1983

Approaches to heterocyclic natural product systems

Jon Owen Nagy
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APPROACHES TO HETEROCYCLIC NATURAL PRODUCT SYSTEMS

Iowa State University PH.D. 1983

Approaches to heterocyclic natural product systems

by

Jon Owen Nagy

A Dissertation Submitted to the

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Requirements for the Degree of

DOCTOR OF PHILOSOPHY

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For the Graduate College

Iowa State University
Ames, Iowa

1983

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GENERAL INTRODUCTION

Success in organic chemistry requires a combination of skill, luck, and persistence. Reagents are constantly being discovered which display more specificity or selectivity than those previously known. Their utilization can lead to the synthesis of a biologically important molecule in a novel or elegant manner. The skill of the chemist is to recognize the utility and be blessed with the good fortune to have it compatible with his complex system. Parts I and II describe the novel assemblage of a heterocyclic system and its elaboration into a natural product. Part III described the utilization of a very old molecule, the 1,2-benzoquinonediazide, in syntheses of useful precursors toward natural product systems.

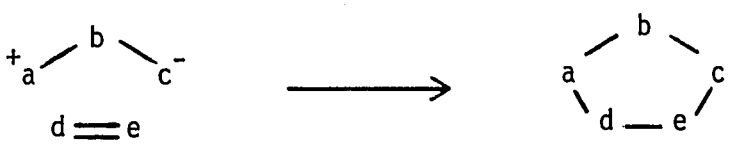
Explanation of Thesis Format

This thesis is written so that each part represents an article in a publishable form. For this reason, the numbering scheme adopted for the figures and tables is independent in each section.

PART I. 1,3-DIPOLAR CYCLOADDITIONS OF STABILIZED AZOMETHINE YLIDES LEADING TO SUBSTITUTED PYRROLES OR PYRROLIDINES

INTRODUCTION

1,3-Dipolar cycloadditions have a rich history in the annals of organic chemistry. In general, a multiply bonded system d-e combines with a 1,3-dipole, a-b-c, where atom a has an incomplete valence shell with a formal positive charge, and atom c possesses a negative charge. A new five membered ring system is formed by the creation of two σ-bonds.



There is some debate as to whether the ylide exists as a charge separated molecule or a spin paired diradical (1,2), but the generally accepted form is the charge separated one, which best explains the reported results.

A milestone in the field of physical organic chemistry was reached when the famous Woodward-Hoffman rules were found to apply also to this type of addition. The 1,3-dipolar cyclizations can be as stereospecific as the Diels-Alder reaction, but uncertainties in the transition state geometry make the results of the calculations of secondary effects somewhat more difficult to predict. With further understanding of the complex mixture of steric and electronic factors, the 1,3-dipolar addition may become a tool comparable in utility to the Diels-Alder reaction.

HISTORICAL

The cyclizations that occur via nitrogen ylides are an interesting and important class of reactions. The general scheme involves converting an amine into a tetravalent salt and creating an anionic center adjacent to it. This ylide, if properly stabilized, can undergo semiconcerted additions to centers of unsaturation such as alkenes, acetylenes, or a variety of other functional groups. Zugravescu and Petrovann have reviewed the subject in a recent text (3).

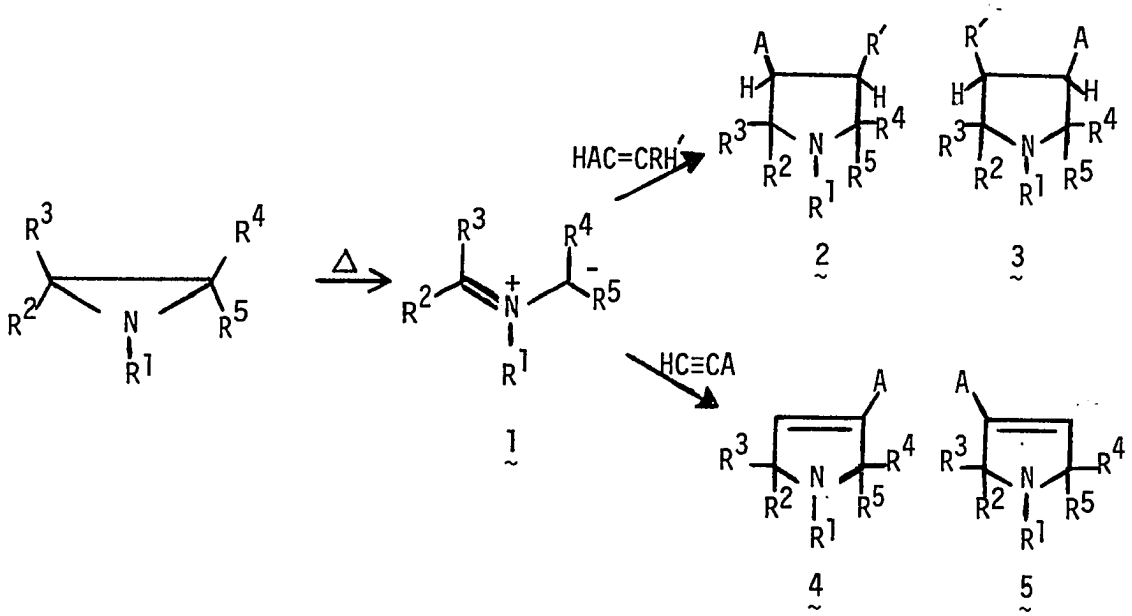
Unlike the ylides of phosphorus, which gain stability by becoming pentavalent, nitrogen cannot adopt this valency, having no 3d-orbitals available to do so. The only stabilization gained involves electrostatic interactions between the two charges located on adjacent atoms. However, stabilizing groups can be appended to either or both ends of the ylide. This class of stabilized nitrogen ylides has received enormous attention due to its versatility as synthetic building blocks.

This literature review will summarize the five known azomethine and nitrile ylide types that have been shown to undergo 1,3-dipolar cycloadditions to activated olefins and acetylenes. They include: (1) acyclic azomethine ylides, (2) pyridinium ylides, (3) diazinium ylides, (4) nitrile ylides, and (5) five-membered N-heterocyclic azomethine ylides.

Acyclic Azomethine Ylides

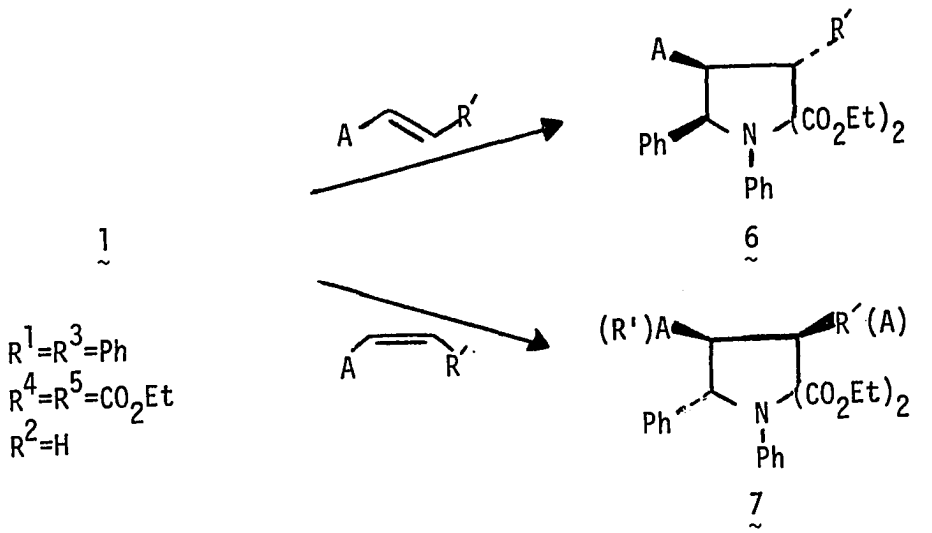
The simplest of these dipoles, the azomethine ylide (1), was first predicted by Huisgen (4,5). Ylides of this type have been formed in

<u>situ</u> by aziridine ring opening. Olefins and acetylenes have been shown to be efficient trapping agents for these 1,3-dipoles, yielding pyrrolidines (<u>2</u> and <u>3</u>) or 1,2-dihydropyrroles (<u>4</u> and <u>5</u>) (6,7,8,9).



The addition orientation of a dipole such as <u>1</u> where $R^1 = R^3 = Ph$, $R^2 = H$, $R^4 = R^5 = CO_2Et$, has been studied by Huisgen and co-workers (10). When the unsymmetrical ethylenic compound was of the <u>trans</u>-geometry with activating group (A) equal to ester, acyl, or nitrile, the product was only that with the regiochemistry of pyrrolidine <u>2</u>. With a <u>cis</u>-activated olefin, the products were mixtures of <u>2</u> and <u>3</u>. Although the regiochemistry is sometimes a mixture, the geometry of the groups attached to the olefin is preserved in the product. This is referred to as "<u>cis</u>" addition and is a general rule for 1,3-dipole cycloadditions (4,11,12).

An interesting anomaly is observed in the resulting stereochemistry of the C-4 and C-5 carbons of the pyrrolidines <u>6</u> and <u>7</u>.



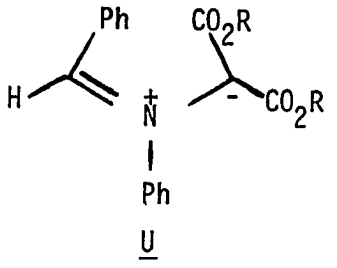
1

$R^1=R^3=Ph$
$R^4=R^5=CO_2Et$
$R^2=H$

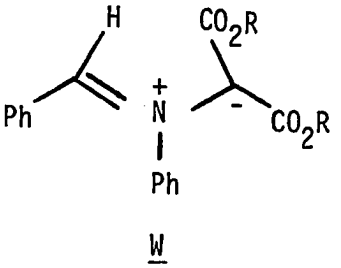
6

7

If a trans-olefin is employed, the product 6 is observed with the more sterically crowded geometry at C-4 and C-5. If a cis-ethylenic compound is used, the less crowded product 7 is obtained. This effect is explained by Texier (13) as resulting from two unique approach orientations of the dipolarophile with respect to the 1,3-dipole. With cis-olefins, the addition seems to preferentially occur in such a direction as to minimize the steric repulsion of the groups that will be attached to C-4 and C-5. With a trans-olefin, the secondary π orbital overlap between the activating group (A) and the phenyl group on the dipole seems to be the controlling factor of the stereochemical outcome in the product (14). This explanation has been refined by Zugravescu and Petrovanu in terms of ylide geometries adopted for cyclization (3). They believe that of the two possible dipolar conformations, U or W, the less stable conformer, U, is the one responsible for the observed product stereochemistry. It is contended that this orientation is taken in additions to both cis- and trans-olefins.

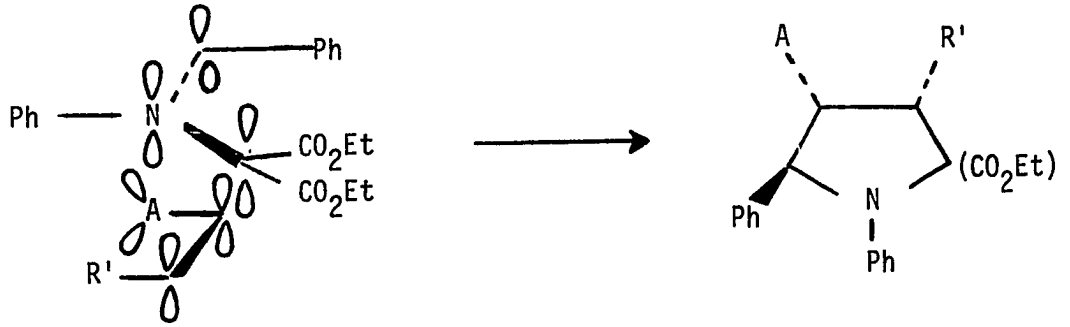


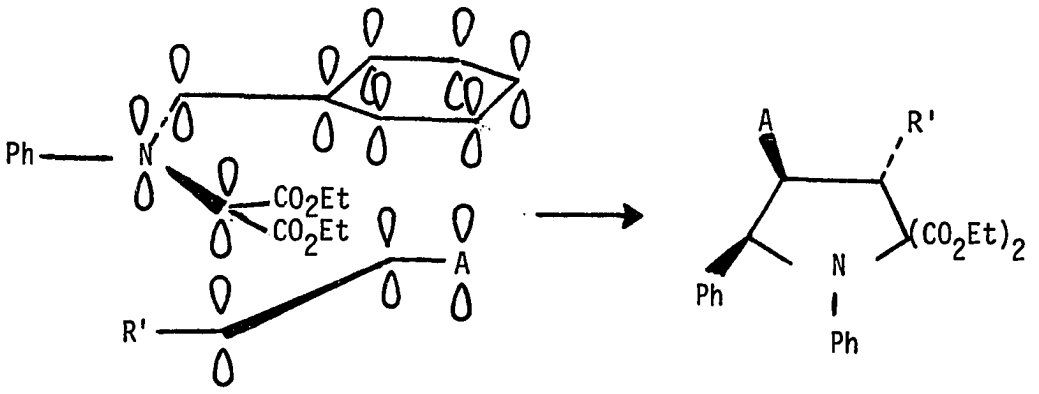
U



W

Cis-olefins approach the dipole so as to maximize the π orbital overlap between the ethelenic activating group (A) and the dipole's π orbitals. This is similar to the endo-rule in Diels-Alder reactions. Trans-olefins, on the other hand, approach the dipole so as to maximize the π orbital overlap between the activating group (A) and the secondary π orbitals on the stabilizing group attached to the dipole, in this case phenyl.

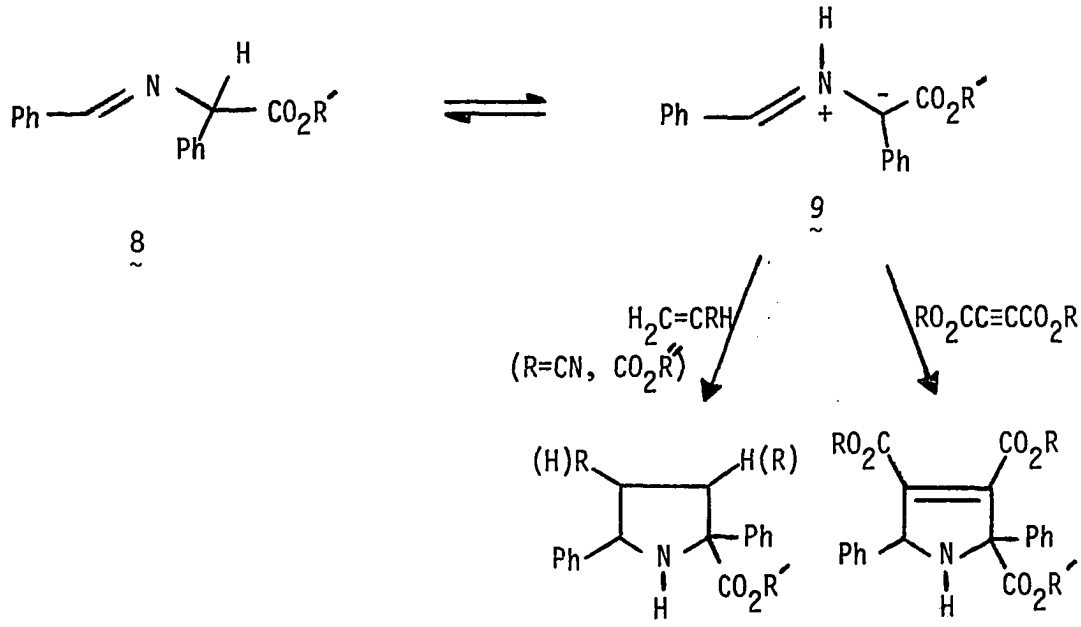




This explanation predicts the observed stereochemistry, but the factors responsible for the different approach paths are as yet not totally understood. In any event, the outcome is always such that cis-addition is obeyed and the groups becoming attached to C-3 and C-5 always adopt a trans-orientation.

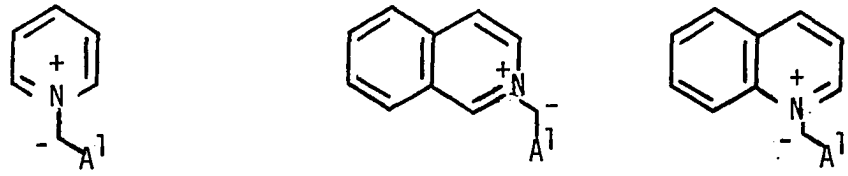
As mentioned earlier, acetylenes add to give dihydropyrroles. Unsymmetrical alkynes yield products (4 and 5) resulting from both addition orientations (13).

Grigg and co-workers report that imines such as 8, which thermally isomerize to the zwitterionic form 9, can be trapped by dipolarophiles. Again, a mixture of regioisomers is obtained with unsymmetrical olefins or acetylenes (15).



Pyridinium Type Ylides

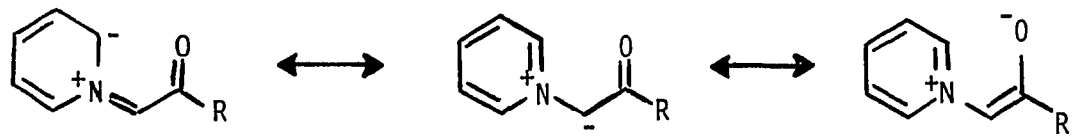
The next important class of azomethine ylides is that containing the nitrogen in a pyridine (10) or benzopyridine ring (11a and 11b).



10 11a 11b

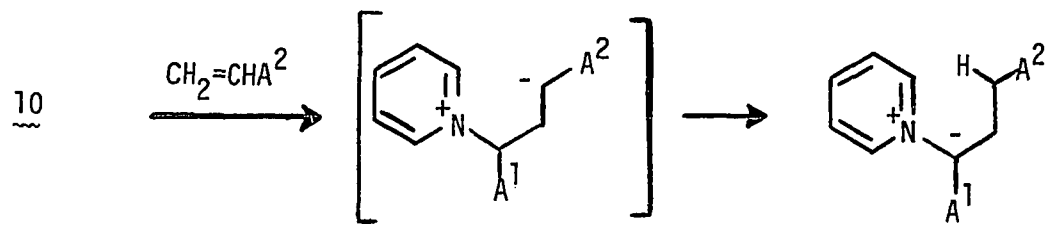
The standard method of preparation is hydrogen halide elimination from the quaternary pyridinium salt (16). The ylides are much more stable than the acyclic azomethine ylides of type 1. The anionic charge

can be stabilized through resonance with the aromatic ring, or through delocalization with the activating group (12a and 12b).



