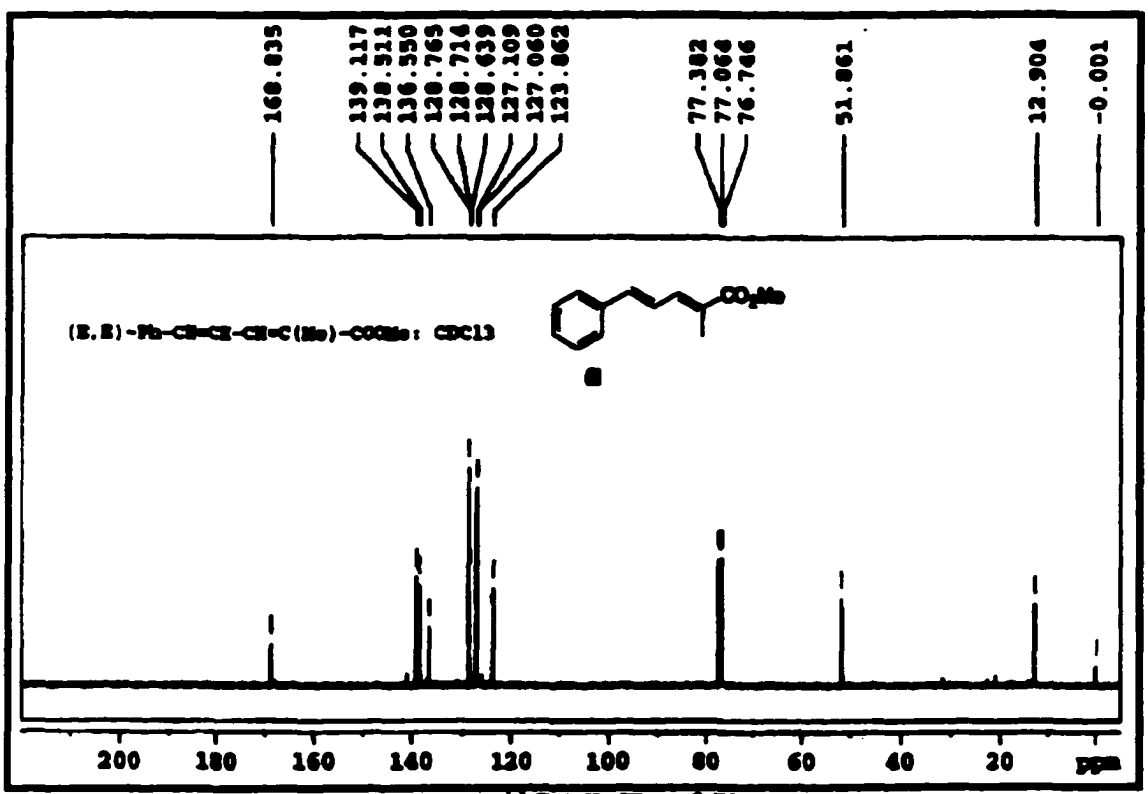
^{1}H NMR of **5k**



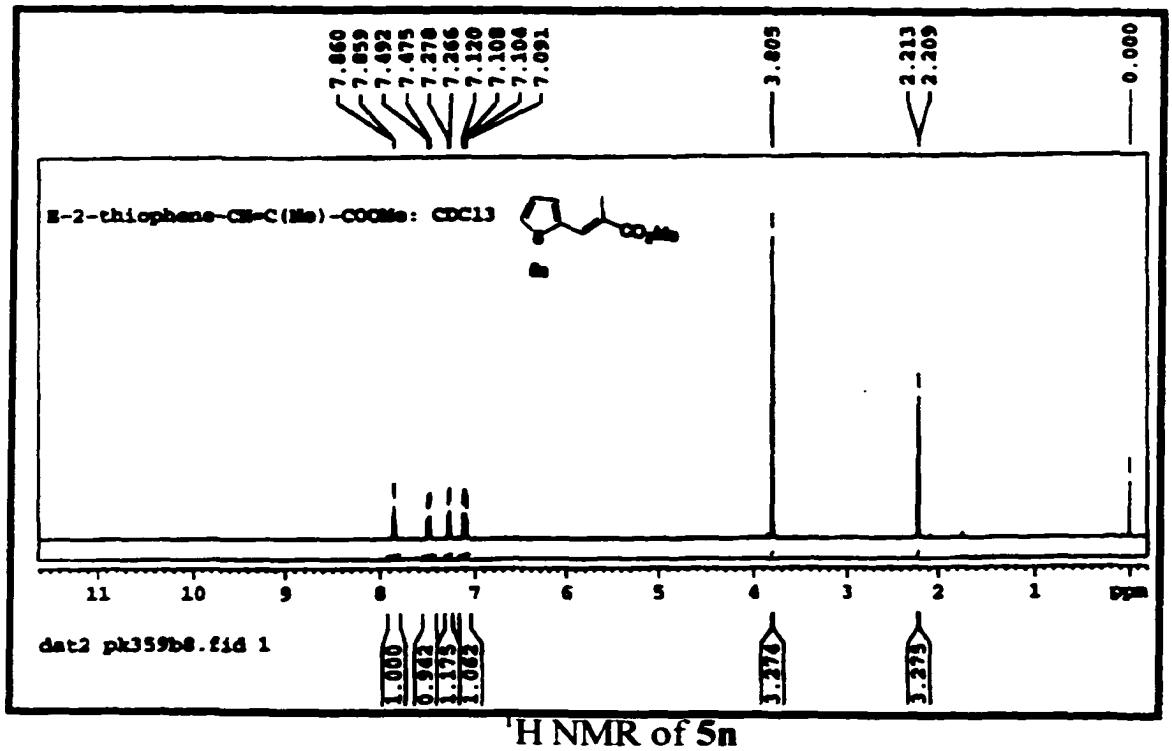
^{13}C NMR of **4k**



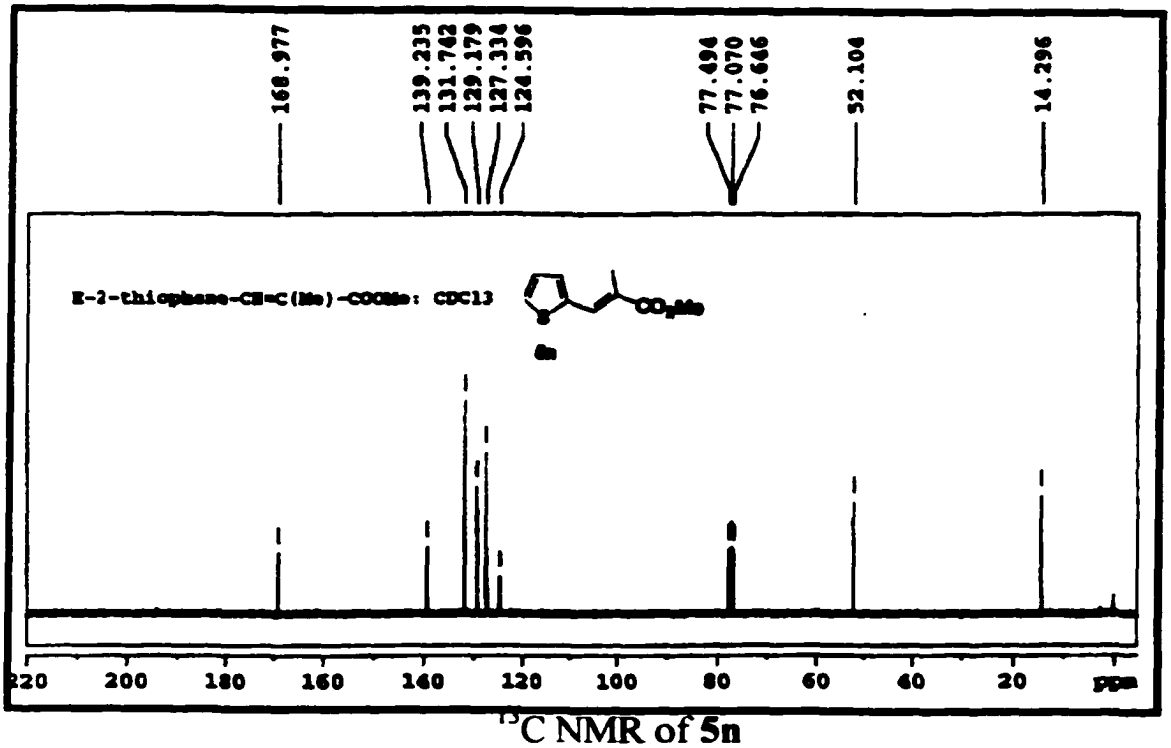
^{1}H NMR of 5l



^{13}C NMR of 5l



^{1}H NMR of **5n**



^{13}C NMR of **5n**

CHAPTER 8

$P(RNCH_2CH_2)_3N$: EFFICIENT 1,4-ADDITION CATALYSTS

A paper to be submitted to the Journal of Organic Chemistry

Philip B. Kisanga,[a,b] Palanichamy Ilankumaran[c] and John G. Verkade[a,d]

Abstract

The 1,4-addition of alcohols, nitroalkanes and imines (derived from α-amino esters) to α,β-unsaturated compounds has been achieved in moderate to excellent yields. These reactions proceed at room temperature in the presence of catalytic amounts of the nonionic strong bases $P(RNCH_2CH_2)_3N$ (R = Me, *i*-Pr, *i*-Bu) in isobutyronitrile. The catalytic amount of base used is easily removed from the product by either column filtration through silica gel or through aqueous work-up.