12a 12 12b

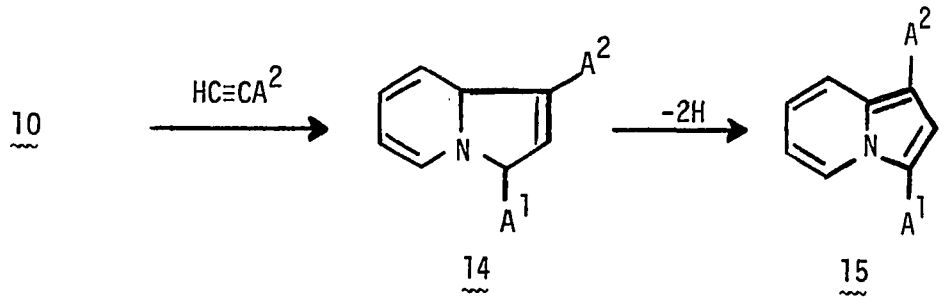
Pyridinium ylides have been shown to add to activated olefins in a Michael addition fashion (17). If there is an available proton in the acidic position α- to the pyridinium nitrogen, anion exchange occurs to regenerate an ylide (13). In many cases, the new ylide can be isolated as a stable product (18). Products arising from further cyclizations (i.e., anion attack on the aromatic ring) are not observed.



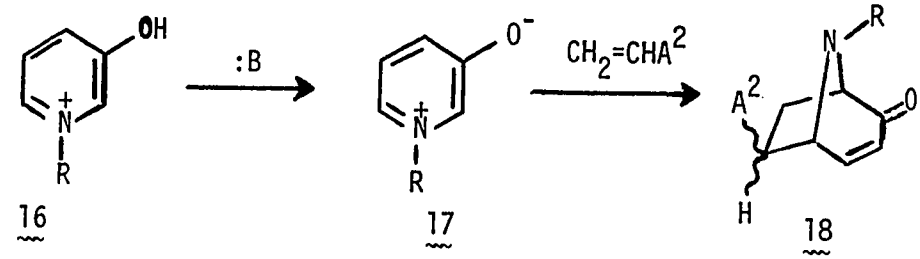
10 13

Additions to acetylenes, conversely, afford bicyclic products. With an activated alkyne, the ylide bonds first in a Michael addition. The resulting vinyl anion then attacks the 2-position of the pyridinium ring, yielding bicyclic 14. Due to the observation that varying amounts of proton-abstracted open chain products are formed, a synchronous

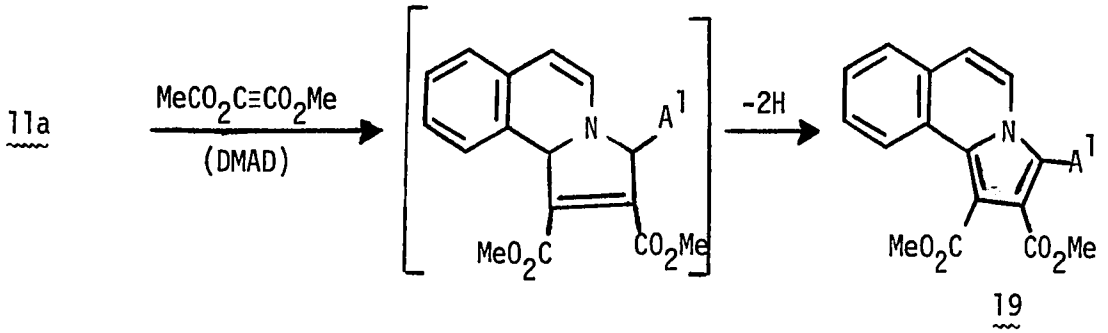
mechanism is not accepted. The products 14 show a marked tendency to dehydrogenate under the reaction conditions to form aromatic systems (15) (4,19,20,21).



The 3-hydroxy-n-alkylpyridinium salt 16 can be easily deprotonated to yield ylide 17. This ylide has been reported to add regiospecifically to unsymmetrical activated olefins to give bicyclic 18, as a mixture of exo- and endo-isomers (22).

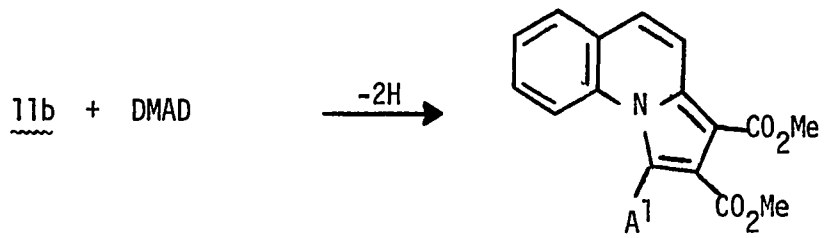


Isoquinolinium ylides (11a) behave like their pyridinium ylide counterparts toward olefins; i.e., normal Michael addition without subsequent cyclization (23). Cycloadducts were, however, observed with activated acetylenes, such as DMAD (dimethylacetylene dicarboxylate). These adducts dehydrogenated to give the aromatic tricyclic system 19 (24).



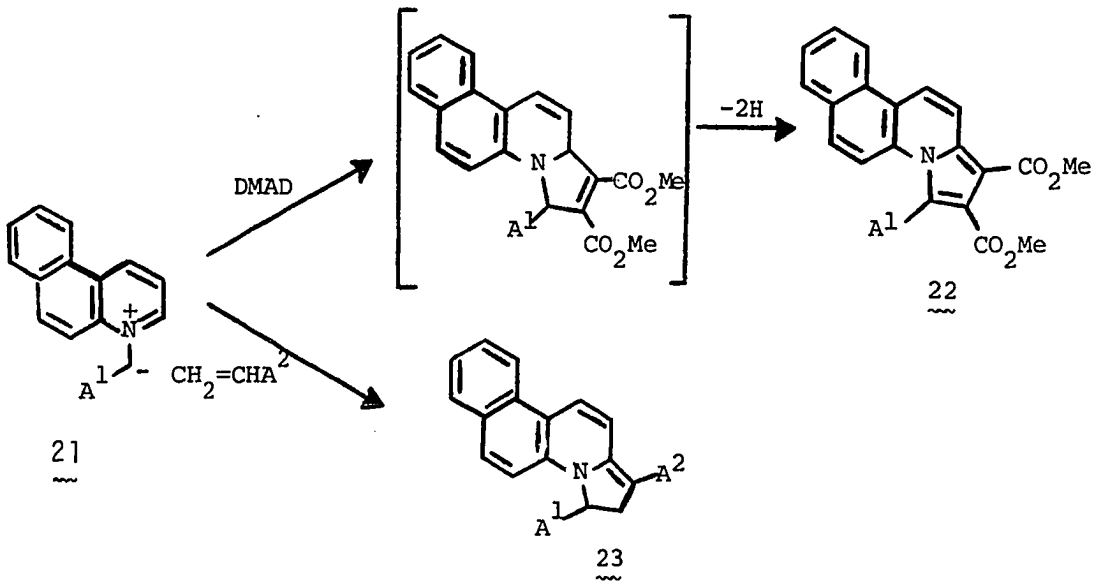
19

No additions to activated olefins were reported for monoactivated quinolinium ylides (11b). They are somewhat less stable than the corresponding isoquinolinium ylides. Dipolar compounds such as 11b do react with DMAD to give aromatic tricyclic systems (20) after dehydrogenation (25).

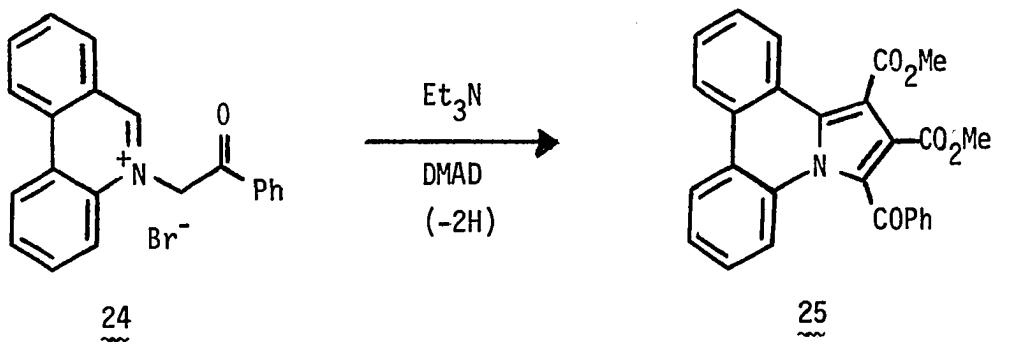


20

The benzo[f]quinolinium ylide 21 will add to both activated acetylenes and olefins. Products 22 and 23 are formed, respectively. Subsequent aromatization of the five-membered ring in product 23 does not occur (26).

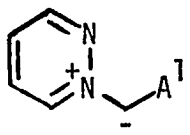


The last ylide of this type reported to undergo a cycloaddition is the dipole generated in situ from N-phenacyl-phenanthridinium bromide (24). Trapping by DMAD gave adduct 25 after dehydrogenation (27).

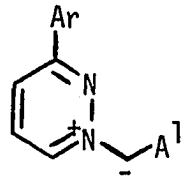


Diazinium Ylides

Ylides derived from the unsubstituted pyridizine (26) are not very stable and little information about cycloaddition to activated olefins and acetylenes is available (28,29).

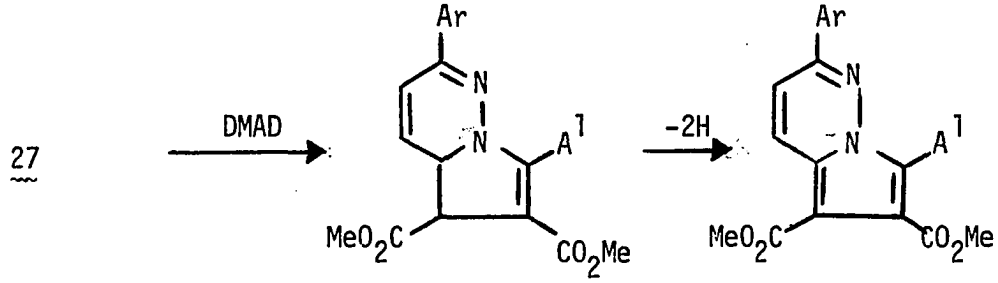


26



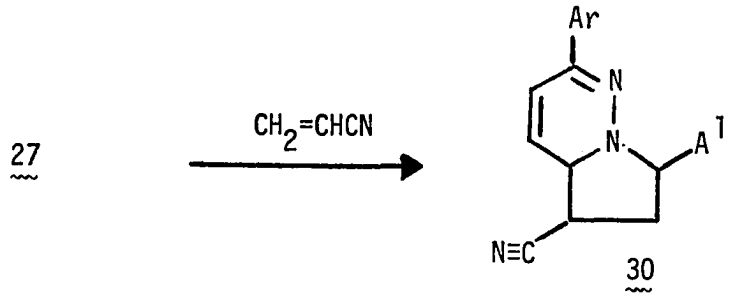
27

Substitution in the 3-position by an aryl group, however, greatly stabilizes the dipole and cycloadditions are reported for these compounds. The addition to DMAD gives the expected ring system (28), wherein the double bond has moved into conjugation with the dipole stabilizing group (A^1). Further dehydrogenation gives the fully aromatic system (29) (30).

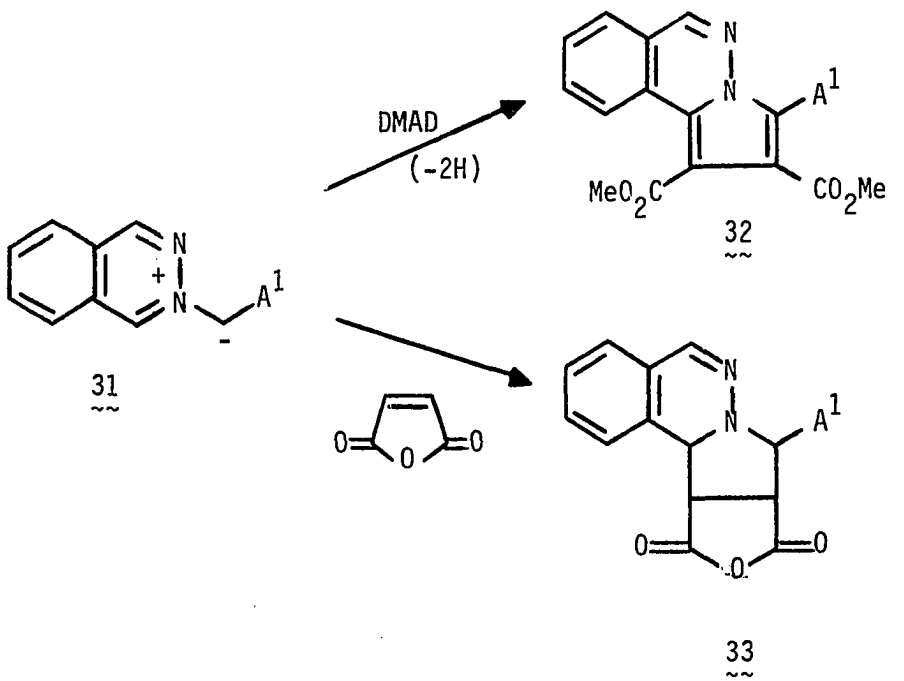


27 → (DMAD) → 28 → (-2H) → 29

Activated alkenes will also add to the ylide. Only one regioisomer is obtained if the olefin is unsymmetrical. Addition to acrylonitrile gives adduct 30. No comment was made concerning the stereochemistry of the three resulting centers (31).

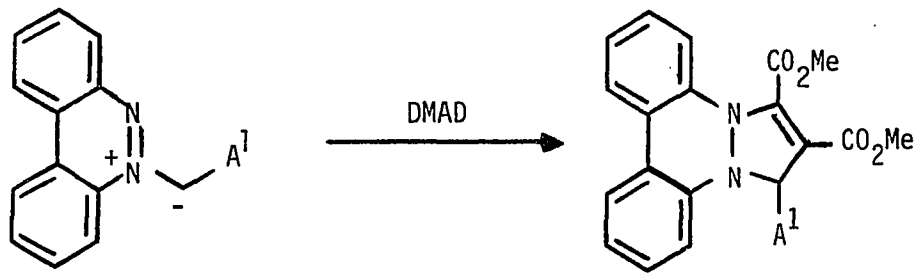


Similarly, the phthalazinium ylides (31) undergo 1,3-dipolar cycloadditions with DMAD or maleic anhydride to give products (32) and (33), respectively (32). It is unclear whether the mechanism leading to these products is a synchronous cyclization or one occurring in two discrete steps.



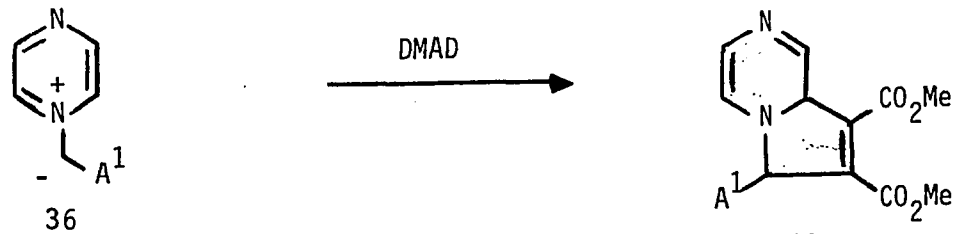
When the position α- to the ylide nitrogen is blocked by an aromatic ring (dipole 34), the addition takes a different course.

Cyclization to the adjacent nitrogen is observed, yielding system (35) (33).

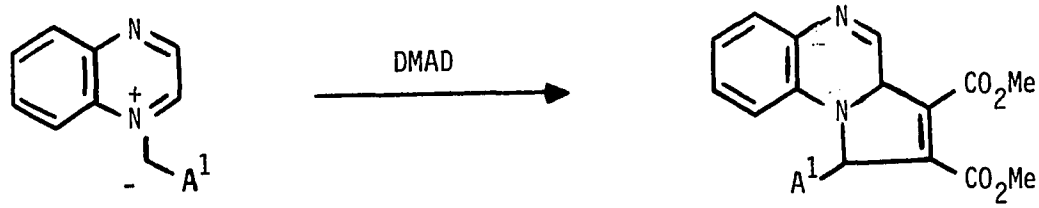


34 35

The isomeric pyrazinium ylide (36) and benzopyrazinium ylides (37) undergo 1,3-dipolar cycloadditions to DMAD to give heterocyclic systems (38) and (39). (34,35).