Introduction

Michael addition is one of the most efficient and effective methods for the formation of C-C bonds.[1] This reaction has wide applications in organic

[a] Graduate student and University Professor, respectively, Department of Chemistry, Iowa State University.
[b] Primary researcher and author.
[c] Postdoctoral research associate, Department of Chemistry, Iowa State University.
[d] Author for correspondence.

synthesis[2] and several new versions of the reaction have recently been introduced.[3] The Michael addition reaction of electron deficient alkenes has been used to produce difunctionalized compounds which have been used extensively in organic synthesis.[2] 1,5-Diketones (prepared by the Michael addition of α-nitroketones to α,β-unsaturated ketones)[4] are used to prepare 2-cyclohexenones[5] and 3-nitroketones can be reduced to 3-aminoketones.[1,6] The nitro group can be denitrated[7] giving rise to β-alkyl subsitution of the starting carbonyl compounds.

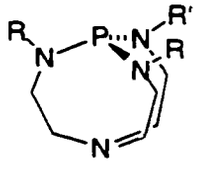
The commonly used anionic alkyl synthons for Michael addition are those derived from nitroalkanes,[8] ethyl cyanocarboxylates,[9] and malonates.[10] Although these types of Michael donors have been extensively studied, and their limitations (such as double additions,[11] requirement of large excess of the nitroalkane,[12] restriction in the type of Michael acceptors allowed,[13] and the low to moderate yields encountered[9a,10b]) have been largely overcome by newer methodologies, such approaches are by no means devoid of drawbacks. Among recent developments are the use of Amberlyst A-27[14] and sodium hydroxide solution in the presence of cetyltrimethylammonium chloride (CTACl) as a cationic surfactant.[15] However, the Amberlyst A-27[14] process requires reaction times ranging from 4 hours (for MVK) to 25 hours for the reactions of higher

nitroalkanes with β-substituted methyl vinyl ketones. The sodium hydroxide process[15] affords only modest yields in the reaction of secondary nitroalkanes even with MVK.[15] The yields in both processes range from moderate to high for most substrates. The Michael addition reactions of higher nitroalkanes to α,β-unsaturated carbonyl compounds generally proceed over lengthy reaction times and the yields are only moderate. Although reactions employing alumina are rapid, four equivalents of the rather expensive nitroalkanes are required.[7b] Oxa-Michael addition reactions are rare despite the fact that such transformations produce protected β-hydroxy carbonyl compounds that are of significant importance in organic synthesis.[16a] The few reports that exist include descriptions of UV irradiation of cycloalkenones in methanol[16b] to produce the β-methoxy cyclic ketones; reactions promoted by NaOMe,[17a] KH,[17b] and potassium *t*-butoxide;[17c] and cynoethylation of alcohols by a Mg-Al hydrotalcite prepared in a process requiring 450 °C for up to 12 hours.[18a] Several other catalysts have also been used for the cyanoethylation of alcohols but their utilities have not been extended to other α,β-unsaturated compounds.[18b,c] Recently, vanadium complexes have been reported to induce hydroalkoxylation of α,β-unsaturated ketones and epoxides.[19] However, the use of transition metals introduce environmental concerns. To our knowledge,

no general reaction has been reported in which β-alkoxy ketones can be prepared through a Michael addition reaction.

The Michael addition reaction of the imines of α-amino esters have long been known to be a convenient method for functionalizing α-amino esters at the α-position.[20] However, this reaction has a propensity to undergo a competing cycloaddition.[20b] The ratio of Michael addition to cycloaddition product has been found to depend upon the metal ions used to chelate the enolate produced upon deprotonation. Although the use of DBU has been found to lead to the production of α-functionalized α-amino esters as the exclusive product,[21] this reaction requires a stoichiometric amount of LiBr which provides the chelating cation. Also, worth mentioning is the fact that a weaker base such as triethylamine produces only the cycloadduct even in the presence of LiBr.[22]

We have previously reported that **1a**,[23a] **1b**,[23b] and **1c**[23c] are strong bases for the deprotonation of activated methyl and methylene groups. Thus, they



	R	R'
1a	Me	Me
1b	*i*-Pr	*i*-Pr
1c	H	*i*-Pr
1d	*i*-Bu	*i*-Bu

deprotonate nitroalkanes, acetonitrile, alkyl halides and carboxylic acid esters leading to the preparation of nitroalcohols,[24] α,β-unsaturated nitriles,[25] β-

hydroxy nitriles,[26] glutatonitriles,[27] alkenes[28] and α,β-unsaturated esters,[29] for example.

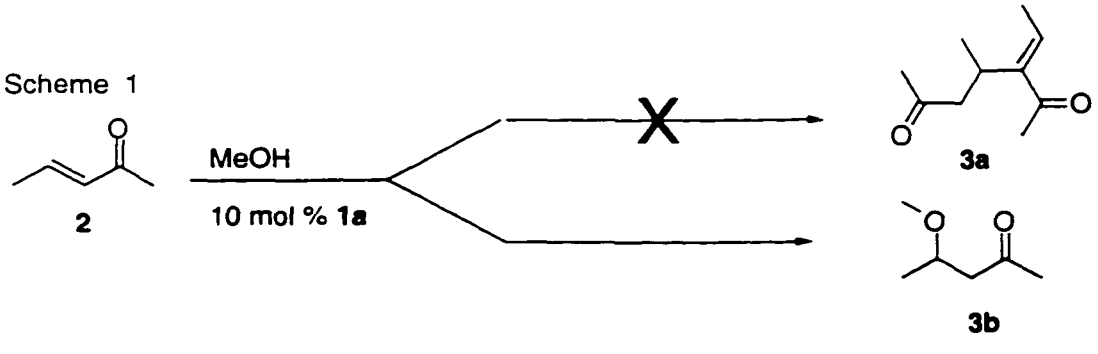
We report herein the use of the nonionic proazaphosphatranes **1a-1c**[23] and the most recently synthesized member of this family **1d**[30] as catalysts for three types of Michael addition reactions. We also report that these catalysts effect the hydroalkoxylation of α,β-unsaturated ketones in a superior manner. Finally, we report that proazaphosphatranes are superior catalysts for the Michael addition of imines derived from α-amino esters, in the absence of any metal ion.

Results and Discussion

Hydroalkoxylation of α,β -unsaturated compounds

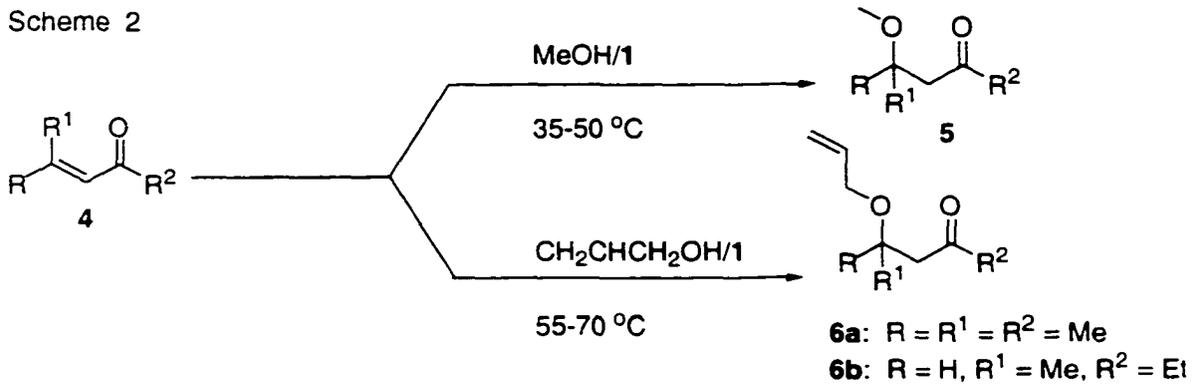
We observed the first Michael addition reaction promoted by bases of type **1** when we attempted to dimerize 3-penten-2-one (**2**) in the presence of 10 mol % of **1a** in methanol (Scheme 1). Although none of the expected dimer

Scheme 1



(**3a**) was observed, we were able to isolate 20-30% of the corresponding β-methoxy ketone (**3b**) Scheme 1. When the reaction was repeated with MVK (**4a**) and with 2-cyclohexen-1-one (**4b**), we were also able to isolate the corresponding β-methoxy compounds in 33 and 24 % yield, respectively (Scheme 2). Both **1a** and **1b** afforded similar yields within experimental error. However, the protonation of these proazaphosphatranes is incomplete in alcohols at room temperature[23a,29] and hydroalkoxylation reactions involving 10 mol % of **1a** or **1b** at this temperature led to substantial substrate oligomerization with only 20-30% of hydroalkoxylation product observed. The