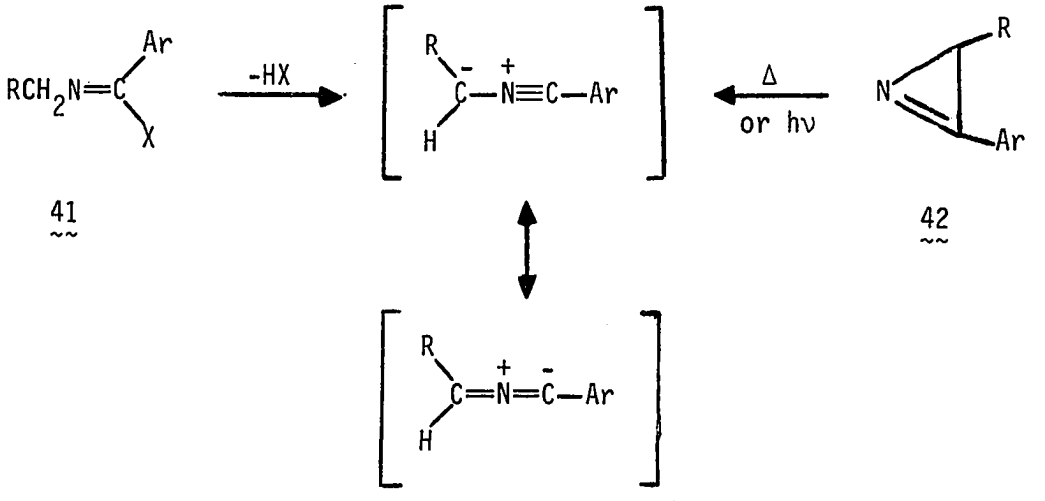
36 38



37 39

Nitrile Ylides

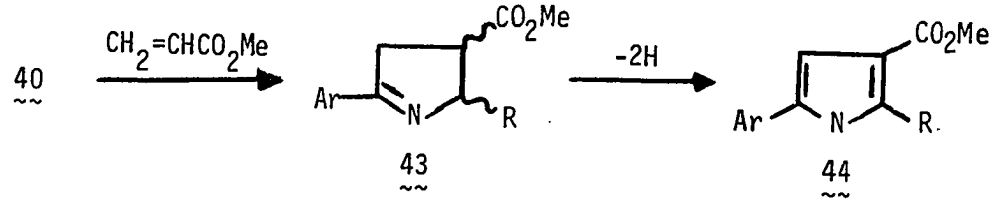
Nitrile ylides (40) are generated via either hydrogen halide elimination from the imidohalide (41) (36) or by ring opening of an arylazirine (42) (37).



41 42

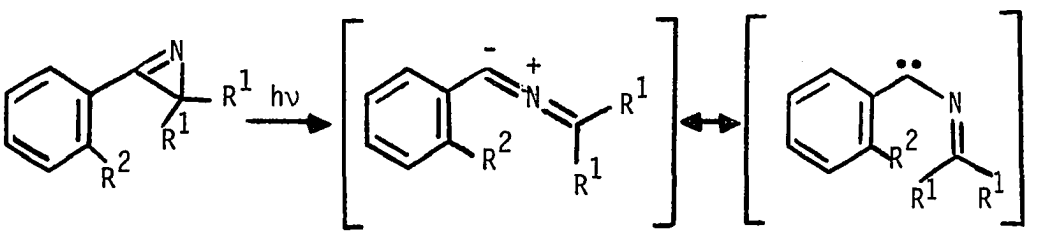
40

These highly reactive ylides add quite readily to olefins and acetylenes. The adducts formed are mixtures of cis- and trans-Δ'-pyrrolidines (43). The products are usually dehydrogenated to pyrroles (44) (36).

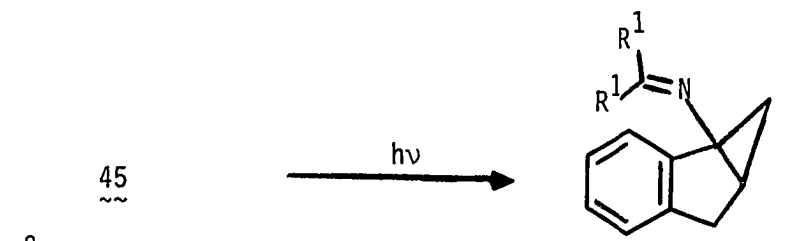


40 43 44

The orientation of addition to activated unsymmetrical olefins is one which yields a five-membered ring with both activating groups located on adjacent carbons. The predominant resonance form for addition seems to be that which has the anionic charge located on the sp^2 carbon (see 40). The secondary orbital interaction as the two units approach each other along parallel planes in the transition state is considered to be the controlling factor for the stereochemical outcome of the product. The work of Padwa and Smolanoff seems to support this theory. They report efficient trapping of the nitrile ylide 45 by both intra- and inter-molecularly activated olefins (38). This ylide is photochemically generated by ring opening of the corresponding arylazirine (46). This ylide is in resonance with its carbene isomer 47. If the parallel plane geometry is attained with difficulty in the transition state, the products are primarily those arising from carbene insertion. This is observed when the intramolecular trap is an allyl group, leading to cyclopropane 48. The dipolar cycloaddition reaction is enhanced by either lengthening the chain attaching the olefinic trap (49), thereby allowing the correct transition state geometry to be attained, or appending an activating group on the terminus of the olefin (50), causing the homo-lumo energy differences between dipole and dipolarophile to decrease and, therefore, suppressing the carbene reaction.

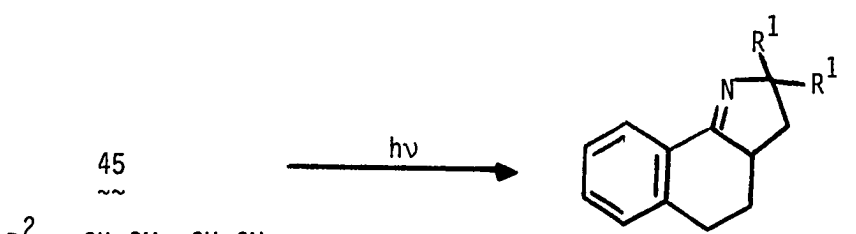


46 45 47



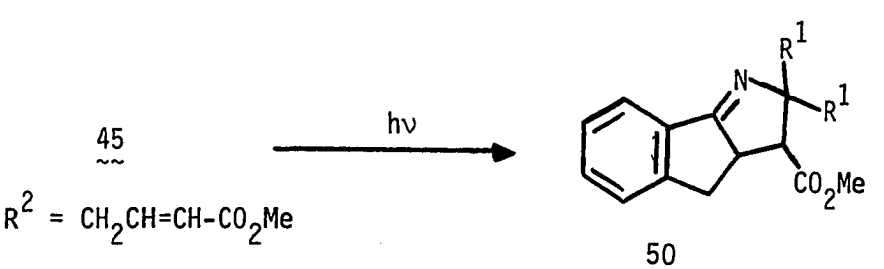
$R^2 = CH_2-CH=CH_2$

48



$R^2 = CH_2CH_2-CH=CH_2$

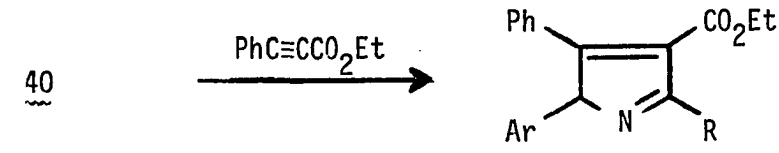
49



$R^2 = CH_2CH=CH-CO_2Me$

50

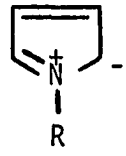
The five-membered heterocyclic systems 51 are obtained when activated acetylenes are added to the 1,3-dipoles (39).



51

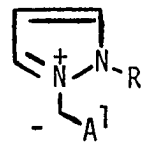
Five-Membered-N-Heterocyclic Azomethine Ylides

This last class of 1,3-dipoles encompasses the azomethine ylides formed from five-membered heterocyclic compounds with a nitrogen in the ring (52-57). The most common method of preparation is quaternization of the nitrogen in the parent aromatic system followed by deprotonation of the acidic methylene group attached to the iminium salt.



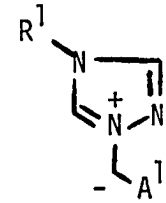
52

pyrrole ylide



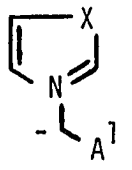
53

pyrazolium ylide



54

triazolium ylide

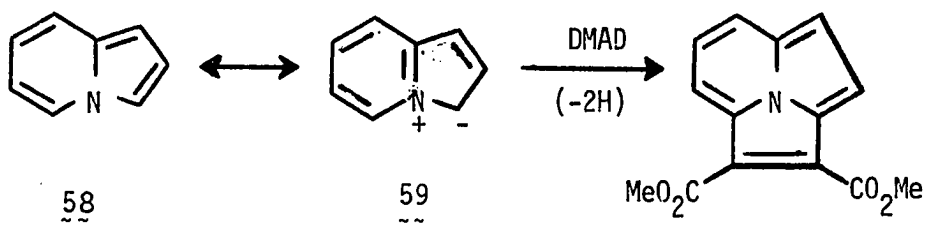


55 X = NR - imidazolium ylide

56 X = O - oxazolium ylide

57 X = S - thiazolium ylide

Ylides of the pyrrole systems (52) show no tendency to undergo cycloadditions. The anionic center will Michael add to DMAD creating a ketene enolate which abstracts a proton to give a 1-substituted pyrrole (40). However, indolizine (58) has a resonance form of an ylide nature (59), and can add to dipolarophiles such as DMAD (41). No examples of additions to olefinic compounds have been reported.

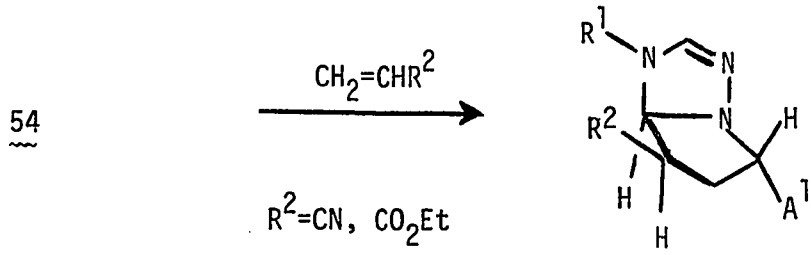


58 59

The pyrazolium ylides (53) are a family of stable dipoles which show no tendency to add to either olefins or acetylenes. Michael addition occurs followed by proton migration to yield a new stable ylide (42).

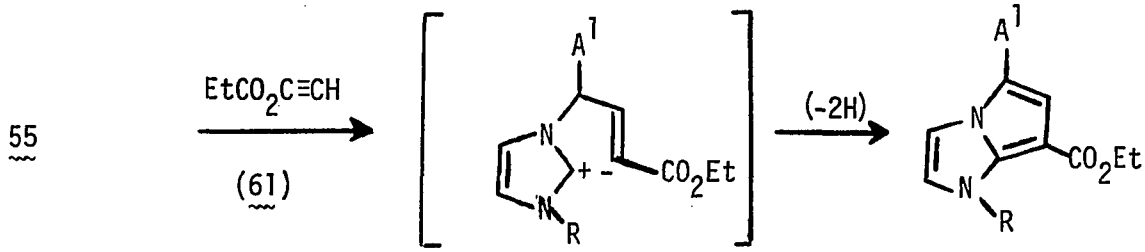
Triazolium ylides (54) are reported to add stereo- and regio-specifically to unsymmetrical olefins to give bicyclic compounds (60).

NMR, NOE and irradiation studies indicate that the cycloaddition occurs to produce adducts with the stereochemistry as shown (43).



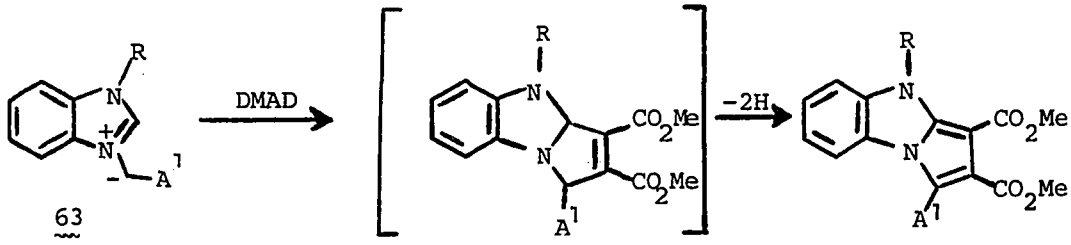
60

Imidazolium ylides (55) show a marked tendency to undergo cycloadditions to activated acetylenes. Addition to ethylpropiolate (61) is believed to go via a two-step mechanism involving a zwitterionic intermediate (62) (44).



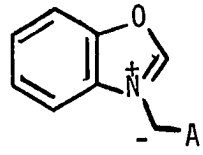
62

The corresponding benzimidazolium ylide (63) undergoes analogous cycloaddition to DMAD (45).



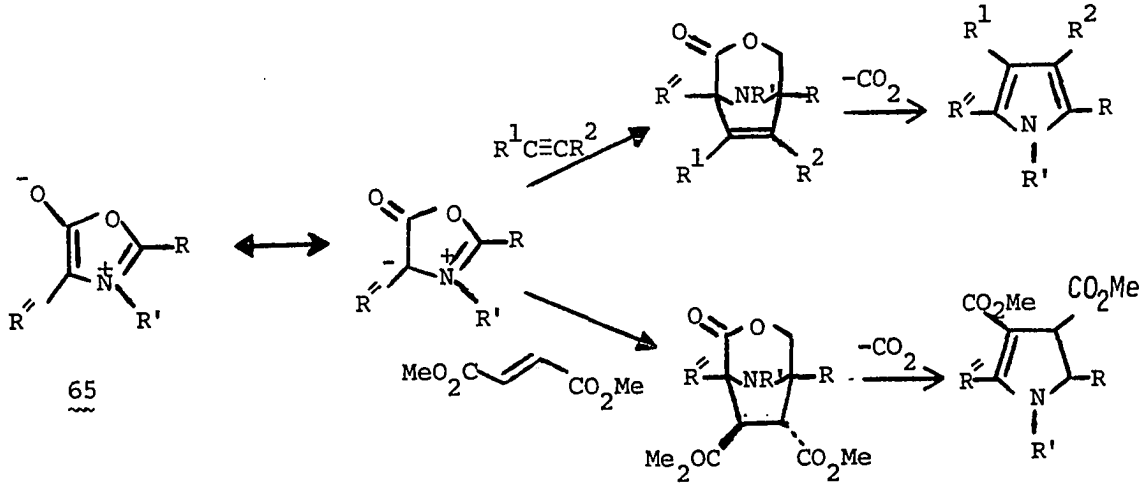
63

Oxazolium ylides (56) are not reported to add to alkenes or alkynes, but benzoxazolium ylides (64) will add to 2 equivalents of DMAD in what is believed to be a two-step mechanism (46).



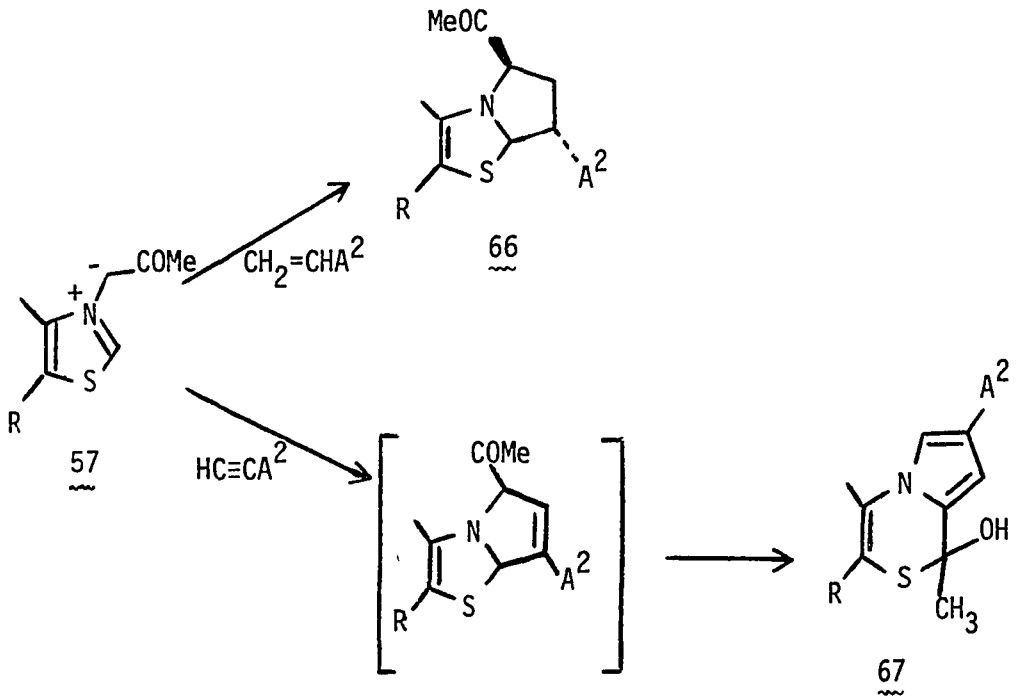
64

It was found that the dipole formed from the 5-hydroxy derivative (65) can be efficiently added to activated acetylenes and olefins (47,48). The initial olefin adduct appears to retain the stereochemistry of the starting compound.



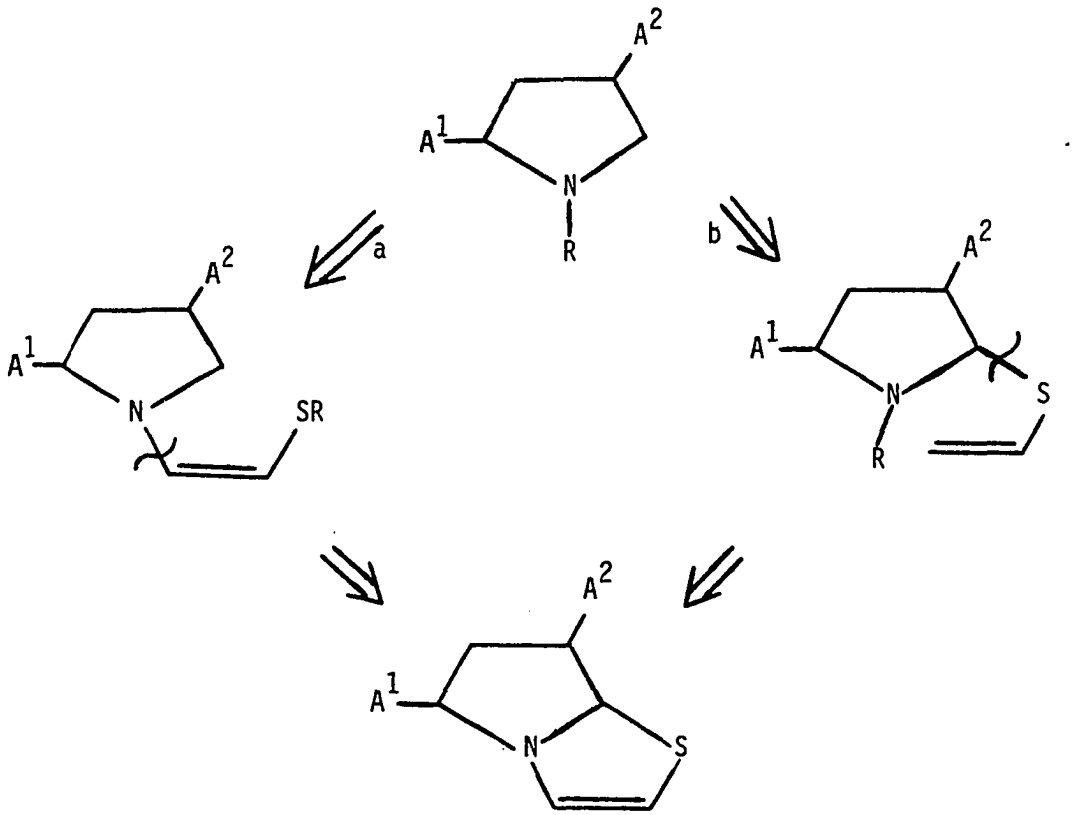
65

Ylides of the thiazolium class (57) are reported to add to a variety of activated olefins and acetylenes, yielding bicyclic structures 66 and 67 (49,50,51). The dipoles, generated in situ, have been shown to add regio- and stereospecifically to the dipolarophiles in what is believed to be a concerted mechanism. The initial acetylenic adduct is observed to undergo a structural rearrangement via cleavage to the vinyl sulfide followed by attack upon the carbonyl group, yielding hemithioketal 67 (50).



RESULTS AND DISCUSSION

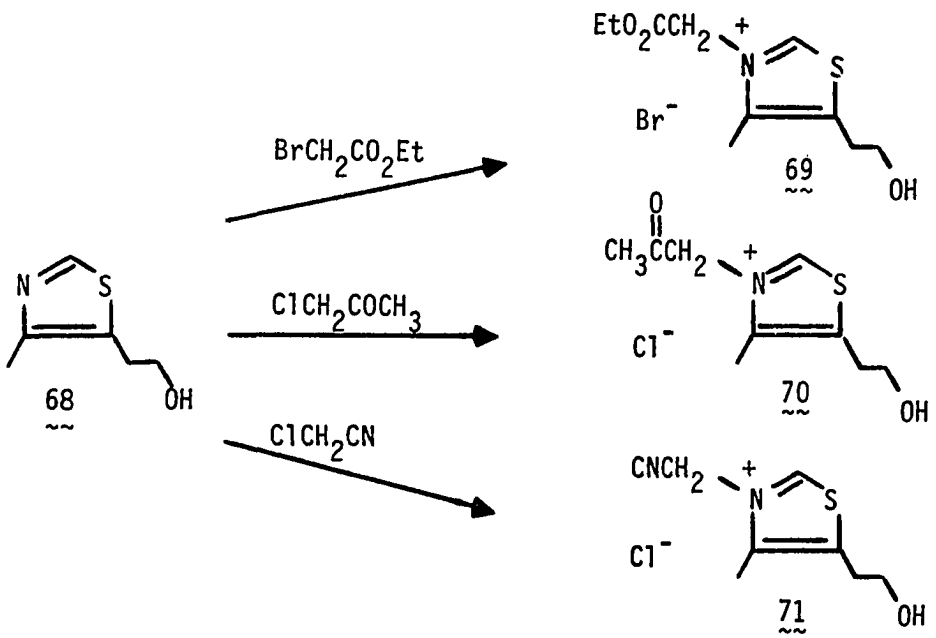
The small number of examples reported for 1,3-dipolar cycloadditions with thiazolium ylides (57) prompted us to investigate the stability and reactivity of these dipoles. It was hoped that selective carbon-hetero atom (N or S) bond cleavage may be achieved to eventually yield a stereospecifically substituted pyrrolidine. The two retrosynthetic modes of bond disconnections are depicted as a and b, both of which lead back to the original 1:1 adduct from the dipolar cycloaddition.



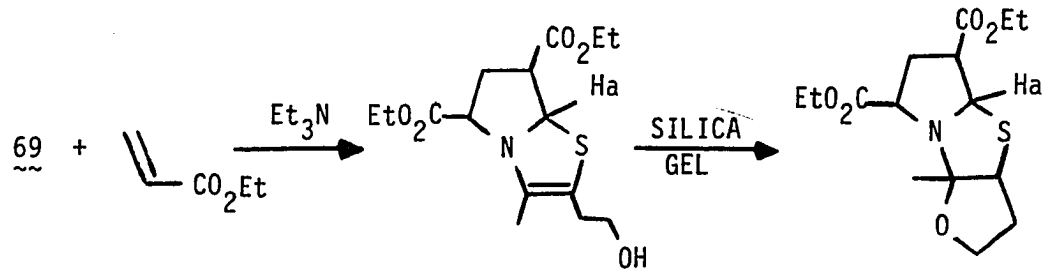
Our goal was threefold: first, to determine the reactivity of the thiazolium ylide with respect to activation and steric hindrance on the dipolarophile; second, to identify the stereochemical configurations at the four new asymmetric centers created in the cyclization; and third,

to demonstrate the utility of the addition reaction by defining conditions for selective cleavage to pyrrolidines.

We chose 5-methyl-thiazol-4-ethanol (68) as our starting material due to its ready availability from an inexpensive source — the hydrolysis of thiamine. This compound is far less expensive than the parent unsubstituted thiazole. Facile salt formation with either ethyl bromoacetate, chloroacetone, or chloroacentonitrile gave thiazolium halides 69, 70 and 71, respectively, by a procedure analogous to that reported by Potts and co-workers (50). These salts proved to be easily purified and amenable to storage indefinitely with no observable signs of decomposition.



The initial study involved creating the ylide of salt 69 with triethylamine and reacting it with one equivalent of ethyl acrylate to produce the bicyclic molecule assigned structure 72a. The proton NMR spectrum seemed to confirm this assignment. It contained two unique ethyl ester groups, a sharp downfield doublet at δ 5.20 (tentatively ascribed to H_a) and a sharp methyl singlet appearing at δ 1.50. A mass spectrum of 72a supported this structure. Along with the adduct, a small amount of colored, very polar material was formed during the course of the reaction. Passage of the crude mixture over a short silica gel column easily separated the two components, but we were quite surprised to find that the isolate had a slightly changed proton NMR spectrum. The downfield doublet now appeared at δ 5.60 and the methyl singlet, at δ 1.60. We reasoned that the bicyclic molecule 72a had undergone a ring closure to form tricyclic diester 73a upon exposure to silica gel.



72a 73a

This structural assignment appeared to fit all of the data, especially the disappearance of both the olefinic absorbance (1550, 1540 cm^{-1}) and the hydroxyl absorbance (3510 cm^{-1}) in the IR spectrum. A single crystal X-ray structure of adduct 73s concretely confirmed this structural assignment (see pg. 28). In some cases, a mixture of

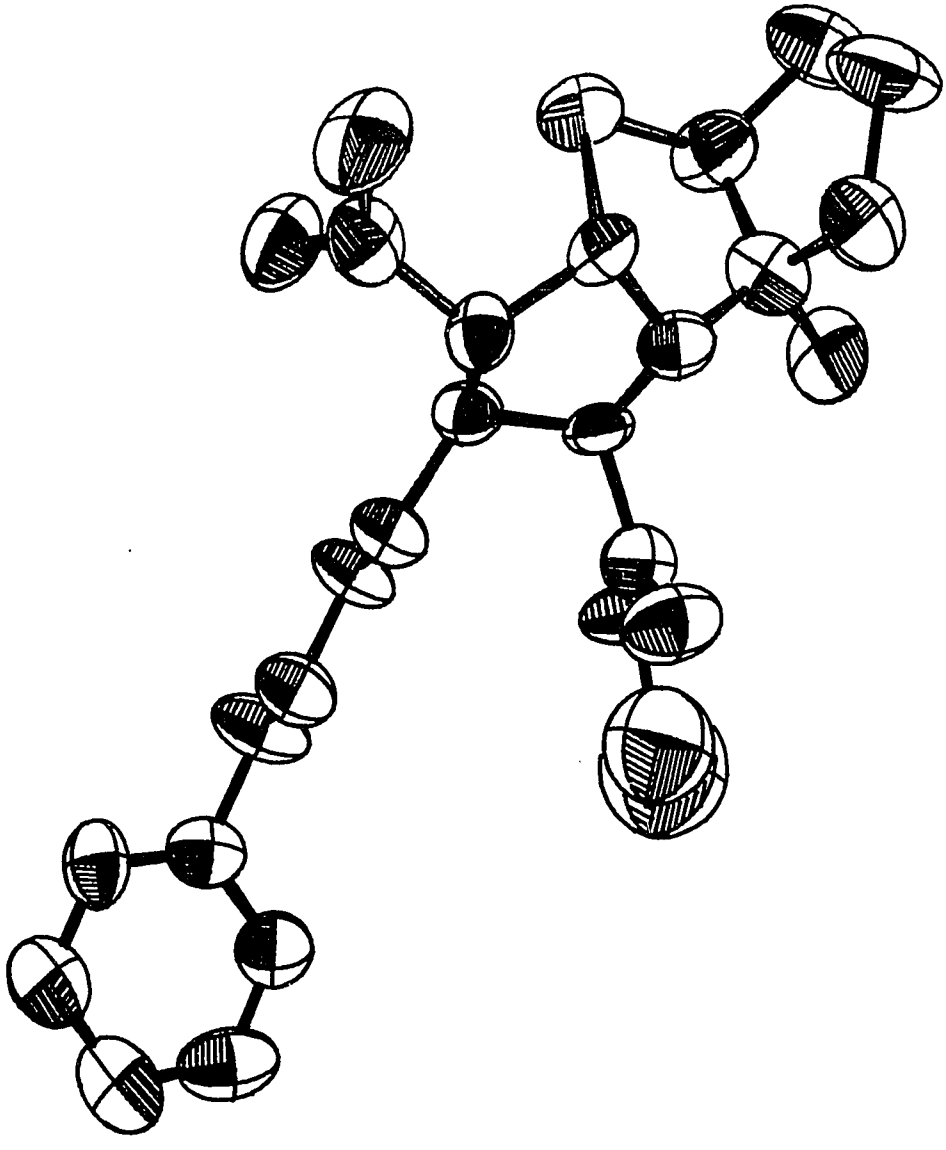
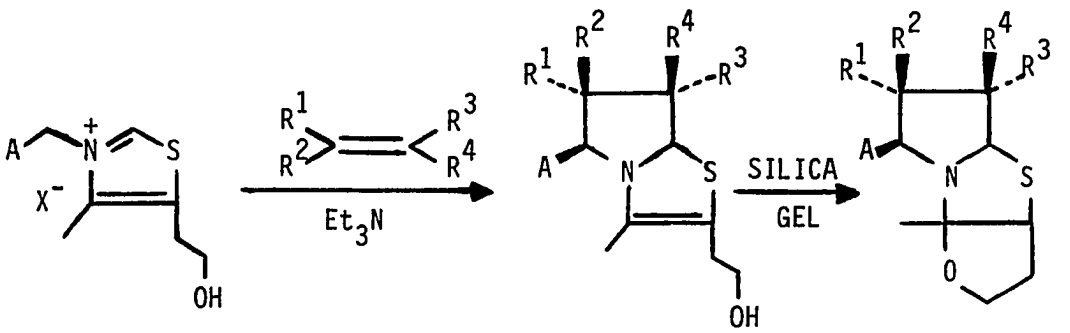


Figure 1. Molecular structure of adduct 73s as determined by a single crystal X-ray analysis

diastereomers were formed, due to the new quaternary center which is created. This is evidenced by two sets of doublets (H_a) appearing downfield between δ 5 and 6.

The results of a study of the cycloadditions of thiazolium salts 69-71, with a variety of mono-, di-, tri- and tetrasubstituted olefins, are compiled in Table 1. A portion of the results has been published as a communication (51).



72 73

69 A = CO_2Et, X = Br^-

70 A = COMe, X = Cl^-

71 A = CN, X = Cl^-

The yields of cycloadducts were found to be significantly higher when a heterogeneous solution of thiazolium salt in acetonitrile was reacted, compared to a homogeneous stirred solution in dimethylformamide. The initial adducts (72) were all converted rapidly into tricyclic compounds (73) by exposure to silica gel, because the tricyclic species tended to be significantly more stable than the open form.

The initial determination of the regiochemistry of the cycloaddition reaction was made by comparing the diethyl-2,4-pyrrole-dicarboxylate

Table 1. The 1,3-dipolar cycloadditions of thiazolium ylides generated *in situ* from thiazolium salts 69-71

Entry	Thiazolium Salt	Olefin	No. Eq.	Solvent[a]	Temp.	% Yield[b]	Adduct	73
1	69	$EtO_2CCH=CH_2$	1	DMF	0°C	55	$R^1=R^2=R^4=H$; $R^3=CO_2Et$	a
2	69	$EtO_2CCH=CH_2$	1	CH_3CN	0°C	82	$R^1=R^2=R^4=H$; $R^3=CO_2Et$	a
3	69	$CH_3COCH=CHCH_3$	1	DMF	0°C	Low	$R^1=R^4=H$; $R^2=CH_3$; $R^3=COCH_3$	b
4	69	$CH_3COCH=CHCH_3$	1	CH_3CN	0°C	70	$R^1=R^4=H$; $R^2=CH_3$; $R^3=COCH_3$	b
5	70	$CH_3COCH=CHCH_3$	1	DMF	0°C	Low	$R^1=R^4=H$; $R^2=CH_3$; $R^3=COCH_3$	c
6	70	$CH_3COCH=CHCH_3$	1	DMF	45°C	45	$R^1=R^4=H$; $R^2=CH_3$; $R^3=COCH_3$	c
7	70	$CH_3COCH=CHCH_3$	1	CH_3CN	23°C	75	$R^1=R^4=H$; $R^2=CH_3$; $R^3=COCH_3$	c
8	70	$CH_3COCH=CHCH_3$	1	CH_3CN	0°C	98	$R^1=R^4=H$; $R^2=CH_3$; $R^3=COCH_3$	c

[a]Reactions run in DMF were homogeneous solutions; those in CH_3CN were heterogeneous.

[b]These yields were all based on material collected after a pass over a silica gel flush column.

Table 1. Continued

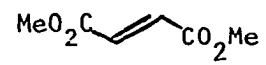
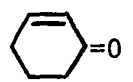
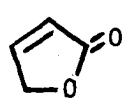
Entry	Thiazolium Salt	Olefin	No. Eq.	Solvent[a]	Temp.	% Yield[b]	Adduct	73
9	70	$p\text{-}MePhSO_2CH{=}CH_2$	1	DMF	0°C	55	$R^1{=}R^2{=}R^4{=}H$; $R^3{=}p\text{-}MePhSO_2$	d
10	70		1	CH_3CN	0°C	89	$R^1{=}R^4{=}H$; $R^2{=}R^3{=}CO_2Me$	e
11	70		1	CH_3CN	0°C	87	$R^2{=}R^4{=}H$; $R^3{=}R^1{=}CO_2Me$	f
12	69		1	CH_3CN	0°C	50	$R^2{=}R^4{=}H$; $R^3{=}R^1{=}CO_2Me$	g
13	69		1	DMF	0°C	--	--	-
14	69	$CH_3(CH_2)_3CH{=}CH_2$	1	DMF	0°C	--	--	-
15	69	$CH_3COCH{=}CHPh$	1	CH_3CN	23°C	77	$R^1{=}R^4{=}H$; $R^2{=}Ph$; $R^3{=}COCH_3$	h
16	71	$EtO_2CCH{=}CH_2$	1	CH_3CN	0°C	57	$R^1{=}R^4{=}R^2{=}H$; $R^3{=}CO_2Et$	i
17	71	$NCCH{=}CH_2$	1	CH_3CN	0°C	53	$R^1{=}R^2{=}R^4{=}H$; $R^3{=}CN$	j
18	70		1	CH_3CN	0°C	--	--	-

Table 1. Continued

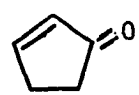
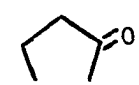
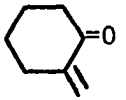
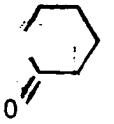
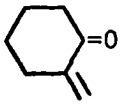
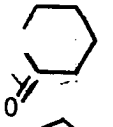
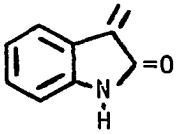
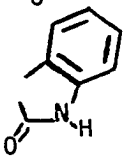
Entry	Thiazolium Salt	Olefin	No. Eq.	Solvent[a]	Temp.	% Yield[b]	Adduct	73
19	70	$NCCH=CH_2$	1	CH_3CN	0°C	56	$R^1=R^2=R^4=H$; $R^3=CN$	k
20	70	$PhCH=CHCHO$	1	CH_3CN	23°C	--	--	-
21	70	$CH_3COCH=CHPh$	1	CH_3CN	23°C	52	$R^1=R^4=H$; $R^2=Ph$; $R^3=COCH_3$	l
22	70	$CH_3CH=CHCH=CHCO_2Me$	1	CH_3CN	0°C	--	--	-
23	71	$CH_3COCH=CHCH_3$	1	CH_3CN	23°C	33	$R^1=R^4=H$; $R^2=CH_3$; $R^3=COCH_3$	m
24	69		1	DMF	0°C	--	--	-
25	69	$CH_2=C(CH_3)CO_2Me$	1	CH_3CN	0°C	30	$R^1=R^2=H$; $R^4=CH_3$; $R^3=CO_2Me$	n
26	70	$(CN)_2C=C(CN)_2$	1	CH_3CN	0°C	--	--	-
27	69		1	CH_3CN	23°C	55	$R^1=R^4=H$; $R^2,R^3=$ 	o

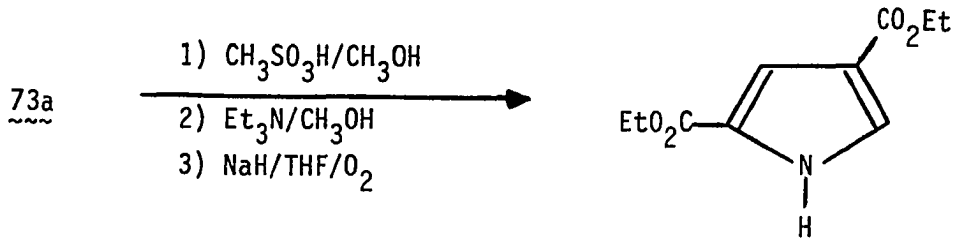
Table 1. Continued

Entry	Thiazolium Salt	Olefin	No. Eq.	Solvent[a]	Temp.	% Yield[b]	Adduct	73
28	69		1	CH_3CN	23°C	~30	$R^1=R^2=H$; $R^3,R^4=$ 	p[c]
29	70		1	CH_3CN	23°C	~30	$R^1=R^2=H$; $R^3,R^4=$ 	q[c]
30	70		1	CH_3CN	23°C	35	$R^1=R^2=H$; $R^3,R^4=$ 	r
31	69	$CH_3COCH=CH(CH_2)_2OBz$	.6	CH_3CN	23°C	59[d]	$R^1=R^4=H$; $R^2=(CH_2)_2OBz$; $R^3=COCH_3$	s
32	69	$CH_3COCH=CH(CH_2)O\overset{|}{\underset{|}{Si}}+$	.4	CH_3CN	23°C	78[d]	$R^1=R^4=H$; $R^2=(CH_2)_2O\overset{|}{\underset{|}{Si}}+$; $R^3=COCH_3$	t

[c]Solutions of exomethylene cyclohexanone were prepared and used immediately with only approximately known concentrations.