Scheme 2



a: R = R¹ = H, R² = Me

b: R = H, R¹, R² = $(CH_2)_3$

c: R = R¹ = R² = Me

d: R = H, R¹ = Me, R² = Et

e: R = R¹ = H, R² = OMe

f: R = H, R¹ = Me, R² = OEt

g: R = H, R¹ = Ph, R² = Me

h: R = H, R¹ = CO_2Me, R² = OMe

i: R = H, R¹ = Me, R² = OMe

remaining reaction product was not recovered upon column chormatography. At 50 °C all of proazaphosphatrane (**1a** and **1b**) is protonated and substantial hydromethoxylation of MVK occurred in 10-15 minutes. However, additional hydromethoxylation occurred over an additional 15 minutes to afford the corresponding β-methoxy ketone in 65% yield. The less stable base **1c** afforded a relatively lower yield (52-61%) probably due to its oligomerization. Because of its low boiling point (38 °C) MVK was added to the warm reaction mixture in a septum-sealed tube whose contents were stirred at 50 °C for 10 min followed by stirring at room temperature for an additional 20 min. When 15 mol % of **1d** was used as the base, an excellent yield to the desired product was obtained with MVK over 24 h (Table 1). Repetition of this reaction with **1a** and with **1b** resulted in the isolation of only trace amounts of the product after column chromatography. Higher alcohols such as *t*-butyl alcohol and 2-propanol were found to be unable to add to 3-penten-2-one (**2**), 2-cyclohexen-1-one (**4b**) or 4-hexen-3-one (**4d**) when reacted at 50–70 °C in the presence of up to 30 mol % of the proazaphosphtranes **1a**, **1b** and **1d**. Allyl alcohol on the other hand required reaction at 70 °C for 3 h to afford higher yields of the β-alkoxy carbonyl compounds using **1b** and **1d** (Table 1). Hence, mesityl oxide (**4c**) reacted with allyl alcohol in the presence of 20 mol % of **1b** and **1d** at 70

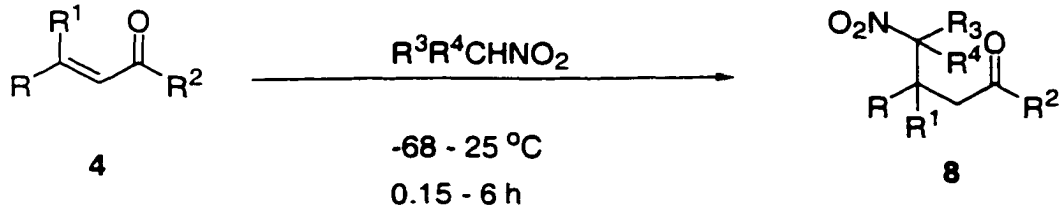
°C to afford the corresponding β-alkoxy ketone in 40 and 88% yield, respectively in 3 h. On the other hand 4-hexen-3-one (**4d**) underwent more efficient reactions under similar conditions to afford the corresponding β-alkoxy ketone **6b** in 71% and 94% yield in the presence of **1b** and **1d**, respectively. At the lower temperature of 55 °C, however, when **1d** was used as the base with allyl alcohol, mesityl oxide (**4c**) reacted efficiently to afford the corresponding β-alkoxy ketone in 88% yield. This is probably due to the higher solubility of **1d** and its protonated form **1dH**$^+$ which allows the occurrence of an efficient reaction at this relatively low temperature. Both **1a** and **1b** failed to produce any appreciable amount of the desired product under these reaction conditions. To the best of our knowledge, 4-allyloxy-4-methylpentan-2-one (**6a**) and its analogues (which are valuable intermediates in ketyl-olefin radical cyclization reactions) have been prepared only once.[31] This was achieved by treating the corresponding alcohols with $CaSO_4$, allyl bromide and silver oxide for 10 h to afford the desired β-alkoxy ketone in 44% yield. Although the inability of 4-phenyl-2-but-3-enone (**4g**) to react under our conditions (employing **1b** and **1d**) is disappointing, this result can be rationalized in terms of the resonance stability of this substrate which would be interrupted by hydroalkoxylation. The reaction of α,β-unsaturated esters [represented by

methyl acrylate (**4e**) and (*E*)-ethyl crotonate (**4f**)] with methanol in the presence of 10 mol % **1d** for 2 **h** undergoes both transesterification and β-methoxylation. When reacted with 3.0 equiv of methanol in a solvent such as THF or Me_2CHCN, **4f** afforded a 14:15 mixture of the two products $MeCH(OMe)CH_2CO_2Et$ and $MeCH(OMe)CH_2CO_2Me$ in 83% total yield that were inseparable on attempted column chromatography. Reducing the amount of methanol below 3.0 equiv afforded total yields lower than 50%. Hence, hydroxymethoxylation of α,β-unsaturated esters under our conditions is only of partial practical utility because of transesterification. Transesterification of esters in the presence of bases of type **1** has previously been reported from our laboratories.[31b]

Michael addition reaction of nitroalkanes

When 2-cyclohexenone (**4b**) was reacted in THF with 1.0 equiv of nitromethane in the presence of 0.1 equiv of **1b** for 1 h, the corresponding

Scheme 3



4 **8**

7a: $MeNO_2$
7b: *n*-$PrNO_2$
7c: Me_2CHNO_2
7d: nitrocyclohexane

8aa = 4a + 7a **8ad = 4a + 7d** **8bd = 4b + 7d**
8ca = 4c + 7a **8ed = 4e + 7d** **8fd = 4f + 7d**
8ab = 4a + 7b **8bb = 4b + 7b** **8fa = 4f + 7a**
8ac = 4a + 7c **8cd = 4c + 7d** **8ed = 4e + 7**

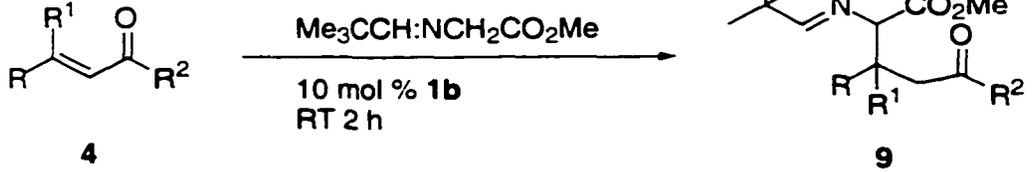
Michael adduct was formed in 89% yield. Because an increase in the ratio of nitromethane or its use as a solvent led to the formation of nitroaldols from the Michael adduct, we investigated several solvents for the reaction. Pertinent data for this study are shown in Table 2 which shows that isobutyronitrile is a far better solvent for the Michael addition of nitromethane. The reaction of MVK with nitromethane, however produced several products including nitroaldols and double Michael addition products as indicated by ^{1}H NMR spectroscopy. This problem was overcome by carrying out the reaction at –68 °C for 10-15 min. Using the reaction of nitromethane (**7a**) with mesityl oxide (**4c**) as a model, 0.1 equiv of each of the bases **1a-1d** (data for reactions employing **1a**, **1c** and **1d** not shown in Table 2) were found to promote a quantitative reaction (99% isolated yield) in Me_2CHCN. However, we found that the yield of the reaction depends on the solvent (Table 2) with isobutyronitrile being more efficient than ether, THF or benzene. The Michael addition of higher nitroalkanes, such as 2-nitropropane (**7c**) and nitrocyclohexane (**7d**), proceeded smoothly in 0.15-6 h. The superiority of our methodology is demonstrated by its ability to promote a quantitative Michael addition of nitrocyclohexane (**7d**) to 2-cyclohexenone (**4b**), mesityl oxide (**4c**) or ethyl crotonate (**4f**) in 4-6 h. Likewise, the Michael addition of 2-

nitropropane (**7c**) to these unsaturated compounds occurred quantitatively in 0.5-3 h. Both DBU and TMG have been reported as catalysts for these transformations.[32] However, reaction times of up to 48 hours are required for both bases to afford the Michael adducts in poor to modest yields.[32] Thus, the proazaphosphatranes serve as superior catalysts for the Michael addition reaction of nitroalkanes, especially of higher nitroalkanes. The Michael addition of nitrocycloalkanes to α,β -unsaturated esters afford intermediates that are useful in the synthesis of spirolactams.[33] Triton B has also been used for the Michael addition of nitrocyclohexane to α,β-unsaturated esters to afford the Michael adducts in 64% yield. Lower yields (70%) and longer reaction times (up to 10 h) were also observed in reactions employing Amberlyst A21.[14] Our methodology is also superior to a reported process in which 1-nitrocyclohexene was reacted with α,β-unsaturated esters in methanol in the presence of $NaBH_4$ to afford Michael addition products (e.g. **8ed**) in 62-95% yield over 24 h.[34] In this process, it is worth mentioning that the more expensive 1-nitrocyclohexene was used as the reactant. The work-up in this process is also cumbersome.[34]

The Michael addition of $Me_3CCH{:}NCH_2CO_2Me$[21b,22]