[d]These yields were based on equivalents of thiazolium salt reacted.

74 (prepared from adduct 73a) with a sample of authentic material synthesized via permanganate oxidation (52) of ethyl-4-formyl-2-pyrrole-carboxylate prepared by the route of Sonnet (53). Adduct 73a was cleaved by treatment with methanesulfonic acid, followed by triethyl-amine, then an unexpected oxidation with a stirred suspension of sodium hydride in THF exposed to the air. Product 74 was identical to authentic 2,4-diethylpyrrole dicarboxylate by proton NMR and R_f values on TLC plates.

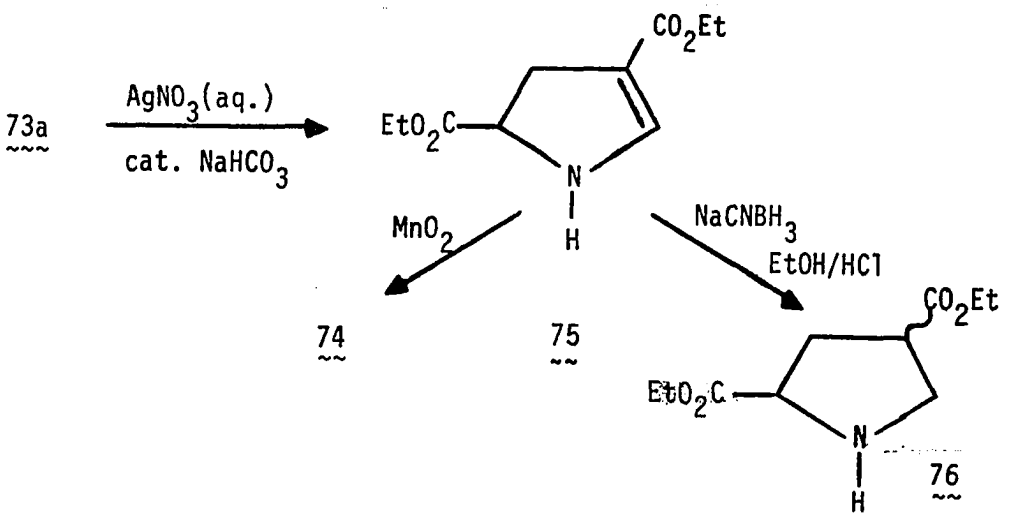


74

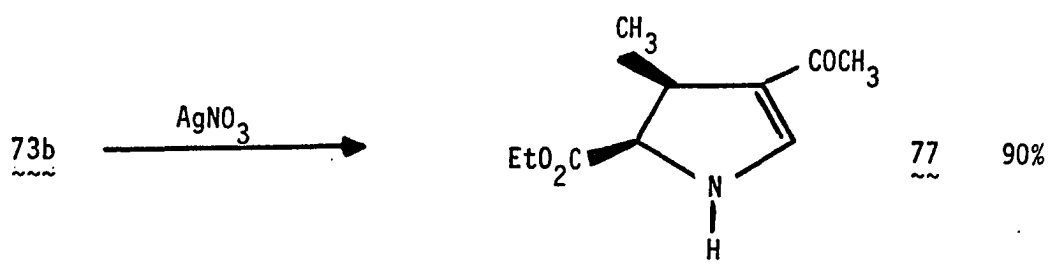
General methods were explored for cleavage of the tricyclic skeletons (73a) to yield pyrrolidines with preservation of the stereochemical centers created by the initial dipolar addition. Our initial attempts using strong acids, strong bases, metal hydrogenation catalysts (Ra-Ni, Rh/C, Ru/C), $NiCl_2 \cdot 6H_2O/NaBH_4$, $CuBr_2/NaCNBH_3$, $BF_3 \cdot OEt_2/Et_3SiH$, CuI/Et_3SiH, MCPBA, Al-Hg, and dissolving metal reductions (Li, Na, Ca in NH_3) were unsuccessful. Either starting material or products arising from attack at other sites in the molecule were recovered.

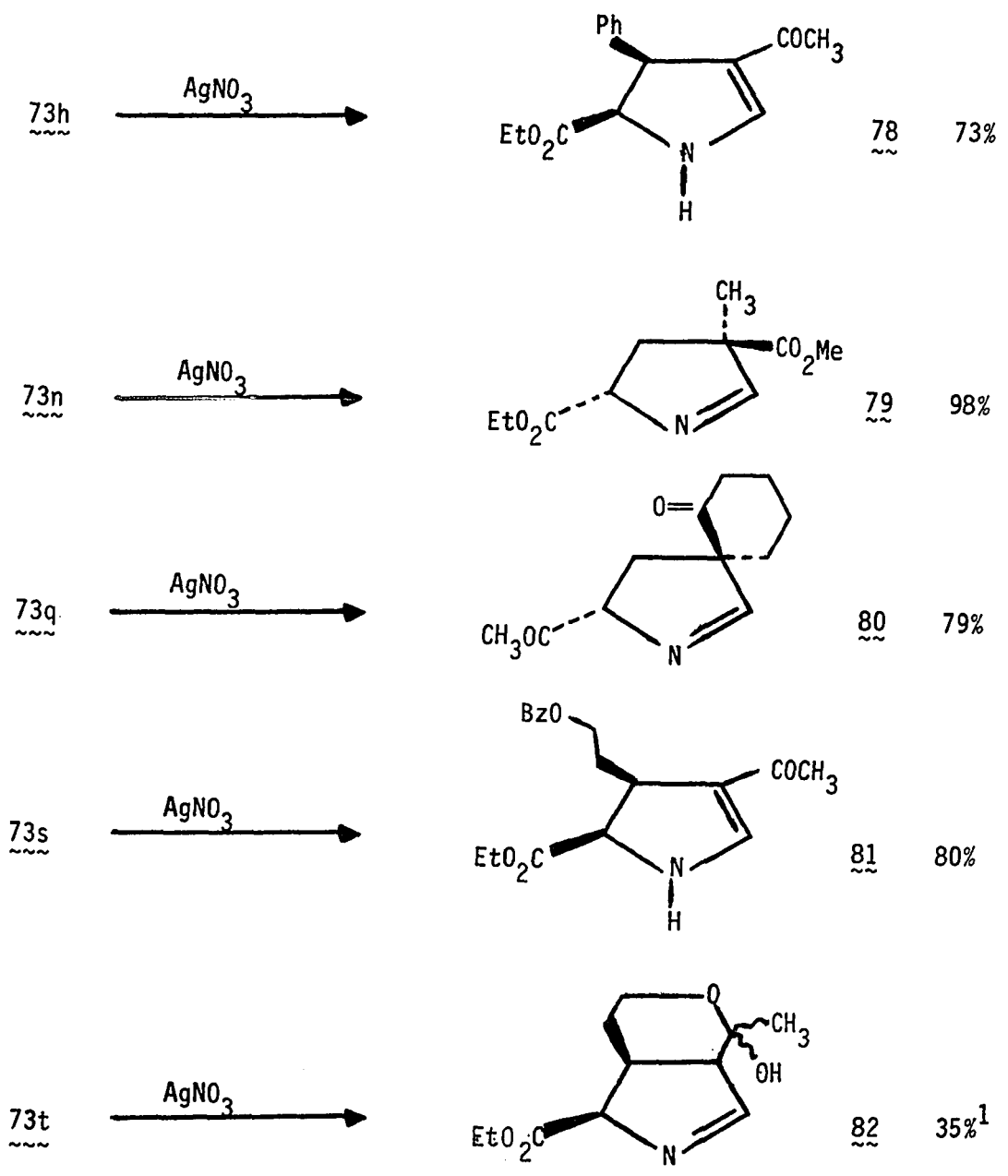
Undaunted, we proceeded to investigate further bond cleavage conditions. A method reported by Luhowy and co-workers (54) for hydrolysis of thiazolidines proved to be moderately successful. Under aqueous conditions in the presence of silver (I), 73a is cleaved in good yield

(67%) to 3,5-dicarbethoxy-Δ^2-pyrroline (75), which compared closely to the similar diester prepared by Saegusa and co-workers (55). The enamine 75 can then be subsequently reduced with sodium cyanoborohydride to diethy-2,4-pyrrolidine-dicarboxylate (76) (as a mixture of diastereomers) in 86% yield, via the method of Borch and co-workers (56). Alternately, 75 can be converted into 74 by MnO_2 oxidation.



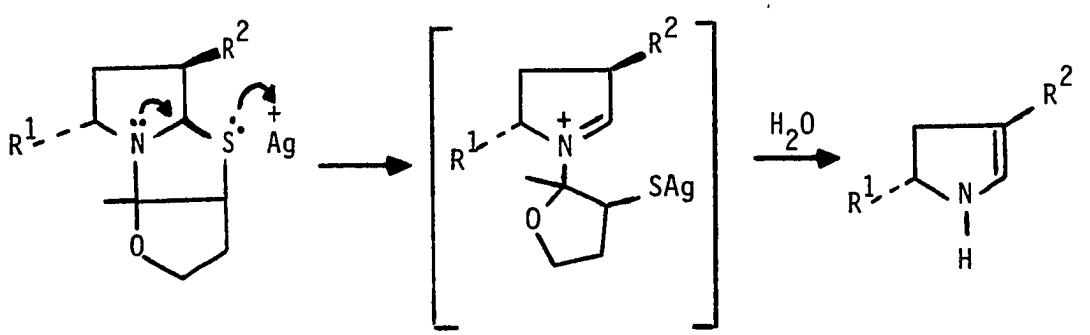
The silver (I) cleavage has been tested on a number of tricyclic systems with mostly gratifying results, although the stereochemistry at C-4 is lost. Compounds 73b, 73h, 73n, 73g, 73s, and 73t yielded Δ^1- and Δ^2-pyrrolines 77-82, respectively, in high yields.





[1]The yield of this compound was rather low due to its high water solubility, causing difficulties in isolation.

Compounds 79, 80, and 82 were isolated as imines. The quaternary center of 73n and 73g makes isomerization to the Δ^2-pyrrolines impossible. In the case of 73t, formation of the hemiketal allows isolation of the imine. This is in keeping with our postulated mechanism: initial coordination of the sulfur atom to the silver ion, followed by cleavage to the iminium salt 83. Subsequent hydrolysis and isomerization allows for formation of compounds of the Δ^2-pyrroline type. Compound 79 was identical to one of the isomers in the diastereomeric mixture synthesized by Saegusa and co-workers (55).

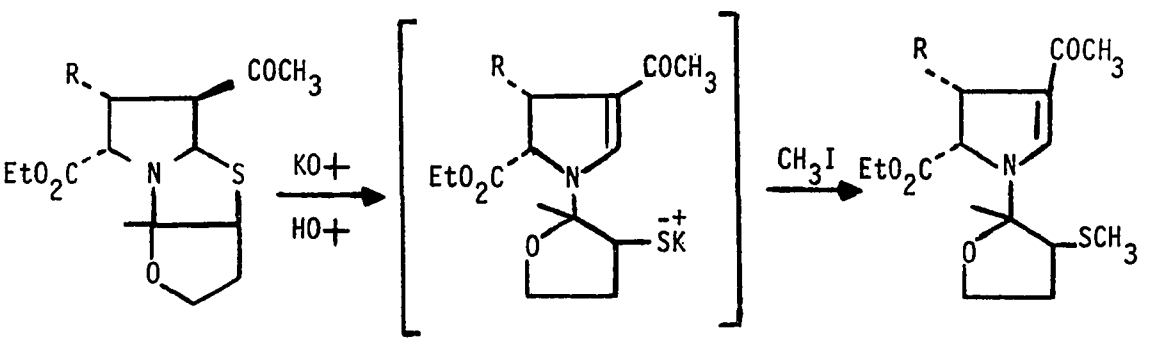


83

Compounds 77-82 have all been reduced to their respective pyrrolidines (by $NaCNBH_3$) with varying degrees of success. The Δ^2-pyrrolines containing ketone groups afforded some overreduction products. This is reasonable since $NaCNBH_3$ is known to reduce carbonyl groups in highly acidic media. In only a few cases, were the reductions reasonably clean. Most of the reactions were contaminated by many side products and the yields of pyrrolidines were quite low. Loss of the C-4 stereochemistry seemed unavoidable by this procedure, since all attempts to reduce the unisomerized intermediate at the iminium ion stage failed.

Although it was an exceedingly useful reaction, the reproducibility of the silver-mediated cleavage in some cases is poor. The reaction is very solvent dependent. The solubility of the starting tricyclic compounds in the very polar solvent can be a problem. In some cases, a precipitate of unknown structure forms and hampers the progress of the reaction. For some systems, the reaction fails completely for no obvious reason.

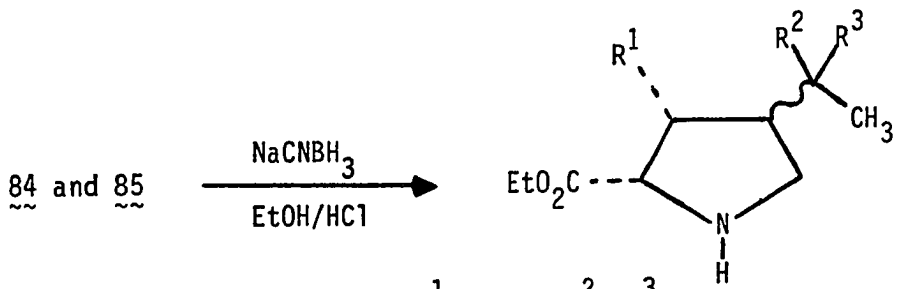
Because of these uncertainties, we sought to develop an improved reaction using somewhat more standard chemical transformations. In the system where an acidic proton is available on the C-4 carbon 73b, 73s, and 73t, we found that strong equilibrating bases such as potassium t-butoxide in t-butanol smoothly created the enolate which spontaneously opened to the Δ^2-pyrroline. An excess of methyl iodide rapidly methylates the resulting thiolate, similar to the work of Brain and coworkers (57). The bicyclic compounds 84-86 are obtained as a mixture of diastereomers on the tetrahydrofuran ring.



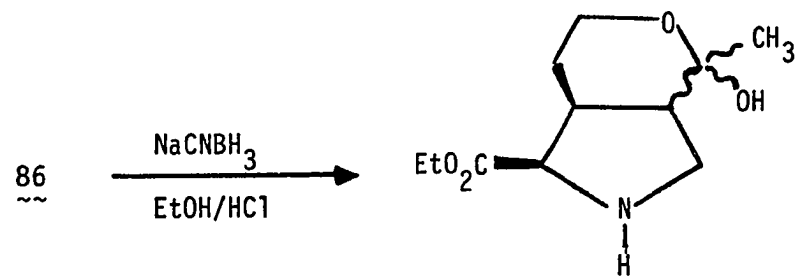
73b R = CH_3
73s R = $(CH_2)_2OBz$
73t R = $(CH_2)_2OSi$+

84 R = CH_3
85 R = $(CH_2)_2OBz$
86 R = $(CH_2)_2OSi$+

The α-amino ethers 84-86 were found to be both cleaved and reduced to pyrrolidines in one step by $NaBH_3CN$ in EtOH/HCl. A mixture of products arising from cis/trans isomers on the newly-created asymmetric centers plus a diastereomeric mixture of secondary alcohols (caused by overreduction) is obtained. Compound 86 showed a tendency to lose the silyl protecting group due to the strongly acidic reaction conditions, and a small amount of hemiketal 89 was obtained.

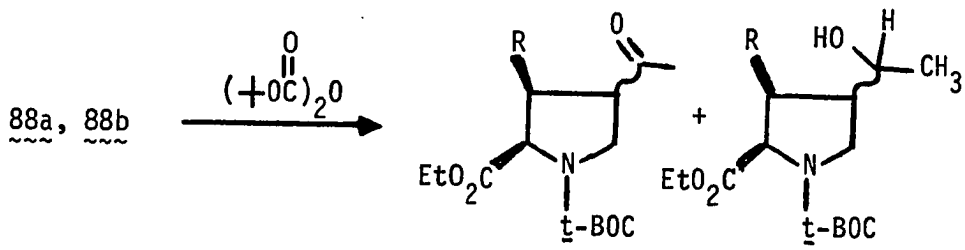


87a $R^1 = CH_3$; R^2, $R^3 = O$
87b $R^1 = CH_3$; $R^2 = H$; $R^3 = OH$
88a $R^1 = (CH_2)_2OBz$; R^2, $R^3 = O$
88b $R^1 = (CH_2)_2OBz$; $R^2 = H$; $R^3 = OH$



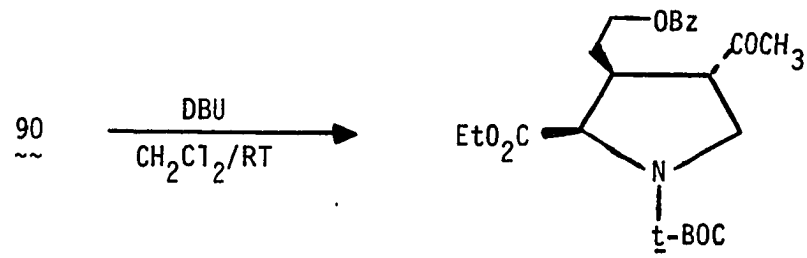
89

The crude mixture of secondary amines 88a and 88b was protected as their N-t-butoxycarbonyl derivatives (58). The ketones 90 were separated chromatographically from secondary alcohols 91.



90 R = $(CH_2)_2OBz$ 91 R = $(CH_2)_2OBz$

The isomers of compound 90 were subjected to epimerization conditions ($DBU/CH_2Cl_2/RT$). The cis-isomer was observed to convert completely into the trans-isomer, as evidenced by both TLC analysis and carbon-13 NMR.

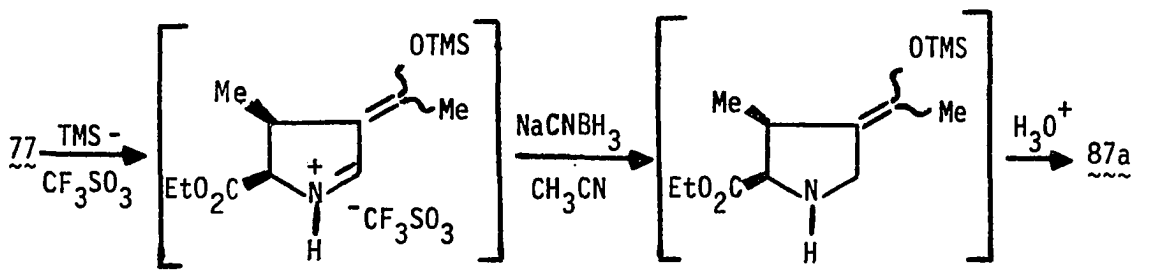


Trans - 90

This route proved to be quite inefficient due to the overreduction by-products created. Since reoxidation of 91 to the acetyl compound with either MnO_2 or DCC proved to be unsuccessful, modified approaches were explored. Elimination with potassium t-butoxide methyl iodide and cleavage of the α-amino ether with 2N NaCl in EtOH afforded the Δ^2-pyrroline 77 (synthesized earlier via the silver ion route). This new two step procedure proved to be more reproducible and slightly easier to carry out on larger scales.

After a substantial amount of 77 had been prepared, conditions for efficient reduction to the corresponding pyrrolidine were sought. Catalytic hydrogenations (Pd/C, Ra-Ni, Rh/Al) proved unsuccessful, yielding either starting material, pyrroles, or unidentifiable resinous matter. Hydride reductions suffered the same fate as observed with $NaCNBH_3$ reduction of bicyclic 84 — that of overreduction to secondary alcohols. Some indication that a reduction by organotin reagents (59) may be effective, prompted us to try tri-n-butyltin hydride with 77, but the reaction yielded only starting material.

We postulated that if an enol ether could be formed with the acetyl group of 77, the resulting iminium salt should be facilely reduced with a borohydride reagent. Enamine 77 smoothly formed the trimethylsilyl enol ether-iminium salt 92 with trimethylsilyl trifluoromethane-sulfonate in CH_2Cl_2 at 0°C (60). This intermediate was not isolated, but reduced *in situ* with a slight excess of $NaCNBH_3$, added in CH_3CN to yield pyrrolidine 93.



92 93

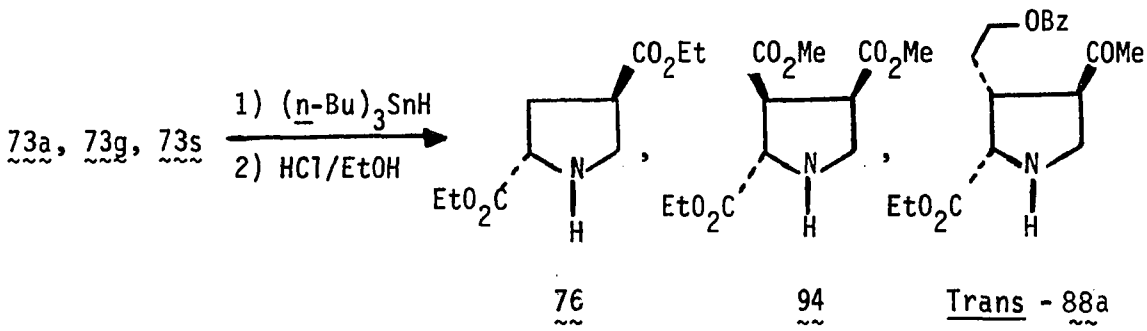
Compound 93 was found to be contaminated by varying amounts of ketone 87a, due to hydrolysis of the enol ether during the course of purification. Subsequent hydrolysis with aqueous acid transformed 93

completely into 87a as an isomeric mixture at C-4. Little overreduced product 87b was observed.

This reaction sequence was carried out on 81 which yielded 88a in a much higher overall yield. The cis-/trans- mixture was transformed into the N-t-butoxycarbonyl derivative, which again epimerized nicely to trans-90.

Shortly after the conditions for the iminium salt reduction were determined, a literature reference (61) prompted us to explore radical cleavages on the initial tricyclic molecules 73. We were quite delighted to find that in the presence of one equivalent of tri-n-butyltin hydride and a catalytic amount of AIBN (2,2'-azobis(2-methylpropionitrile)) in benzene at reflux temperature, 73s was smoothly cleaved to trans-88a after treatment with acidic ethanol. The N-t-butoxycarbonyl derivative was identical (^{1}H NMR, C-13 NMR, and R_f values on TLC plates) to the epimerized material, trans-90.

The utilization of this radical cleavage process represents an extremely rapid route from tricyclic adducts 73 to highly substituted pyrrolidines. It preserves the stereochemistry produced at three of the four centers derived from the 1,3-dipolar cycloaddition of thiazolium ylides with activated olefins. The generality of this route has been demonstrated with a few representative tricyclic systems 73a, 73g, and 73s, which yielded pyrrolidines 76, 94, and trans-88a, respectively.



76 94 Trans - 88a

EXPERIMENTAL

General

Diethyl ether, benzene and THF were distilled from lithium aluminum hydride, ethanol from CaH_2, and t-butyl alcohol from NaH. DMF and acetonitrile were dried over 4 Å molecular sieves. All organic extracts were dried over Na_2SO_4. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman Acculab 2 spectrometer. Nuclear magnetic resonance spectra were determined in $CDCl_3$ on a Hitachi Perkin-Elmer R-20B 60 MHz or a Varian EM-360 instrument with absorptions recorded in ppm downfield from internal Me_4Si. High resolution mass spectra were recorded on an AEI MS-902 high resolution mass spectrometer. Low resolution mass spectra were recorded on a Finnigan 4023 mass spectrometer. Carbon-13 NMR spectra were determined on a JEOL FX-90Q Fourier transform spectrometer, with absorptions expressed in ppm relative to the chemical shift of Me_4Si.

General Procedure for Thiazolium Salts 69, 70, and 71 Formation

The 5-methyl-thiazol-4-ethanol (68) (0.1 mole, 14.3 g) was dissolved in 200 ml of anhydrous ethanol. One equivalent of the halide was added and the solution was allowed to reflux overnight. After cooling the solution, the solvent was removed and a brown solid formed upon standing.

3-(2-Ethoxy-2-oxoethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide (69)

Crude 69 crystallized from isopropyl alcohol after cooling to 0°C. A white solid was collected by filtration, resulting in 27.6 g (0.089

moles, 89%) of pure 69. IR (film in $CDCl_3$) 3310, 2990, 1745, 1590, 1220 cm^{-1}; 60 MHz NMR (D_2O, Ref.: Tier's salt) δ 1.30 (t, J = 7 Hz, 3 H), 2.49 (s, 3 H), 3.15 (t, J = 5 Hz, 2 H), 3.85 (t, J = 5 Hz, 2 H), 4.31 (q, J = 7 Hz, 2 H), 4.60 (s, 1 H), 5.49 (s, 2 H), 9.88 (s, 1 H); 90 MHz C-13 NMR (D_2O, with TMS cap.) δ 11.77, 13.98, 30.04, 54.17, 61.00, 64.64, 136.04, 143.59, 158.03, 167.45.

3-(2-Oxopropyl)-5-(2-hydroxyethyl)-4-methylthiazolium chloride (70)

Crude 70 was recrystallized from isopropyl alcohol and cooled to 0°C. A white solid was collected by filtration yielding 18 g (0.08 mole, 80%) of pure 70. 60 MHz NMR (D_2O, Ref.: Tier's salt) δ 2.50 (s, 3 H), 2.59 (s, 3 H), 3.20 (t, J = 7 Hz, 2 H), 4.00 (t, J = 7 Hz, 2 H), 4.60 (s, 1 H), 5.80 (s, 2 H), 9.85 (s, 1 H).

3-Cyanomethyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (71)

Crude 71 was recrystallized from isopropyl alcohol and cooled to 0°C. A tan solid was collected by filtration to give 15.0 g (0.069 moles, 69%) of pure 71. 60 MHz NMR (D_2O, Ref.: Tier's salt) δ 2.50 (s, 3 H), 3.02 (t, J = 7 Hz, 2 H), 3.77 (t, J = 7 Hz, 2 H), 4.60 (s, 1 H), 5.55 (s, 2 H), 10.03 (s, 1 H).

General Procedure for 1,3-Dipolar Cycloadditions of Thiazolium Ylides Generated from Salts 69-71 to Olefins

DMF as solvent

A solution of the thiazolium salt (2.0 mmoles) in DMF (5.0 ml) with the olefinic adduct was prepared. The reaction temperature (see Table 1) was adjusted and neat triethylamine (2.0 mmoles) was slowly

added. The resulting orange-colored solution was stirred at the reaction temperature for 3 hours, at which time the mixture was diluted with ether (25 ml) and was washed three times with brine. The organic extract was dried over Na_2SO_4 and removal of the solvents gave a colored residue of the crude addition product. Passage of the residue over a short silica gel column (with ethyl acetate/hexane: 1/10) gave pure adduct 73 as a mixture of isomers at C-8a and C-9a. Only the major isomer is reported in the 60 MHz NMR spectra.

CH_3CN as solvent

A slurry of the thiazolium salt (2.0 mmoles) in CH_3CN (3.0 ml) with the olefinic adduct was prepared. The reaction temperature (see Table 1) was adjusted and neat triethylamine (2.0 mmoles) was slowly added. The resulting solution was stirred at the reaction temperature for 3 hours, at which time the mixture was diluted with ether (25 ml) and was washed 3 times with brine. The organic extract was dried over Na_2SO_4. Removal of the solvents gave a residue of the crude addition product. Passage of the residue over a short silica gel column (with ethyl acetate/hexane: 1/10) gave pure adduct 73 as a mixture of isomers at C-8a and C-9a. Only the major isomer is reported in the 60 MHz NMR spectra.

Adduct 73a

The melting point was found to be 76-78.5°C (from hexane). IR (film) 2980, 1730, 1440, 1365, 1170, 1020 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz, 6 H), 1.60 (bs, 3 H), 2.0-3.0 (m, 4 H), 3.5-4.6 (m, 5 H), 4.45 (bq, J = 7 Hz, 4 H), 5.5 (bd, J = 8 Hz, 1 H); 90 MHz C-13

NMR ($CDCl_3$) δ 13.78 (2C), 22.24, 29.20, 33.62, 46.30, 55.08, 60.67 (2C), 60.80, 65.87, 74.98, 109.83, 107.18, 172.72. High resolution mass spectrum for $C_{15}H_{23}NO_5S$ requires m/e 329.12970; found m/e 329.13084.

Adduct 73b

60 MHz NMR ($CDCl_3$) δ 1.00 (d, J = 6 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.45 (s, 3 H), 2.1-2.4 (m, 3 H), 2.23 (s, 3 H), 3.6-4.3 (m, 5 H), 4.25 (bq, J = 7 Hz, 2 H), 5.55 (bd, J = 5 Hz, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 14.11, 21.72, 27.05, 30.24, 33.49, 34.47, 34.79, 40.90, 58.14, 59.83, 60.22, 60.54, 61.91, 63.21, 63.66, 64.23, 65.48, 68.61, 71.53, 71.99, 103.72, 107.69, 172.66, 203.61, 205.82.

Adduct 73c

The melting point was found to be 155-159°C (from hexane). IR (film) 2990, 1710, 1580, 1160 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.92 (bd, J = 7 Hz, 3 H), 1.34 (bs, 3 H), 2.1-2.4 (m, 3 H), 2.24 (bs, 6 H), 3.2-3.5 (m, 2 H), 3.7-4.1 (m, 3 H), 5.52 (bd, J = 5 Hz, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 14.37, 22.50, 28.81, 29.72, 33.95, 42.73, 56.71, 61.84, 66.33, 72.25, 74.85, 109.97, 203.09, 210.96. High resolution mass spectrum for $C_{12}H_{18}NO_2S$ (parent minus C_2H_3O) 240.10583; found 240.10536.

Adduct 73d

60 MHz NMR ($CDCl_3$) (major isomer) δ 1.50 (s, 3 H), 2.20 (s, 3 H), 2.2-2.8 (m, 4 H), 2.43 (s, 3 H), 3.2-4.6 (m, 5 H), 5.66 (d, J = 8 Hz, 1 H), 7.2-8.0 (m, 4 H).

Adduct 73e

60 MHz NMR ($CDCl_3$) δ 1.42 (s, 3 H), 1.55 (s, 3 H), 2.0-2.4 (m, 4 H), 2.22 (bs, 6 H), 3.6-4.5 (m, 10 H), 3.70 (bs, 12 H), 5.0-5.5 (m, 4 H); 90 MHz C-13 NMR ($CDCl_3$) δ 22.43, 22.63, 25.23, 25.62, 26.53, 27.51, 32.84, 33.82, 46.69, 48.64, 49.74, 50.98, 51.24, 52.41, 52.74, 56.05, 56.51, 56.64, 66.27, 66.98, 69.26, 69.52, 70.82, 71.86, 73.74, 110.03, 110.23, 169.73, 170.64, 170.77, 171.22, 171.49, 172.01, 208.68, 209.01.

Adduct 73f

60 MHz NMR ($CDCl_3$) δ 1.55 (bs, 3 H), 2.15-2.65 (m, 2 H), 2.33 (s, 3 H), 3.5-4.3 (m, 11 H), 4.31 (d, J = 4 Hz, 1 H), 5.30 (d, J = 5 Hz, 1 H).

Adduct 73g

IR (film) 2950, 1735, 1430, 1185, 1025 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 1.60 (s, 3 H), 1.9-2.6 (m, 2 H), 3.5-4.4 (m, 6 H), 3.70 (s, 3 H), 3.75 (s, 3 H), 4.20 (q, J = 7 H, 2 H), 5.28 (d, J = 5 Hz, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 13.85, 22.11, 33.62, 48.58, 49.10, 51.63, 52.41, 55.34, 61.39, 61.91, 65.74, 72.57, 108.21, 169.73, 170.64, 171.87. High resolution mass spectrum for $C_{16}H_{23}NO_7S$ requires m/e 373.11953; found m/e 373.11858.

Adduct 73h

60 MHz NMR ($CDCl_3$) δ 0.75 (t, J = 7 Hz, 3 H), 1.38 (s, 3 H), 1.96 (s, 3 H), 2.0-2.4 (m, 2 H), 3.3-4.1 (m, 6 H), 4.00 (bq, J = 7 Hz, 2 H), 5.45 (d, J = 4 Hz, 1 H), 7.03 (s, 5 H); 90 MHz C-13 NMR ($CDCl_3$) 13.53, 22.43, 29.72, 34.14, 46.11, 56.19, 60.22, 60.61, 66.53, 67.18, 74.98, 109.90, 127.46, 127.85, 128.30, 129.02, 137.47, 170.96, 203.09.

Adduct 73i

60 MHz NMR ($CDCl_3$) δ 1.21 (bt, J = 7 Hz, 3 H), 1.45 (bs, 3 H), 1.8-2.7 (m, 4 H), 3.3-4.5 (m, 5 H), 4.08 (bq, J = 7 Hz. 2 H), 5.10 (bd, J = 7 Hz, 1 H).

Adduct 73j

60 MHz NMR ($CDCl_3$) δ 1.42 (s, 3 H), 1.60 (s, 3 H), 1.9-2.8 (m, 8 H), 3.4-4.6 (m, 10 H), 4.95 (d, J = 6 Hz, 1 H), 5.22 (d, J = 5 Hz, 1 H).

Adduct 73k

60 MHz NMR ($CDCl_3$) δ 1.80 (bs, 3 H), 2.2-2.6 (m, 4 H), 2.30 (s, 3 H), 3.3-3.8 (m, 4 H), 4.27 (t, J = 7 Hz, 1 H), 5.12 (d, J = 6 Hz, 1 H).

Adduct 73l

60 MHz NMR ($CDCl_3$) δ 1.40 (bs, 3 H), 1.58 (bs, 3 H), 1.9-2.4 (m, 4 H), 2.40 (bs, 12 H), 3.5-4.5 (m, 12 H), 5.10 (d, J = 7 Hz, 1 H), 5.52 (d, J = 7 Hz, 1 H), 7.16 (bs, 10 H).

Adduct 73m

60 MHz NMR ($CDCl_3$) δ 1.22 (bd, J = 7 Hz, 3 H), 1.82 (bs, 3 H), 2.0-2.5 (m, 3 H), 2.10 (bs, 3 H), 2.9-3.6 (m, 4 H), 4.13 (d, J = 8 Hz, 1 H), 5.70 (d, J = 6 Hz, 1 H).

Adduct 73n

60 MHz NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H), 1.43 (s, 3 H), 1.58 (s, 3 H), 1.6-2.4 (m, 3 H), 3.05 (bt, J = 11 Hz, 1 H), 3.5-4.3 (m, 4 H), 3.70 (s, 3 H), 4.20 (q, J = 7 Hz, 2 H), 5.13 (s, 1 H); 90 MHz C-13 NMR

($CDCl_3$) δ 13.72, 21.91, 25.62, 33.36, 36.48, 51.57, 52.80, 55.02, 60.54, 61.00, 65.88, 81.55, 109.97, 172.98. 173.89.