The reaction of this Schiff's base was found to proceed smoothly in the presence of 0.1 equiv of **1b**. When 10 mol % of **1d** was employed, the conversion obtained for the reaction of methyl acrylate with $Me_3CCH{:}NCH_2CO_2Me$ was found to be equal to that employing **1b** within experimental error. Although base-catalyzed reactions of this type have been reported previously, the ratio of the Michael adduct to cycloaddition product formed depended on the presence of a metal ion.[21,22] However, bases of type **1** do not require any metal ion and we observe no evidence of cycloaddition. The superiority of bases of type **1** is shown by their ability to induce a clean Michael addition of the imine with various α,β-unsaturated compounds in the absence of any lithiating agent. Bases known to induce this reaction such as DBU and

Scheme 4



4 **9**

9a: R = R¹ = H, R² = OMe

9b: R = H, R¹, = Me, R² = OMe

9c: R = R¹ = R² = Me

9d: R = H, R¹, R² = $(CH_2)_3$

9e: R = H, R¹ = R² = Me

9f: R = H, R¹ = CO_2Me, R² = OMe

9g: R = H, R¹ = Ph, R² = Me

triethylamine all require the presence of LiBr. Chelation has always been cited as the possible reason for the higher diastereoselectivities observed in the Michael addition reaction of the *N*-lithiated azomethine ylides (or lithium enolates) produced upon deprotonation of the imines. We too, observe high disatereoselecivity with 4-hexen-3-one, 3-penten-2-one and methyl crotonate, 3-penten-2-one, dimethyl maleate and (*E*)-4-phenyl-3-buten-2-one despite the fact we employ no metal ion.

Experimental Section

All the reactions were conducted under nitrogen. Isobutyronitrile (Aldrich) was dried over 4Å molecular sieves and stored under nitrogen. The unsaturated compounds (Aldrich) were used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker VRX300 or Bruker DRX400 machine and calibrated using TMS as an internal standard. The melting and boiling points of the products were obtained in sealed tubes and are uncorrected. The bases **1a**,[23a] **1b**[23b] and **1c**[23c] were prepared according to previously reported methods although **1a** is commercially available (Strem). $Me_3CCH{:}NCH_2CO_2Me$ was prepared according to a published procedure.[22]

General procedure for the Oxa-Michael addition of alcohols to enones

The required weight of the proazaphosphatranes was weighed in a small test tube under nitrogen. To this was added 3.0 mL of the alcohol and then the colorless solution was placed in an oil bath that has been preheated to the required temperature (Table 1) and stirred for 2-3 minutes. The Michael acceptor (2.00 mmol) was added in one portion. Stirring was then continued for the time periods specified in Table 1. At the end of the reaction time, the reaction mixture was added to 20 mL of brine and then extracted with 3x30 mL of ether, dried over anhydrous sodium sulfate and the volatiles removed in *vacuo* to afford the crude alkoxy ketones that were purified as detailed below (when necessary). Alternatively, the reaction mixture was allowed to cool to room temperature and then loaded onto a small silica gel column and eluted with 70 mL of 5% methanol in ether. Removal of the volatiles under reduced pressure afforded the crude alkoxy ketones that were also purified as detailed below (when necessary). The crude alkoxy ketones were purified by elution on a silica gel column using ether in hexane. The ratio of ether was increased in 5% increments and the products eluted at 40% ether in hexane.

General procedure for the Michael addition of nitroalkanes to α,β-unsatuarated compounds

The base (0.2 mmol) was weighed in a small test tube under nitrogen and a small stirring bar added. To this was added 2.0 mL of the appropriate solvent (Table 2) followed by 2.1 mmol of the Michael donor. The mixture was stirred for 5 minutes at the temperature given in Table 2 after which 2.0 mmol of the Michael acceptor was added in one portion. After stirring had been continued for the required time, the reaction mixture was loaded onto a small silica gel column and eluted with 5% MeOH in ether. Removal of the solvent under reduced pressure afforded the crude product that was fractionated on a silica gel column using an eluent system made up of hexane and EtOAc.

General Procedure for the Michael addition of $Me_3CCH{:}NCH_2CO_2Me$ to unsatuarated compounds

The base (0.2 mmol) was weighed in a small test tube under nitrogen and a small stirring bar was added. To this was added 2.0 mL of isobutyronitrile followed by 2.1 mmol of the Michael donor. The mixture was stirred for 5 minutes at room temperature after which 2.0 mmol of the Michael acceptor was added in one portion and stirring continued for 2 h. The reaction mixture was then added to 20 mL of ethyl acetate and then the mixture was washed with 10

mL of water and 10 mL of brine. The organic layer was dried over anhydrous sodium sulfate and the volatiles removed in *vacuo* to afford the Michael adducts. However, these compounds were too labile to be purified by column chromatography. This result is in accord with previous reports by Yamamoto[21a] *et al.* and Kanamesa and co-workers.[21b] Since the Michael aducts were essentially NMR-pure, only the ^{1}H NMR and ^{13}C NMR spectra were recorded.

References

1. Reviews: (a) Ono, N.; Kaji, A. *Synthesis*, **1986**, 693. (b) Rosini, G.; Ballini, R. *ibid*, **1988**, 833. (c) Tumara, R.; Kamimura, A.; Ono, N. *ibid*, **1991**, 423.
2. (a) Angelo, J.; Revial, C.; Costa, P. R. R.; Castro, R. N.; Antunes, O. A. C.; *Tetrahedron Asymmetry*, **1991**, *2*, 199. (b) Hagiwara, H.; Okamoto, T.; Harada, N.; Uda, H. *Tetrahedron*, **1995**, *51*, 9891. (c) Seebach, D.; Colvin, E. W.; Leher, F.; Weller, T. *Chimia*, **1979**, *33*, 1.
3. (a) Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J. S. *Synth. Commun.*, **1998**, *28*, 653. (b) Yamagushi, M.; Igarashi, Y.; Redyy, R. S.; Shiraishi, T.; Hirama, M. *Tetrtahedron*, **1997**, *53*, 11223. (c) Hanyuda, K.; Hirai, K.; Nakai, T. *Synlett*, **1997**, 31.

4. Ono, N.; Miyaka, H.; Kaji, H. *J. Chem. Soc. Chem. Commun.* **1983,** 875.

5. Grieco, P. A.; Pogonowski, C. S. *Synthesis*, **1973**, 425.

6. Rosini, G. In *Comprehensive Organic Synthesis*, Vol. 2, Trost, B. M. Ed.: Pergamon, New York, **1991**, 321-340.

7. Ono, N.; Miyake, H.; tamuta, R.; Kaji, A. *Tetrahedron Lett.* **1981**, 1705. (a) Bergbreiter, D. E.; Lalonde, J. J. *J. Org. Chem.* **1987**, *52*, 1601. (b) Bryce, M. R.; Gardiner, J. M.; Horton, P. J.; Smith, S. A. *J. Chem. Res, Synop.*, **1989**, *1*, 1. (c) Macquarrie, D. J. *Tetrahedron Lett.* **1998**, *39*, 4125. (d) Yamagushi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520.

8. See (a) Rao, Y. V. S.; De Vos, D. E.; Jacobs, P. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2661. (b) Wada, M.; Tsuboi, A.; Nishimura, K.; Erabi, T.*Nippon Kagaku Kaishi*, **1987**, *7*, 1284. *Chem. Abstr* **1987**, *108*, 149866.

9. (a) Ranu, B. C.; Sanjay, S.; Dipak, C. *Tetrahedron Lett.* **1991**, *32*, 2811. (b) Ranu, B. C.; Saha, M.; Sanjay, B. *Synth. Commun.*, **1997**, 27, 621.

10. (a) Sreekumar, R.; Rugmini, P.; Padmakumar, R. *Tetrahedron Lett.* **1997**, *38*, 6557. (b) Ranu, B. C.; Bhar, S. *Tetrahedron*, **1992**, *48*, 1327.

11. (a) Pollini, G. P.; Barco, A.; De Giuli, G. *Synthesis* **1972**, 44. (b) Miller, D. D.; Moorthy, K. B.; Hamada, A. *Tetrahedron Lett.* **1983**,*24*, 555. (c) Bazukis, P.; Bazukis, M. L. F.; Weingartner, T. F. *ibid.* **1978**, 2371.

12. Clark, J. H.; Cork, D. G.; Gibbs. H. W. *J. Chem. Soc., Perkin Trans. 1* **1983**. 2253.

13. Ballini R.; Petrini, M.; Rosini, G. *Synthesis*, **1987**, 711.

14. Ballini, R.; marziali, P.; Mozzicafreddo, A. *J. Org. Chem.* **1996**, *61*, 3209.

15. Ballini, R.; Bosica, G. *Tetrahedron Lett.* **1996**, *37*, 8027.

16. Noyori, R.; Kato, M. *Bull. Chem. Soc. Jpn.* **1974**, *46*, 1460.

17. (a) Titova, T. F.; Krysin, A.P.; Shakirov, M. M.; Mamatyuk, V. I. *J. Org. Chem. USSR (Engl. Transl.)*, **1984**, *20*, 294. (b) Duffy, J. L.; Kurth, J. A.; Kurth, M. J. *Tetrahredron Lett.* **1993**, *34*, 1259. (c) Dumez, E.; Rpdriguez, J.; Dulcère, J. P.; *J. Chem . Soc. Chem. Commun.* **1997**, 1831

18. Kumhar, P. S.; Sanchez-Valente, J.; Figueras, F. *Chem. Commun.* **1998**, 1091.

19. Dumez, E.; Rodriguez, J.; Dulcère, J. -P. *Chem. Commun.* **1997**, 1831.

20. (a) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277. (b) Bey, P.; Vevert, J. P. *J. Org. Chem.* **1980**, *45*, 3249. (c) Stork, G.; Leong, A. Y.; Touzin, A. M. *ibid.* **1976**, *41*, 3491.

21. (a) Yamamoto, H.; Kanemasa, S.; Wada, E. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2739. (b) Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411.

22. Tsuge, O.; Kanemasa, S.; Yoshioba, M. *J. Org. Chem.* **1988**, *53*, 1384.

23. (a) Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75. (b) Wroblewski, A.; Pinkas, J.; Verkade, J. G. *Main Group Chemistry* **1995**, *1*, 69. (c) D'Sa, B.; Verkade, J. G. *Phosphorus Sulfur Silicon* **1997**, *123*, 301.

24. Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4298.

25. D'Sa, B.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3691.

26. Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3090.

27. Kisanga, P.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 10057.

28. Arumugam, S.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827.

29. Kisanga, P.; D'Sa, B.; Verkade, J. G. manuscript in preparation.

30. Kisanga, P.; Verkade, J. G. manuscript in preparation.

31. (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872. (b) Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086.

32. (a) Andruszkiewicz, R.; Silverman, R. B. *Synthesis* **1989**, *12*, 953. (b) Ono, N.; Kamimura, A.; Miyake, H.; Hamamoto, I.; Kaji, A. *J. Org. Chem.* **1985**, *50*, 3692.

33. Bryce, M. R.; Gradiner, J. M.; Horton, P. J.; Smith, S. A. *J. Chem. Res.*, *Synop.* **1989**, *1*, 1.

34. Ho, T. L. *Synth. Commun.* **1982**, *12*, 339.

Table 1. The reaction of α,β-unsaturated compounds with alcohols in the presence of **1**.

Michael acceptor	Michael donor	base/ mol %	reaction conditions	% yield
3-penten-2-one (**2**)	MeOH	**1a**/10	50 °C; 1 h	78
MVK (**4a**)	MeOH	**1a**/10	50 °C; 0.5 h	65
2-cyclohexenone (**4b**)	MeOH	**1b**/20	50 °C; 0.5 h	76
(*E*)-PhCHCHCOMe (**4g**)	MeOH	**1b**/10	50 °C; 2 h	0
4-hexen-3-one (**4d**)	MeOH	**1b**/10	50 °C; 0.5 h	96
4-hexen-3-one (**4d**)	CH_2CHCH_2OH	**1b**/20	70 °C; 3 h	71
4-hexen-3-one (**4d**)	Me_3COH	**1b**/20	70 °C; 3 h	0
2-cyclohexenone (**4b**	CH_2CHCH_2OH	**1b**/20	70 °C; 3 h	58
mesityl oxide (**4c**)	MeOH	**1b**/10	50 °C; 0.5 h	79
mesityl oxide (**4c**)	Me_2CHOH	**1b**/20	70 °C; 3 h	0
mesityl oxide (**4c**)	CH_2CHCH_2OH	**1b**/20	70 °C; 3 h	40
MVK (**4a**)	MeOH	**1c**/20	50 °C; 0.5 h	61
mesityl oxide (**4c**)	CH_2CHCH_2OH	**1d**/20	55 °C; 7 h	89
mesityl oxide (**4c**)	CH_2CHCH_2OH	**1d**/20	70 °C; 3 h	88
4-hexen-3-one (**4d**)	CH_2CHCH_2OH	**1d**/20	70 °C; 3 h	94
mesityl oxide (**4c**)	Me_2CHOH	**1d**/20	70 °C; 3 h	0
MVK (**4a**)	MeOH	**1d**/10	35 °C; 24 h	62
MVK (**4a**)	MeOH	**1d**/15	35 °C; 24 h	93
2-cyclohexenone (**4b**	MeOH	**1d**/10	50 °C; 3 h	89

Table 2. The Michael addition of nitroalkanes to α,β-unsaturated compounds in the presence of **1**.

Michael acceptor	Michael donor	conditions base[a]/ °C / h.	% yield
mesityl oxide (**4c**)	$MeNO_2$ (**7a**)	**1b**/RT/0.5	99
mesityl oxide (**4c**)	$MeNO_2$[b] (**7a**)	**1b**/RT/0.5	95
mesityl oxide(**4c**)	$MeNO_2$[c] (**7a**)	**1b**/RT/0.5	91
mesityl oxide (**4c**)	$MeNO_2$[d] (**7a**)	**1b**/RT/0.5	92
MVK (**4a**)	$MeNO_2$ (**7a**)	**1b**/-68/0.15	78
MVK (**4a**)	*n*-$PrNO_2$ (**7b**)	**1b**/-68/0.15	81
MVK (**4a**)	Me_2CHNO_2 (**7c**)	**1b**/RT/0.25	99
MVK (**4a**)	nitrocyclohexane (**7d**)	**1b**/RT/0.25	93
2-cyclohexenone (**4b**)	Me_2CHNO_2 (**7c**)	**1b**/RT/0.5	99
CH_2:$CHCO_2Me$ (**4e**)	nitrocyclohexane (**7d**)	**1b**/RT/4	100
(*E*)-ethyl crotonate (**4f**)	nitrocyclohexane (**7d**)	**1b**/RT/4	100
2-cyclohexenone (**4b**)	*n*-$PrNO_2$ (**7b**)	**1b**/-68/0.25	71
(*E*)-ethyl crotonate (**4f**)	$MeNO_2$ (**7a**)	**1b**/-68/0.25	99
2-cyclohexenone (**4b**)	nitrocyclohexane (**7d**)	**1b**/RT/1	99
mesityl oxide (**4c**)	nitrocyclohexane (**7d**)	**1d**/RT/1	95[e]
MVK (**4a**)	nitrocyclohexane (**7d**)	**1d**/RT/0.25	99
CH_2:$CHCO_2Me$ (**4e**)	nitrocyclohexane (**7d**)	**1d**/RT/1	99
(*E*)-ethyl crotonate (**4f**)	nitrocyclohexane (**7d**)	**1d**/RT/1	99
mesityl oxide (**4c**)	Me_2CHNO_2 (**7c**)	**1d**/RT/0.33	99

Table 2 (continued).

[a]The amount of base used was 10 mol % in isobutyronitrile unless stated otherwise. [b]The solvent was THF. [c]The solvent was benzene. [d]The solvent was ether. [e]The amount of **1d** used was 20 mol %.

Table 3. The Michael addition of $Me_3CCH{:}NCH_2CO_2Me$ in the presence of **1b**.

Michael acceptor	yield (*anti:syn*)[a]
methyl crotonate (**4i**)	76 (9:1)
methyl acrylate (**4e**)	72
mesityl oxide (**4c**)	86
2-cyclohexenone (**4b**)	97 (single)
3-penten-2-one(**2**)	85(7:1)
dimethyl maleate(**4h**)	94 (single)
(*E*)-4-phenyl-3-buten-2-one (**4g**)	91 (single)

[a]Determined by ^{1}H NMR integration based on a comparison with literature spectra.[22]

CHAPTER 9

$P(RNCH_2CH_2)_3N$-CATALYZED DIASTEREOSELECTIVE SYNTHESIS OF OXAZOLIDINES

A paper to be submitted to the Journal of Organic Chemistry

Philip Kisanga,[a,b] Palanichamy Ilankumaran[c] and John G. Verkade[a,d]

Abstract

We report herein a diastereoselective synthesis of oxazolidines in a reaction catalyzed by 5-30% of the strong nonionic bases of the type $P(i\text{-}PrNCH_2CH_2)_3N$. The formation of the oxazolidines proceed with high diastereoselectivity (>95:5) with the *trans* isomer as the major product.