Adduct 73o

IR (film) 2990, 1740, 1455, 1380, 1280, 1260, 1175, 1035 cm^{-1}; 60 MHz NMR ($CDCl_3$) (major isomer) δ 0.85 (m, 2 H), 1.28 (t, J = 7 Hz, 3 H), 1.43 (s, 3 H), 1.8-2.7 (m, 6 H), 2.9-3.6 (m, 2 H), 3.5-4.2 (m, 2 H), 4.18 (q, J = 7 Hz, 2 H), 5.25 (d, J = 7 Hz, 1 H).

Adduct 73p[1]

60 MHz NMR ($CDCl_3$) δ 1.27 (bt, J = 7 Hz, 3 H), 1.2-1.7 (m, 6 H), 1.57 (bs, 3 H), 1.9-2.6 (m, 6 H), 3.4-3.7 (m, 2 H), 3.8-4.6 (m, 4 H), 5.80 (s, 1 H). Low resolution mass spectrum for $C_{17}H_{25}NO_4S$ requires m/e 339.0; found m/e 339.0, fragments: 315.0, 275.0, 256.0, 229.0. 196.0.

Adduct 73q[1]

60 MHz NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.4-2.8 (m, 12 H), 2.20 (s, 3 H), 3.2-4.3 (m, 4 H), 5.40 (s, 1 H).

Adduct 73r[2]

60 MHz NMR ($CDCl_3$) δ 1.45 (bs, 3 H), 1.9-2.7 (m, 4 H), 2.30 (bs, 3 H), 3.5-4.5 (m, 4 H), 5.30 (s, 1 H), 6.6-7.4 (m, 4 H). Low resolution

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[1]Exomethylene cyclohexanone was prepared according to the method of G. M. Ksander, J. E. McMurry and M. Johnson, J. Org. Chem. 1977, 42, 1180.

[2]Exomethylene indole was prepared according to the method of R. L. Hinman and C. P. Bauman, J. Org. Chem. 1964, 29, 2431.

mass spectrum for $C_{18}H_{20}N_2O_3S$ requires m/e 344.0; found m/e 343.9, fragments: 300.9, 228.0, 207.0, 145.0

Adduct 73s[1]

IR (film) 2950, 1740, 1720, 1180, 1160 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3 H), 1.42 (s, 3 H), 2.08 (s, 3 H), 2.1-2.3 (m, 5 H), 3.1-4.5 (m, 9 H), 4.35 (s, 2 H), 5.45 (d, J = 5 Hz, 1 H), 7.28 (s, 5 H); 90 MHz C-13 NMR ($CDCl_3$) δ 13.89, 21.84, 22.24, 27.12, 29.85, 30.63, 33.30, 34.08, 37.20, 38.89, 56.51, 57.75, 59.76, 60.28, 60.74, 63.47, 65.35, 66.20, 68.02, 68.67, 68.93, 70.82, 72.57, 74.65, 107.62, 109.64, 127.52, 128.17, 138.19, 171.94, 172.53, 203.22, 203.87.

Adduct 73t[2]

60 MHz NMR ($CDCl_3$) δ 0.01 (s, 6 H), 0.83 (s, 9 H), 1.21 (t, J = 7 Hz, 3 H), 1.3-1.7 (m, 2 H), 1.40 (bs, 3 H), 2.1-2.5 (m, 3 H), 2.12 (bs, 3 H), 3.3-4.4 (m, 7 H), 4.11 (bq, J = 7 Hz, 2 H), 5.32 (d, J = 7 Hz,

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[1] 7-Benzyloxy-3-hexene-2-one (bp 135-140°C/∿1 mm Hg) was prepared via PCC oxidation (E. J. Corey, J. W. Suggs Tetrahedron Lett. 1975, 2647) of 3-benzyloxy-n-propanol (C. L. Butler, A. G. Renfrew, M. Clapp J. Amer. Chem. Soc. 1938, 60, 1472) followed by a Wittig reaction with triphenyl phosphineacetylmethylene (F. Ramirez, S. Dershowitz J. Org. Chem. 1957, 22, 41).

[2] 7-t-Butyldimethylsilyloxy-3-hexene-2-one was prepared as follows: alkylation of 4-litho-4-p-toluenesufonyl butanone ethylene ketal with allyl bromide (K. Kondo, D. Tunemoto Tetrahedron Lett. 1975, 1397) followed by ozonolysis (O_3/MeOH) with reductive work-up ($NaBH_4$/0°C) and deketalization (HOAc/H_2O/$(CH_3)_2CO$/25°C), yielding 1-methyl-1-hydroxy-3-(p-toluene sulfone)-tetrahydropyran, which was opened and protected with a t-butyldimethylsilyl group (E. J. Corey; A. Venkateswarlu J. Amer. Chem. Soc. 1972, 94, 6190) and, finally, eliminated with Na_2CO_3 in DMF (J. Fayos, J. Clardy, L. J. Dolby, T. Farnham J. Org. Chem. 1977, 42, 1349) (bp 85-95°C/∿1 mm Hg).

1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 14.11, 18.14, 22.24, 25.82, 27.12, 30.50, 32.71, 32.91, 33.23, 38.30, 57.62, 59.70, 60.15, 60.61, 60.80, 61.71, 63.14, 65.10, 67.83, 70.43, 107.49, 172.40, 203.61.

Diethyl-2,4-pyrrole-dicarboxylate (74)

Adduct 73a (0.44 g, 1.3 mmoles) was treated with methane sulfonic acid (0.20 ml, 3.1 mmoles) in methanol (20 ml). A TLC analysis (silica gel, hexane: ethyl acetate, 1:1) revealed only origin material. The solution was poured into a mixture of triethylamine (2.5 ml, 18 mmoles) and methanol (10 ml) and stirred for four hours. The solution was evaporated to a residue and then redissolved in dry THF (10 ml). Excess NaH (hexane-washed) was added and the reaction was allowed to stir at room temperature protected by a drying tube ($CaSO_4$) for 24 hours. Addition of H_2O (50 ml) followed by extraction with CH_2Cl_2 three times, drying (Na_2SO_4) and evaporation gave a small amount of 74 (0.05 g). Compound 74 had identical R_f on TLC plates (silica gel) and 60 MHz NMR spectra as diethyl-2,4-pyrrole-dicarboxylate prepared by the known procedure (52,53). 60 MHz NMR ($CDCl_3$) δ 1.38 (bt, J = 7 Hz, 6 H), 4.37 (dq, J = 7 Hz, 4 H), 7.37 (dd, J = 1 Hz, 1 H), 7.64 (dd, J = 1 Hz, 1 H). Low resolution mass spectrum for $C_{10}H_{13}NO_4$ requires m/e 211.0; found 211.1, fragments: 196.1 183.0, 166.0, 140.1, 120.0.

3,5-Dicarbethoxy-Δ^2-pyrroline (75)

A suspension of adduct 73a (0.33 g, 1.0 mmole) stirred in H_2O (10 ml) containing a catalytic amount of $NaHCO_3$ was prepared. To this suspension a $AgNO_3$ (2.2 ml, 0.5 N(aq)) solution was added drop-wise.

The mixture became turbid and after about 1 hour, a yellow residue had settled out and the solution was extracted four times with CH_2Cl_2. Drying of the organic layer over Na_2SO_4 followed by evaporation gave 0.14 g (0.67 mmoles, 67%) of 75, as a very pure yellow isolate which tended to decompose upon standing: 60 MHz NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H), 1.32 (t, J = 7 Hz, 3 H), 3.04 (bs, 1 H), 3.17 (bs, 1 H), 4.2-4.8 (m, 1 H), 4.22 (q, J = 7 Hz, 2 H), 4.30 (q, J = 7 Hz, 2 H), 5.1 (s,1 H), 7.3-7.4 (m,1 H). The NMR data compared favorably to the literature (55). Low resolution mass spectrum for $C_{10}H_{15}NO_4$ requires m/e 213.0; found m/e 213.0, fragments: 140.1, 96.1, 68.1.

Diethyl-2,4-pyrrolidine-dicarboxylate (76)

Enamine 75 (0.40 g, 1.8 mmoles) was dissolved in dry ethanol (4 ml) containing a trace amount of bromocresol green (as indicator). 2N HCl in ethanol was added until the solution turned yellow. Solid $NaCNBH_3$ (0.13 g, 2.1 mmoles) was added in one portion, followed by subsequent small additions of 2N HCl in ethanol when the indicator turned green. After the color no longer changed to green, within 20 minutes excess solid Na_2CO_3 (∿1 g) was added and the ethanol was removed by evaporation. The residue was taken up in CH_2Cl_2 and washed 3 times with saturated $NaHCO_3$ solution. Drying over Na_2SO_4, followed by evaporation, gave 0.33 g (1.54 mmoles, 86%) of 76 as a mixture of diastereomers: IR (film) 3500, 2990, 1730, 1450, 1375, 1185, 1030 cm^{-1}; 60 MHz NMR ($CDCl_3$) (major isomer) δ 1.28 (t, J = 7 Hz, 6 H), 2.2-2.5 (m, 2 H), 2.75 (bs, 1 H), 3.9-3.4 (m, 2 H), 3.65-4.1 (m, 2 H), 4.22 (q, J = 7 Hz,

4 H). High resolution mass spectrum for $C_{10}H_{17}NO_4$ requires m/e 215.11576; found m/e 215.11526.

MnO_2 oxidation of 75 to 74

Enamine 75 (0.24 g, 0.93 mmoles) was stirred at room temperature for 48 hours in benzene with excess MnO_2 (2.3 g). Filtration through celite, followed by evaporation of the solvent and chromatography (silica gel), gave 0.113 g (0.44 mmoles, 47%) of pyrrole 74 which was identical to authentic material by TLC and 60 MHz NMR.

3-Acetyl-4α-methyl-5α-carbethoxy-Δ^2-pyrroline (77)

Adduct 73b (0.313 g, 1.00 mmoles) was cleaved by $AgNO_3$ as in the procedure for 73a. Isolation gave 0.147 g (0.73 mmoles, 73%) of 77 as a light-colored oil: IR (film) 3020, 2990, 1730, 1570, 1370, 1250, 1180, 1030 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.05 (d, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 2.10 (s, 3 H), 3.2-3.6 (m, 1 H), 4.20 (q, J = 7 Hz, 2 H), 4.60 (d, J = 10 Hz, 1 H), 6.00 (bs, 1 H), 7.22 (bs, 1 H); 90 MHz C-13 NMR ($CDCl_3$) 14.243 (2 C), 25.56, 37.52, 61.13, 65.74, 119.85, 148.53, 170.70, 191.19. Low resolution mass spectrum for $C_{10}H_{15}NO_3$ requires m/e 197.0; found m/e 197.1, fragments: 182.1, 156.1, 124.1, 116.1.

3-Acetyl-4α-phenyl-5α-carbethoxy-Δ^2-pyrroline (78)

Adduct 73h (0.17 g, 0.46 mmoles) was cleaved by $AgNO_3$ as in the procedure for 73a. A mixture of methanol:H_2O (2:1) was used as the solvent system. Isolation gave 0.087 g (0.33 mmoles, 73%) of 78 as a

light-colored oil: 60 MHz NMR ($CDCl_3$) δ 0.84 (t, $\underline{J}$ = 7 Hz, 3 H), 2.10 (s, 3 H), 3.40-3.95 (m, 2 H), 4.77 (q, $\underline{J}$ = 7 Hz, 2 H), 5.95 (bs, 1 H), 7.30 (s, 5 H), 7.3-7.5 (m, 1 H); 90 MHz C-13 NMR ($CDCl_3$) 13.33, 25.43, 48.64, 60.67, 66.66, 118.03, 127.65, 128.11, 128.82, 139.10, 150.28, 169.73, 190.60.

3α-Carboxymethyl-3β-methyl-5β-carboxyethyl-Δ^1-pyrroline (79)

Adduct 73n (0.331 g, 1.00 mmoles) was cleaved by $AgNO_3$ as in the procedure for 73a. Methanol was used for the solvent. The reaction was followed by TLC analysis (silica gel, hexane:ethyl acetate, 1:1). Isolation gave 0.209 g (0.98 mmoles, 98%) of 79 as an oil: IR (film) 3560, 2990, 1740, 1630, 1450, 1370, 1190, 1040 cm^{-1} (lit. (55) 1620, 1720 cm^{-1}); 60 MHz NMR ($CDCl_3$) δ 1.30 (t, $\underline{J}$ = 7 Hz, 3 H), 1.48 (s, 3 H), 1.82 (d, $\underline{J}$ = 7 Hz, 1 H), 2.05 (d, $\underline{J}$ = 7 Hz, 1 H), 3.74 (s, 3 H), 4.26 (q, $\underline{J}$ = 7 Hz, 2 H), 4.7-5.1 (m, 1 H), 7.66 (d, $\underline{J}$ = 3 Hz, 1 H) (This spectrum was identical to the literature (55) NMR spectrum.); 90 MHz C-13 NMR ($CDCl_3$) δ 13.86, 21.79, 36.49, 52.42, 60.35, 61.20, 74.33, 171.16, 171.62, 172.27.

3α-(Spiro-2-oxocyclohexyl)-5β-acetyl-Δ^1-pyrroline (80)

Adduct 73q (0.122 g, 0.39 mmoles) was cleaved by $AgNO_3$ as in the procedure for 73a. Ethanol was used as the solvent. After 4 hours of stirring, 2N HCl in ethanol (3 ml) was added and allowed to react overnight. Isolation gave 0.055 g (0.31 mmoles, 79%) of 80: 60 MHz NMR ($CDCl_3$) δ 0.9-2.5 (m, 10 H), 2.25 (s, 3H), 3.8-4.2 (m, 1 H), 7.60 (bs, 1 H).

3-Acetyl-4α-(2-benzyloxyethyl)-5α-carbethoxy-Δ^2-pyrroline (81)

Adduct 73s (1.00 g, 2.30 mmoles) was cleaved by $AgNO_3$ as in the procedure for 73a. Methanol:H_2O (5:1) was used as the solvent system. Isolation gave 0.58 g (1.8 mmoles, 80%) of 81 as a yellow oil: IR (film) 3280, 2940, 1740, 1570, 1450, 1370, 1200, 1090 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3 H), 1.8-2.5 (m, 2 H), 2.15 (s, 3 H), 3.46 (t, J = 7 Hz, 2 H), 3.4-3.9 (m, 1 H), 4.18 (q, J = 7 Hz, 2 H), 4.44 (s, 2 H), 4.57 (d, J = 12, 1 H), 4.96 (bs, 1 H), 7.32 (bs, 6 H); 90 MHz C-13 NMR ($CDCl_3$) δ 14.11, 25.56, 29.46, 39.67, 61.26, 65.88, 68.28, 72.64, 118.68, 127.34, 127.65, 128.17, 138.71, 148.85, 170.57, 191.19.

Hemiketal 82

Adduct 73t (1.46 g, 3.20 mmoles) was cleaved by $AgNO_3$ as in the procedure for 73a. Methanol was used as the solvent. Isolation gave 0.30 g (1.3 mmoles, 35%) of 82 as a mixture of diastereomers: IR (film) 3400, 2990, 1740, 1680, 1555, 1390, 1265, 1180, 1045 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3 H), 1.9-2.2 (m, 3 H), 1.96 (s, 3 H), 2.7-3.3 (m, 1 H), 3.6-4.4 (m, 2 H), 4.14 (q, J = 7 Hz, 2 H), 4.9 (d, J = 10 Hz, 1 H), 5.8 (bs, 1 H), 8.00 (s, 1 H). Low resolution mass spectrum for $C_{11}H_{15}NO_3$ (82-H_2O) requires m/e 209.0; found 209.1, fragments: 181.1, 163.1, 136.2, 109.1.

Enamine 84

Adduct 73b (1.20 g, 3.80 mmoles) was dissolved in CH_2Cl_2:t-butyl alcohol (20 ml:40 ml) containing CH_3I (0.5 ml, 8.0 mmoles) and cooled to

0°C. Solid t-butanol:t-butoxide complex (1:1) (0.74 g, 4.00 mmoles) was added in one portion yielding an orange-yellow heterogeneous solution. The reaction was stirred under N_2 for 3 hours, then warmed to room temperature. A TLC analysis (silica gel, hexane:ethyl acetate, 1:1) indicated that no starting material was present.

The solvents were then removed by evaporation. The last traces of t-butanol were carefully eliminated by azotropic evaporation with benzene. The residue was taken up in methanol (20 ml) and filtered. The solvent was once again evaporated, then redissolved in CH_2Cl_2 and washed once with saturated aqueous NaCl solution. The aqueous layer was extracted three times with CH_2Cl_2. All the organic layers were combined and dried over Na_2SO_4. Evaporation gave 1.05 g (3.20 mmoles, 84%) of 84 as a set of diastereomers: (major) 60 MHz NMR ($CDCl_3$) δ 1.14 (d, J = 7 H, 3 H), 1.33 (t, J = 7 Hz, 3 H), 1.53 (s, 3 H), 2.0-2.5 (m, 2 H), 2.22 (s, 3 H), 2.25 (s, 3 H), 3.12 (t, J = 8 Hz, 2 H), 3.4-4.0 (m, 2 H), 4.28 (q, J = 7 Hz, 2 H), 4.54 (d, J = 10 Hz, 1 H), 7.49 (s, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 14.24, 15.35, 25.88, 26.47, 31.54, 33.29, 37.65, 56.97, 60.48, 66.98, 68.28, 95.33, 117.77, 148.79, 170.44, 190.93. Low resolution mass spectrum for $C_{16}H_{25}NO_4S$ requires m/e 327.0; found 327.1, fragments: 197.1, 154.1, 130.0, 84.0.