Introduction

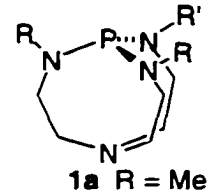
Oxazolidines are versatile intermediates in the synthesis of various β-substituted serines[1] which are of significant importance because of their utility in the synthesis of various antibiotics.[2] Thus, the serine moiety constitutes the primary core structure of various antibiotics, such as hypeptin[2b] and leucinostatin.[3] Ethyl isocyanoacetate, a synthon for the formation of

[a] Graduate student and University Professor respectively, Department of Chemistry, Iowa State University.
[b] Primary researcher and author.
[c] Postdoctoral research associate, Department of Chemistry, Iowa State University.
[d] Author for correspondence.

oxazolidines is relatively acidic and can be deprotonated by a variety of bases for coupling with aldehydes to afford the oxazolidines. The lack of diastereoselectivity of such reactions has rendered this synthetic route of limited utility. Among catalysts that have been reported to effect the conversion of aldehydes and ethyl isocyanoacetate to oxazolidines are $ZnCl_2$,[4] $ZnCl_2$/CuCl system,[5] NaCN/EtOH,[6] and Cu_2O.[7] The copper(I) oxide-catalyzed process leads to the formation of varying ratios (1.5:1.0 - 0.4:1.0) of diastereomers[7] and this catalyst also induces migration of the imine double bond with the resultant formation of two tautomers giving a complex mixture of products.[7] Furthermore, the presence of α,β-unsaturation leads to Michael addition, rendering this method of very limited practical utility. Although the NaCN/EtOH system affords the oxazolidines in high yields,[6] its inability to induce excellent distareoselectivity in aldehydes other than phenyl acetaldehyde has limited its use.[8] The $ZnCl_2$/CuCl catalyzed process also leads to the formation of diastereomeric mixtures (7:1-1:1, *trans:cis*).[5] As a result of these poor selectivities, alternative routes to β-hydroxy α-amino acids have been developed,[9] among which are the condensation of glycine with aldehydes on Ni(II) complexes[9a] and an electrophilic amination reaction.[9b] Since nickel is highly toxic, this methodology is not attractive in an industrial setting. The

elctrophilic amination process requires 2.5-4.2 equiv of LDA and also 1.5 equiv of di-*t*-butylazodicarboxylate.[9b] Moreover, the diastereoselectivity in this reaction ranges from 94:6-75:25 (*trans:cis*).[9b] Enzyme systems[10a,b] have also been investigated for the synthesis of an intermediate oxazolidine used in the synthesis of thiamphenicol and florfenicol.[10c]

The proazaphosphatranes **1a** and **1b**[11] synthesized first in our laboratories have recently attracted interest as versatile catalysts and reagents for various useful transformations such as the isomerization of double bounds,[12] alcohol



1a R = Me
1b R = *i*-Pr

silylation,[13] transesterification,[14] the synthesis of β-hydroxy nitriles,[15] α,β-unsaturated esters,[16] α,β-unsaturated nitriles,[17] homoallylic alcohols,[18] β-nitroalkanols,[19] glutaronitriles,[20] α,α-dicyanoalkenes,[21] benzofurans,[22] coumarins[16] and alkenes via dehydrohalogenation;[23] and the trimerization of isocyanates.[24] A proazaphosphatrane has also been used to prepare a Wittig ylide[25a] and to facilitate Wittig[25b] and Stille reactions.[26] We have recently found that **1a** and **1b** can be used stoichiometrically to synthesize α,β-unsaturated esters with excellent selectivities for the *E*-isomer.[16] We therefore decided to

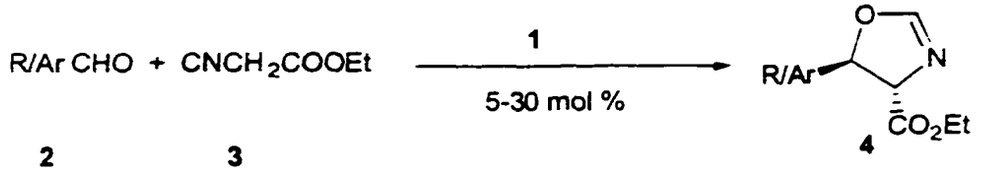
explore additional reactions in which stereoselectivity is an issue. Since oxazolidines are versatile intermediates for the synthesis of serine derivatives, which in turn could open a route to interesting unnatural amino acids, we decided to investigate the possibility of inducing a diastereoselective reaction between aldehydes and ethyl isocyanoacetate.

We report here the use of catalytic amounts of the proazaphosphatranes **1b** as a catalyst in the synthesis of oxazolidine ethyl carboxylates with high diastereoselectivity.

Results and Discussion

The reaction of benzaldehyde (**2a**) with isocyanoacetate **3** in THF in the presence of 20 mol % of **1b** at room temperature for 1 h afforded a product mixture that contained the *trans*-oxazolidine as the major product as determined by ^{1}H NMR spectroscopy. However, the reaction was not clean and led to the formation of other uncharacterized side products. No significant improvement was observed upon reducing the temperature to -68 °C or raising the temperature to 40 °C. However, upon changing the solvent to isobutyronitrile (a solvent that we have previously found to induce clean reactions),[16] the desired oxazolidine ethyl carboxylate **4a** was isolated in 95% yield. Both **1a** and **1b** afforded similar yields within experimental error (data not shown in

Table 1). Comparison of both the ^{1}H and ^{13}C NMR data of this product (**4a**) to literature data[5] revealed that the *trans*-oxazolidine ethyl carboxylate was the only product of the reaction. Attempted reaction of *p*-chlorobenzaldehyde and *p*-fluorobenzaldehyde in isobutyronitrile did not afford clean reactions.



a : Ar = Ph

b: Ar = *p*-FC_6H_4

c: Ar = *p*-ClC_6H_4

d: Ar = *p*-NCC_6H_4

e: Ar = *p*-$O_2NC_6H_4$

f: Ar = *p*-$MeOC_6H_4$

g: Ar = *p*-$MeSO_2C_6H_4$

h: Ar = 2,5-diMeC_6H_3

i: Ar = 2,5-di$OMeC_6H_3$

j: R = *i*-Pr

k: R = Me_3C

l: R = $CH_3(CH_2)_5$

m: R = *E*-PhCH=CH

n: R = *n*-Pr

o: R = *o*-$MeOC_6H_4$

p: Ar =

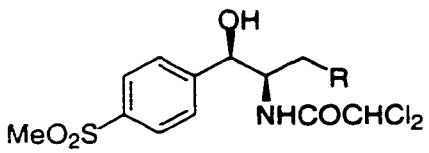
q: Ar =

r: Ar =

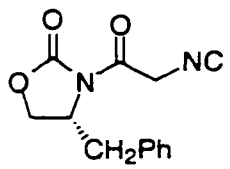
However, by reducing the temperature to -68 °C, aromatic aldehydes bearing electron withdrawing groups (**2d**, **2e**, and **2g**) and aliphatic aldehydes (**2j**-**2n**) reacted to afford *trans*-oxazolidines ethyl carboxylates as the only products. On the other hand, aromatic aldehydes bearing electron donating groups (**2h**, **2i** and **2o**-**2r**) required room temperatures to afford similar yields (Table 1). Excellent yields were obtained by reacting *p*-fluorobenzaldehyde (**2b**) and *p*-

chlorobenzaldehyde (**2c**) in the presence of 20 mol % of **1b** at –5 and –20 °C repectively. The oxazolidine ethyl carboxylate **4g** was obtained in 97% yield which is of significance because it has previously been used as an intermediate in the synthesis of thiamphenicol (**5a**) and florfenicol (**5b**).[10b,c]

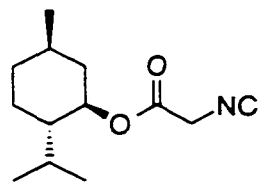
Since oxazolidine ethyl carboxylates and their hydrolysis products, i.e., β-hydroxy-α-amino acids, serve as intermediates to chiral compounds, such as the broad spectrum antibiotics thiamphenicol (**5a**) and florfenicol (**5b**),[10b,c] we attempted to synthesize a chiral oxazolidine. We have previously reported the



5a R = OH
5b R = F



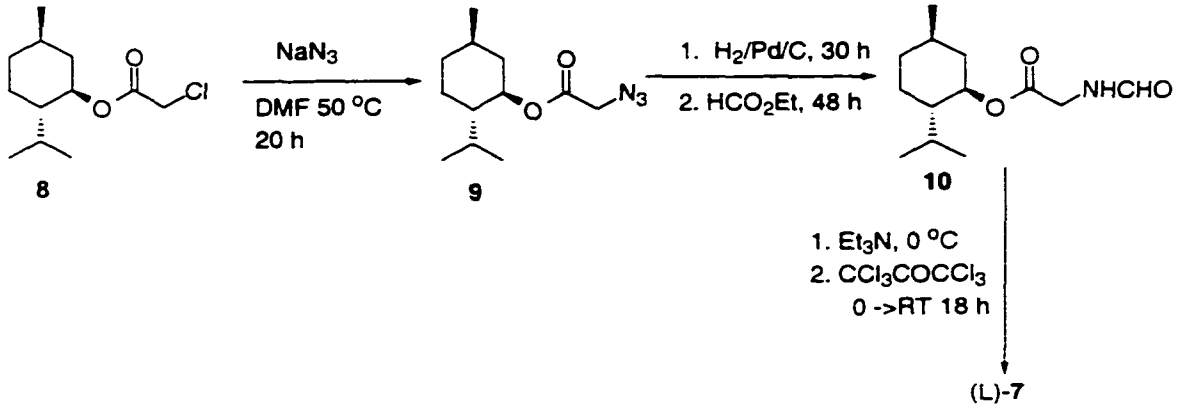
(R)-**6**



(L)-**7**

synthesis of (R)-**6**,[26] a chiral auxiliary bearing the isocyanide functionality. However, the synthesis was achieved in six steps and it bears the oxazolidinone functionality that requires a two-step procedure for removal.[27] We therefore investigated the synthesis of a chiral isocyanide possessing an easily removable chiral auxiliary. The menthol group has recently emerged as an easily cleaved chiral auxiliary.[28] The incorporation of this group as the chiral auxiliary in the isocyanide (L)-**7** is shown in Scheme 1. The commercially available chloro compound **8** was reacted with sodium azide in DMF at 50 °C for 20 h.

Scheme 1

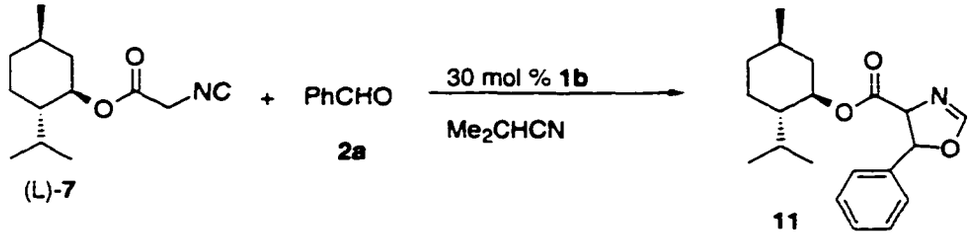


Upon work-up and purification, the azide **9** that was obtained in 81% yield was converted to the formate **10** in a one pot reaction in which **9** was reduced with hydrogen on Pd/C for 30 h in ethyl formate followed by stirring for 48 h. The formate **10**, obtained in 99% yield, was further reacted with the phosgene equivalent CCl_3COCCl_3 to afford the target isocyanide (L)-**7** in 73% yield. Thus, isocyanide (L)-**7** was obtained in three steps in 59% overall yield.

With the isocyanide (L)-**7** in hand, an attempt was made to prepare a chiral oxazolidine menthyl carboxylate by coupling (L)-**7** with benzaldehyde. Reactions in the presence of 20 mol % of **1b** attempted in THF for 2 h at room temperature led to the formation of complex reaction mixtures. When the reaction was repeated in isobutyronitrile under conditions similar to that employing ethyl isocyanoacetate (Table 1), the reaction was incomplete. Although an increase in the amount of **1b** to 30 mol % led to a complete

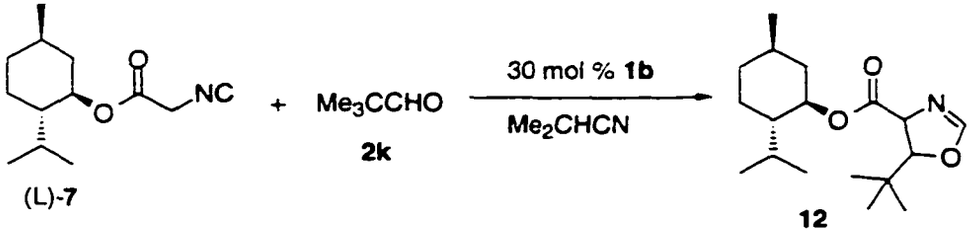
conversion to the desired *trans*-oxazolidine **11** (Scheme 2), the observed diastereoselctivity was only 7:4. When the amount of the base was reduced to 5

Scheme 2



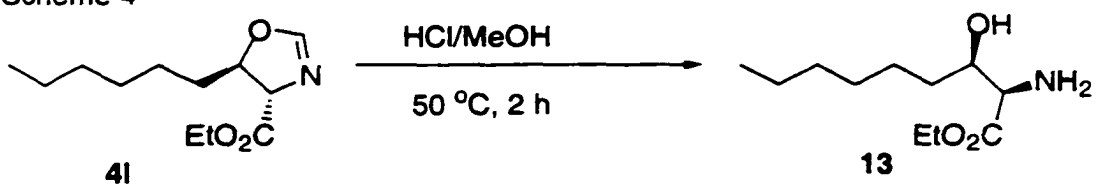
mol % and the reaction run overnight in an attempt to induce higher diastereoselectivity, a complex reaction mixture was obtained. The reaction of (L)-**7** with pivalaldehyde was equally successful at –68 °C employing 20 mol % of **1b** to afford a diastereoselectivity of 5:3 (Scheme 3) in 2 h.

Scheme 3



Although the diastereoselectivities observed here are disappointing, **4l** was converted into the serine derivative **13** by a slight modification of a reported procedure (Scheme 4).[9b]

Scheme 4



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Experimental Section.

All reactions were conducted under nitrogen. The bases **1a**[11a] and **1b**[11b] were prepared according to previously reported procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker VRX300 or Bruker DRX400 machine and calibrated using TMS as an internal standard.

General Method for the Preparation of Oxazolidine Ethyl Carboxylates

In a round-bottomed flask was weighed the desired amount of **1b** (Table 1) under nitrogen. To this was added 3.0 mL of isobutyronitrile, followed by 2.0 mmol of ethyl isocyanoacetate. The reaction mixture was placed in a constant temperature bath adjusted to the suitable temperature (Table 1) with continuous stirring for 5 min. To this solution was added 2.0 mmol of the aldehyde and then the solution stirred at this temperature for 15 more minutes after which it was allowed to stir at room temperature for 1 h. The reaction mixture was loaded onto a small silica gel column and eluted with ethyl ether. Removal of the solvent in *vacuo* afforded a crude mixture that was purified by eluting on a silica gel column with ether/hexane. The ratio of ether was

increasd in 5 % increments. The oxazolidines eluted with 40% ether in hexane. The more polar oxazolidines **4b-4e** and **4g** were purified by eluting with ethyl acetate in hexane and eluted at 40% ethyl acetate in hexane.

Preparation of Azide 9

A mixture of 11.6 g (50 mmol) of the chloro compound **8** and 13.0 g (200 mmol) of sodium azide were weighed under nitrogen in a round-bottomed flask. To this mixture was added 30 mL of DMF and the flask was connected to a water condenser. The reaction mixture was then warmed at 50 °C for 20 h. At the end of this, the reaction mixture was cooled to room temperature and the reaction mixture dissolved in 150 mL of diethyl ether. This solution was then washed with 3x100 mL of water. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Removal of the solvent in *vacuo* afforded the azide **9** that was purified by flush chromatography using 20% ethyl acetate in hexane to afford 9.70 g (81% yield) of the pure azide.

Synthesis of Formate 10

To 2.00 g (8.83 mmol) of the azide **9** dissolved in 10 mL of ethyl formate was added 200 mg of Pd/C. Hydrogen was bubbled through the reaction mixture for 30 h followed by stirring at room temperature for 48 more hours.

The solid particles were then filtered from the reaction mixture and then the excess solvent was removed under reduced pressure to afford 2.00 g (99% yield) of the formate **10** which was found to be essentially pure by both ^{1}H and ^{13}C NMR spectroscopic analysis.

Synthesis of the isocyanide (L)-7

In a small round-bottomed flask was weighed under nitrogen 1.2 g (5.04 mmol) of the formate **10**. To this was added 5 mL of methylene chloride and then 2.7 mL (20 mmol) of triethylamine. The reaction mixture was cooled to 0 °C followed by dropwise addition of 2 mL (594 mmol) of hexachloroacetone. The temperature of the reaction mixture was allowed to warm to room temperature while the mixture was stirred for 18 h. The reaction mixture was then filtered to remove triethylamine hydrochloride. The solvent was removed under reduced pressure and the crude product was purified by flush chromatography on silica gel using 20% ethyl acetate in hexane to afford 818 mg (73% yield) of the target isocyanide.

Preparation of β-hydroxy-α-amino ester 13.

To 5 mL of concentrated HCl in 5 mL of dry methanol in a round-bottomed flask was added 227 mg (0.10 mmol) of the oxazolidine ethyl carboxylate **4l** dissolved in 5 mL of the same solvent. The reaction flask was connected to a water condenser and the reaction mixture was heated at 50 °C for 2 h and at the end of that time the reaction mixture was allowed to cool to room temperature. The reaction mixture was then quenched with 10 mL of 50% sodium hydroxide solution diluted to 20 mL with water. The reaction mixture was extracted with 3x30 mL of ethyl acetate. The organic fractions were combined, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to afford a crude product that was eluted on a silica gel column with 100% ethyl acetate to afford 154 mg (71% yield) of the β-hydroxy-α-amino ester **13**.

References

1. (a) Hining, H.; Seufer-Waserthal, P.; Weber, H. *Tetrahedron* **1990**, *46*, 3841. (b) Gaparski, C. M.; Miller, M. J. *ibid.* **1991**, *47*, 5367. (c) Togni, A.; Pastor, S. D.; Ribs, G. *J. Organomettalic Chem.* **1990**, *381*, C21.
2. (a) Saeed, A.; Young, D. W. *Tetrahedron* **1992**, *48*, 2507. (b) Shoji, J.; Hinoo, H.; Hattori, T.; Kirooka, K.; Kimura, Y.; Yoshida, T. *J. Antibiotics*

1988, *42*, 1460.

3. Hukushima, K.; Arai, T.; Mori, Y.; Tsuboi, M.; Suzuki, M. *J. Antibiotics* **983**, *36*, 1613.
4. (a) Badr, M. Z. A. B.; Aly, M. M; Fahmy, A. M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1844. (b) Kirihata, M.; Kawahara, S.; Ichimoto, I.; Ueda, H. *Agric. Biol. Chem.* **1990**, *54*, 753.
5. Ito, Y.; Matsura, T.; Saegusa, T. *Tetrahedron Lett.* **1985**, *26*, 5781.
6. Hoppe, D.; Schollkopf, U. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 300.
7. (a) Saegusa, T.; Ito, Y.; Kinoshita, H.; Tomita, S. *J. Org. Chem.* **1971**, *36*, 3316. (b) Rich, D. H.; Dhaon, M. K.; Dunlap, B.; Millaer, S. P. F. *J. Med. Chem.* **1986**, *29*, 978.
8. Rao, M. N.; Holkar, A. G.; Ayyanger, N. R. *J. Chem Soc., Chem. Commun.* **1991**, 1007.
9. (a) Soloshonok, V. A.; Avilov, D. V.; Kukhar, N. S.; Kochetkov, K. A.; Orlova, S. A.; Pysarevsky, A. P.; Struchkov, Y. T.; Raevsky, N. I.; Belokon, Y. N. *Tetrahedron Asymmetry* **1995**, *6*, 1741. (b) Gunati, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5562.
10. (a) Clark, J. E.; Fischer, P. A.; Schumacher, D. P.; *Synthesis* **1991**, 891. (b) Wu, G.; Schumacher, D. P.; Tormos, W.; Clark, J. E.; Murphy, B. L. *J. Org.*

Chem. **1997**, *62*, 2996. (c) Clark, J. E.; Fischer, P. A.; Schumacher, D. P. *Synthesis* **1991**, 891.

11. (a) Schmidt, H.; Lensink, C.; Xi, S. -K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75. (b) Wroblewski, A.; Pinkas, J.; Verkade, J. G. *Main Group Chemistry* **1995**, *1*, 69. (c) Kisanga, P.; Verkade, J. G. manuscript in preparation.
12. D'Sa, B.; Kisanga, P.; Verkade, J. G. manuscript in preparation.
13. D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963.
14. Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086.
15. Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3090.
16. Kisanga, P.; D'Sa, B.; Fei, X.; Verkade, J. G. submitted.
17. D'Sa, B.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3691.
18. Wang, Z.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* in press.
19. Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 4298.
20. Kisanga, P.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 10057.
21. McLaughlin, P.; Verkade, J. G. manuscript in preparation.
22. D'Sa, B.; Kisanga, P.; Verkade, J. G. submitted.
23. Arumugam, S.; McLeod, D.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4927.

24.Tang, J. –S.; Verkade, J. G. *J. Org. Chem.* **1994,** *59*, 7793.

25. (a) Giordano, C.; Cavicchioli, S.; Levi, S.; Villa, M. *J. Org. Chem.* **1991**, *56*, 6114. (b) Wu, G.; Schumacher, D. P.; Tormos, W.; Clark, J. E.; Murphy, B. L. *ibid.* **1997**, *62*, 2996.

26. Tang, J. –S.; Verkade, J. G.; *J. Org. Chem.* **1996**, *61*, 8750.

27. Evans, D. A.; Mathre, D. J. *J. Org. Chem.* **1985**, *50*, 1830.

28. (a) Barluenga, J.; Tomás, M.; Lopéz, L. A.; Suárez-Sobrino, A. *Synthesis* **1997**, 967. (b) Barluenga, J.; Suárez-Sobrino, A.; Lopéz, L. A. *Aldrichimica Acta* **1999**, *32*, 4.

Table 1. Reaction of aldehydes with ethyl isocyanoacetate in isobutyronitrile.

substrate	base /ratio	(T °C/ t min)	% product yield
benzaldehyde (**2a**)	**1b**/0.20	25/60	95
p-fluorobenzaldehyde (**2b**)	**1b**/0.20	-5 /60	98
p-chlorobenzaldehyde (**2c**)	**1b**/0.20	-20 /60	94
p-cyanobenzaldehyde (**2d**)	**1b**/0.30	-78/75	99
p-nitrobenzaldehyde (**2e**)	**1b**/0.30	-78/75	94
p-anisaldehyde (**2f**)	**1b**/0.20	25/120	78
p-methylsulfonylbenzaldehyde (**2g**)	**1b**/0.30	-78/75	97
2,5-dimethylbenzaldehyde (**2h**)	**1b**/0.30	25/90	93
2,5-dimethoxybenzaldehyde (**2i**)	**1b**/0.30	25/90	91
isobutyraldehyde (**2j**)	**1b**/0.05	-78/60	80
pivalaldehyde (**2k**)	**1b**/0.05	-78/60	67
n-heptaldehyde (**2l**)	**1b**/0.05	-78/60	71
(*E*)-cinnamaldehyde (**2m**)	**1b**/0.2	-78/75	68
n-butyraldehyde (**2n**)	**1b**/0.05	-78/60	88
o-anisaldehyde (**2o**)	**1b**/0.20	25/60	75
2-naphthaldehyde (**2p**)	**1b**/0.20	25/60	97
thiophene carboxaldehyde (**2q**)	**1b**/0.20	25/60	89
furfuraldehyde (**2r**)	**1b**/0.20	25/60	93

CHAPTER 10

GENERAL CONCLUSIONS

This study has demonstrated that proazaphosphatranes are likely to become widely used catalysts/reagents. This has been demonstrated in six applications: synthesis of glutaronitriles, β-hydroxy nitriles, β-nitroalkanols, α,β-unsaturated esters, oxazolidines and three important Michael addition reactions. The observation that either $MgBr_2$ or $MgSO_4$ may act as carbonyl activators in the presence of proazaphosphatranes may be relevant in further applications such as the preparation of α,β-unsaturated nitriles from ketones, a transformation that has not yet been achieved in a clean fashion using these reagents. Other Lewis acids may also be found to be compatible with the proazaphosphatrane system. Additional potential applications include the synthesis of β-hydroxy esters and the synthesis of pyrans, indoles and quinolines. The wide range of applications of proazaphosphatranes discussed herein coupled with the preparation of variously substituted proazaphosphatranes by the methods described in this dissertation can potentially increase the marketability of these bases since the starting aldehydes are inexpensive and might reduce the price of a Verkade superbase to about 50% of the present market price for $P(MeNCH_2CH_2)_3N$ ($238.00/ g). However,

this also depends upon future studies that would lead to further discoveries of new applications of these compounds in useful organic transformations.

ACKNOWLEDGEMENTS

I would like to thank Dr. John G. Verkade for his unceasing support and guidance throughout my career at Iowa State University. My thanks also go to the members of my Graduate Committee for advice and support, and to the Chemistry Faculty and entire supporting staff for continued support and help.

It is my priviledge to acknowledge the contribution of the staff of the Chemical Instrumentation Facility for their effort towards the realization of the objectives of this study. I would like to thank Dr. Dave Scott and Dr. Shu Xu for their help with NMR spectroscopic analysis, Dr. Kamal Harratta and Miss Sahana Mollah for MS data, Steve Veysey for MS and elemental analysis data and Ilia Gezei for X-ray crystallographic results.

My thanks also go to the members of J. G. Verkade research group (present and past) for their useful discussions, suggestions and cooperation that contributed significantly towards the success of this work. My special thanks go to Dr. Bosco D'Sa with whom we collaborated on a number of projects including Chapters 2, 5 and 6 in this dessertation. Dr. D'Sa provided an important data point in Chapter 2 and in Chapter 5, in addition to independently discovering the project reported in Chapter 6. I would like to thank Dr. Ilankumaran Palanichamy for his useful suggestions and his efforts in

collaborating with me towards the realization of the researches reported in Chapters 8 and 9. I also would like to extend my gratitude to Mr. Dale McLeod for some of the data in Table 1 of Chapter 5 and Dr. Xiangshu Fei for his supplementary work on the catalytic preparation of coumarins reported in Chapter 6. My thanks and appreciation are also to Dr. Zhigang Wang for his collaboration on the synthesis of homoallylic alcohols reported elsewhere and to Dr. Zhengkun Yu for his useful suggestions and discussions. My sincere thanks also go to Dr. Reddi Madhav, Dr. Subramaniam Arumugam, Mrs. Yeping Zhu, Mr. Jinchao Yang, Mr. Xiaodong Liu, Dr. Guangtao Zhang, Dr. Patrick McLaughlin and Mr. Rodney Hall for useful discussions.

Sincere thanks go to Dr. George Kraus for allowing me (and other members of Verkade's research group) to attend his group meeting and for the group's useful discussions and suggestions.

Lastly but not least, I would like to thank the Iowa State Center for Advanced Technology and the Donors of the Petroleum Research Fund administered by the American Chemical Society for grant support, without which this work would not have been possible.