Enamine 85

Adduct 73s (4.46 g, 10.3 mmoles) was eliminated with t-butanol:t-butoxide (1:1) in a similar procedure as that employed for 73b. Isolation gave 3.33 g (7.4 mmoles, 72%) of 85 as a mixture of 3 diastereomers

which were separated by flash chromatography (silica gel: 230-400 mesh): IR (film) 2990, 1745, 1575, 1455, 1380, 1185, 1025 cm^{-1}; (major) 60 MHZ NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 3 H), 1.43 (s, 3 H), 1.7-2.5 (m, 4 H), 2.16 (s, 3 H), 2.18 (s, 3 H), 3.00 (t, J = 8 Hz, 2 H), 3.3-4.3 (m, 2 H), 3.45 (t, J = 7 Hz, 2 H), 4.12 (q, J = 7 Hz, 2 H), 4.45 (s, 2 H), 4.45 (d, J = 10 Hz, 1 H), 7.23 (s, 5 H), 7.37 (s, 1 H); 90 MHz C-13 NMR ($CDCl_3$) 14.11, 25.17, 25.82, 25.95, 29.52, 31.60, 33.23, 39.34, 55.54, 60.54, 67.37, 68.61, 72.38, 95.01, 116.27, 127.20, 127.59, 128.11, 138.84, 149.96, 169.99, 191.32; (1st minor) 60 MHz NMR ($CDCl_3$) δ 1.19 (t, J = 7 Hz, 3 H), 1.64 (s, 3 H), 1.9-2.6 (m, 4 H), 2.15 (s, 3 H), 2.19 (s, 3 H), 2.8-3.2 (m, 2 H), 3.3-4.1 (m, 4 H), 4.12 (q, J = 7 Hz, 2 H), 4.19 (d, J = 14 Hz, 1 H), 4.50 (s, 2 H), 7.21 (s, 1 H), 7.27 (s, 5 H); (2nd minor) 60 MHz NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3 H), 1.66 (s, 3 H), 1.9-2.6 (m, 4 H), 2.11 (s, 3 H), 2.13 (s, 3 H), 2.8-3.2 (m, 2 H), 3.3-4.1 (m, 4 H), 4.09 (q, J = 7 H, 2 H), 4.15 (d, J = 14 Hz, 1 H), 4.45 (s, 2 H), 7.09 (s, 1 H), 7.23 (s, 5 H).

Enamine 86

Adduct 73t (1.07 g, 2.34 mmoles) was eliminated with t-butanol:t-butoxide (1:1) in a similar procedure as that employed for 73b. Isolation gave 0.978 g (2.07 mmoles, 89%) of 86 as a mixture of diastereomers: (major) 60 MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.94 (s, 9 H), 1.36 (t, J = 7 Hz, 3 H), 1.77 (s, 3 H), 2.0-2.8 (m, 4 H), 2.20 (s, 3 H), 2.23 (s, 3 H), 3.0-3.4 (m, 2 H), 3.6-4.2 (m, 4 H), 4.33 (q, J = 7 Hz, 2 H), 4.51 (d, J = 11 Hz, 1 H), 7.36 (s, 1 H).

Reduction of 84 with sodium cyanoborohydride

The diastereomeric mixture 84 (0.163 g, 0.5 mmoles) was reduced by $NaCNBH_3$ (0.07 g, 1.1 mmoles) at 0°C with a procedure similar to that for the reduction of 75. Isolation gave 0.045 g (0.23 mmoles, 45%) of a 1:1 mixture of cis- and trans-ketones 87a: 60 MHz NMR ($CDCl_3$) δ 0.81 (d, J = 7 Hz, 3 H), 1.27 (t, J = 7 Hz, 6 H), 1.47 (d, J = 8 Hz, 3 H), 2.17 (s, 6 H), 2.5-3.8 (m, 8 H), 3.70 (d, J = 5 Hz, 1 H), 3.98 (d, J = 7 Hz, 1 H), 4.16 (q, J = 7 Hz, 4 H); and 0.040 g (0.20 mmoles, 40%) of a 1:1 mixture of cis- and trans-alcohols 87b: 60 MNz NMR ($CDCl_3$) δ 0.9-1.4 (m, 3 H), 1.09 (t, J = 7 H, 3 H), 1.20 (d, J = 3 Hz), 2.5-3.0 (m, 2 H), 3.5-4.2 (m, 4 H), 4.13 (q, J = 7 H, 2 H).

Reduction of 85 with sodium cyanoborohydride

The diastereomeric mixture 85 (0.822 g, 1.84 mmoles) was reduced by $NaCNBH_3$ (0.243 g, 3.86 mmoles) at 0°C with a procedure similar to that for the reduction of 75. Isolation gave 0.374 g of a diastereomeric mixture of cis- and trans-ketones 88a and cis- and trans-alcohols 88b (approximately 1:1, ketone:alcohol): 60 MHz NMR ($CDCl_3$) δ 1.1-1.4 (m, 10 H), 1.22 (bt, J = 7 Hz, 6 H), 2.05 (bs, 3 H), 3.2-4.9 (m, 12 H), 4.10 (bq, J = 7 Hz, 4 H), 4.44 (s, 4 H), 7.25 (s, 10 H).

Reduction of 86 with sodium cyanoborohydride

The diastereomeric mixture 86 (0.542 g, 1.15 mmoles) was reduced by $NaCNBH_3$ (0.152 g, 2.42 mmoles) at 0°C with a procedure similar to that for the reduction of 75. Isolation gave a small amount of 89,

along with a variety of other products as evidenced by a low resolution mass spectrum.

N-t-butoxycarbonyl derivatives of 88a and 88b

The crude mixture of pyrrolidines 88a and 88b (0.63 g, 2.00 mmoles) were dissolved in $CHCl_3$ (20 ml), H_2O (3 ml) and a catalytic amount of $NaHCO_3$. Di-t-butylcarbonate (0.48 g, 2.20 mmoles) was added to the rapidly stirred solution. The mixture was allowed to stir overnight, then diluted with $CHCl_3$ (30 ml) and washed three times with saturated aqueous $NaHCO_3$ solution. Drying (Na_2SO_4) of the organic layer, followed by evaporation, gave a mixture of 90 and 91 which could be easily separated by flash chromatography (silica gel: 230-400 mesh; hexane: ethyl acetate, 10:1). Isolation gave 0.26 g (0.62 mmoles, 28%) of 90 as a mixture of cis- and trans-diastereomers: IR (film) 2990, 1740, 1700, 1400, 1390, 1365, 1195, 1135 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.23 (bt, J = 7 Hz, 3 H), 1.40 (s, 9 H), 1.8-2.5 (m, 3 H), 2.08 (bs, 3 H), 3.2-4.2 (m, 6 H), 4.10 (bq, 2 H), 4.45 (bs, 2 H), 7.23 (s, 5 H): and 0.18 g (0.43 mmoles, 22%) 91 as a diastereomeric mixture of cis- and trans-alcohols: IR (film) 3500, 2990, 1740, 1700, 1395, 1185 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 1.31 (d, J = 8 Hz, 3 H), 1.40 (s, 9 H), 1.9-2.7 (m, 4 H), 2.8-4.4 (m, 6 H), 4.13 (q, J = 7 Hz, 2 H), 4.50 (s, 2 H), 7.28 (s, 5 H); 90 MHz C-13 NMR ($CDCl_3$) δ 14.31, 21.13, 21.59, 21.91, 28.29, 29.13, 42.99, 47.93, 48.25, 60.67, 62.88, 63.21, 63.66, 67.89, 68.61, 69.84, 70.23, 73.03, 79.92, 127.72, 127.98, 128.37, 137.99, 171.88.

Epimerization of 90

The mixture of cis-:trans-isomers of 90 (0.26 g, 0.62 mmoles) was dissolved in CH_2Cl_2 (10 ml) containing a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature. The solution was allowed to stir overnight, after which a TLC analysis (silica gel; hexane:ethyl acetate, 10:1) indicated that the two isomers had coalesced into one. Passage over a short silica gel column to remove the catalyst gave 0.26 g (0.62 mmoles, 100%) of trans-90:60 MHz NMR ($CDCl_3$) δ 1.27 (t, J = 7 H, 3 H), 1.41 (s, 9 H), 1.60 (q, J = 6 H, 2 H), 2.0-2.4 (m, 1 H), 2.11 (s, 3 H), 2.8-3.7 (m, 3 H), 3.47 (t, J = 6 Hz, 2 H), 4.18 (q, J = 7 H, 2 H), 4.28 (d, J = 6 Hz, 1 H), 4.40 (s, 2 H), 7.30 (s, 5 H); 90 MHz C-13 NMR ($CDCl_3$) δ 14.24, 28.22, 40.58, 41.03, 48.84, 53.45, 54.30, 60.80, 62.88, 68.02, 72.70, 80.25, 127.59, 128.24, 138.12, 153.28, 171.68, 206.73.

Cleavage of 84 with acidic ethanol

Compound 84 (0.96 g, 2.93 mmoles) was dissolved in anhydrous 2N HCl in ethanol (3 ml) and allowed to stir for four hours at ambient temperature. After making the solution basic with solid $NaHCO_3$, the solvent was evaporated and the residue was purified by flash chromatography (silica gel: 230-400 mesh, methanol:ethyl acetate, 1:100). Isolation gave 0.43 g (2.20 mmoles, 75%) of 77.

Reduction of 77 to 87a via the silyl enol ether

Compound 77 (0.048 g, 0.25 mmoles) was dissolved in CH_2Cl_2 (3 ml) and cooled to 0°C. Trimethylsilyl trifluoromethanesulfonate (0.042 ml,

0.25 mmoles) was added slowly and allowed to stir for two hours. $NaCNBH_3$ in CH_3CN (2.03 ml, 0.128 M) was added. A TLC analysis indicated the presence of some starting material. Further additions of the $NaCNBH_3$ solution drove the reaction to near completion. The reaction was diluted with CH_2Cl_2 (20 ml) and was washed once with saturated aqueous $NaHCO_3$ solution. Drying of the organic layer over Na_2SO_4, followed by evaporation, gave a mixture of 93 and 87a. The crude mixture was hydrolyzed with dilute HCl (aq.) (1 ml, 0.5N) in acetone (3 ml) at room temperature for 2 hours. The solution was diluted with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 to give 0.031 g (0.16 mmoles, 64%) of 87a after a pass over a silica gel column: (cis-:trans-isomers, 1:1).

Reduction of 81 to 88a via the silyl enol ether

Compound 81 (0.462 g, 1.46 mmoles) was transformed into the enol ether and then reduced with $NaCNBH_3$ in a reaction sequence similar to that for 87a. Isolation gave 0.190 g (0.60 mmoles, 41%) of 88a in a 1:1 mixture of cis-:trans-isomers. The low resolution mass spectrum for $C_{18}H_{25}NO_4$ requires m/e 320.0; found m/e 320.0, fragments: 302.0, 290.0, 276.0, 248.0, 230.0, 184.0.

Reduction and cleavage of 73a by tri-n-butyl tin hydride

Adduct 73a (0.474 g, 1.44 mmoles) was added to a solution of distilled benzene (10 ml) and tri-n-butyl tin hydride containing a catalytic amount (10 molar percent) of ABIN. The solution was heated at reflux for 1 to 3 hours. A TLC analysis (silica gel, hexane:ethyl acetate, 1:1) indicated that there was no starting material present.

After the reaction was cooled to room temperature, excess 2N HCl in ethanol (anhydrous, 5 ml) was added and the mixture was stirred for 3 hours. The solvents were then removed by evaporation, and the yellow residue was taken up into 2N (aq.) HCl and washed three times with ether. The aqueous layer was made basic with solid $NaHCO_3$ and then extracted four times with CH_2Cl_2. The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated giving 0.136 g (0.63 mmoles, 45%) of 76 as a viscous yellow oil.

Reduction and cleavage of 73g by tri-n-butyl tin hydride

Adduct 73g (0.252 g, 0.67 mmoles) was reduced and cleaved by tri-n-butyl tin hydride followed by acidic ethanol in a procedure similar to that employed for 73a. Isolation gave 0.103 g (0.42 mmoles, 63%) of 94 as a yellow oil: IR (film) 3500, 2990, 1730, 1600, 1530, 1435, 1200, 1020 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H), 3.2-4.3 (m, 5H), 3.65 (s, 3 H), 3.70 (s, 3 H), 4.20 (q, J = 7 H, 2 H); 90 MHz C-13 NMR ($CDCl_3$) δ 13.92, 49.16, 51.76, 52.28, 52.54, 61.52, 61.73, 61.91, 170.77, 171.16, 172.00.

Reduction and cleavage of 73s by tri-n-butyl tin hydride

Adduct 73s (1.81 g, 4.18 mmoles) was reduced and cleaved by tri-n-butyl tin hydride, followed by acidic ethanol, in a procedure similar to that employed for 73a. Isolation gave 1.08 g (3.39 mmoles, 81%) of trans-88a as a yellow oil: IR (film) 3440, 2940, 2870, 1730, 1710, 1450, 1365, 1180, 1090 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3 H), 1.5-1.8 (m, 2 H), 2.06 (s, 3 H), 2.7-3.2 (m, 3 H), 3.2-3.6 (m, 3 H),

3.86 (d, $\underline{J}$ = 7 Hz, 1 H), 4.14 (q, $\underline{J}$ = 7 Hz, 2 H), 4.40 (s, 2 H), 7.28 (s, 5 H); 90 MHz C-13 NMR ($CDCl_3$) δ 13.85, 29.20, 29.78, 42.20, 49.36, 56.77, 60.28, 63.92, 68.35, 72.44, 127.33 (3C), 127.91 (2C), 137.86, 172.72, 208.16.

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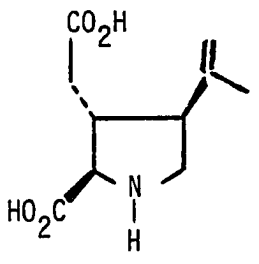
PART II. TOTAL SYNTHESIS OF α-ALLOKAINIC ACID

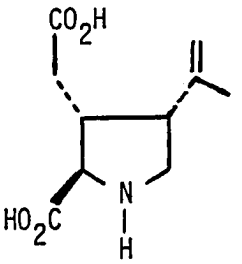
INTRODUCTION

(±)α-Allokainic acid (1) is a member of a class of pyrrolidine alkaloids isolated from the marine algae Digenea simplex (1). Other members of this class include α-kainic acid (2) and domoic acid (3). Aminoacid 1 has been shown to have antihelmintic properties (2) and potent neurophysiological activity in mammals (3).

At the time this work was initiated, no synthesis which involved a 1,3-dipolar addition for either of these compounds had been reported. This section will detail a study, which resulted in the total synthesis of (±)α-allokainic acid via a dipolar cyclization of a stabilized thiazolium ylide (4).



1



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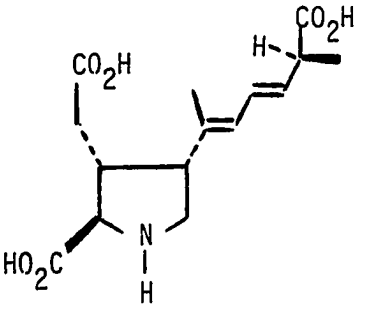
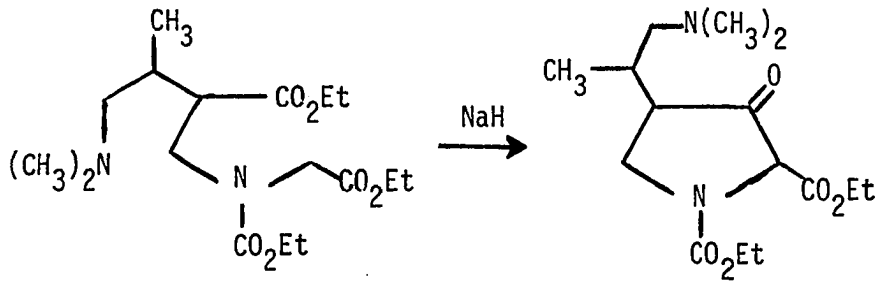


3

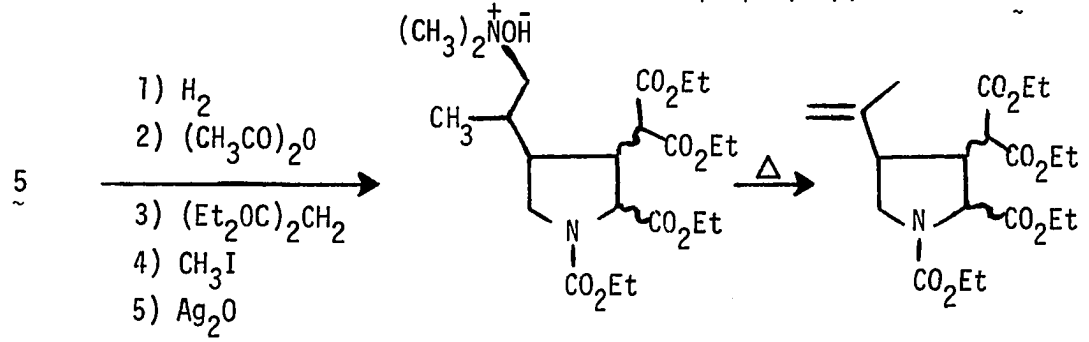
HISTORICAL

α-Allokainic acid was first synthesized in a nonstereospecific manner by Miyamoto and co-workers (5). Their key intermediate was 4, which underwent an intramolecular Dieckmann condensation to form ketone 5.



4 5

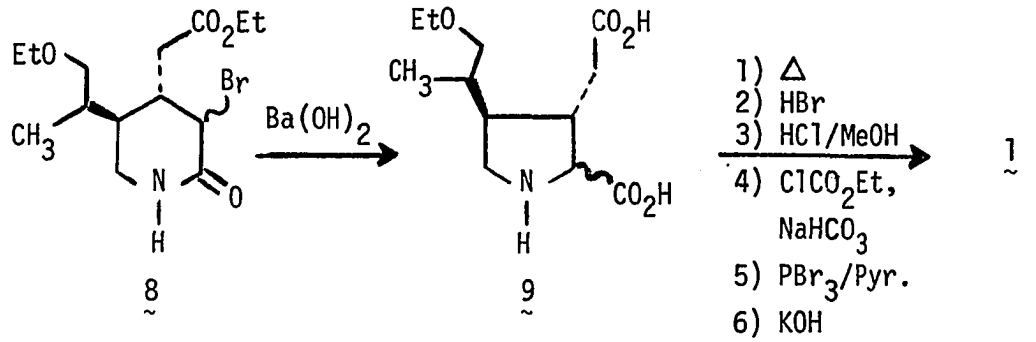
Diester 5 was then transformed into the triester ammonium salt 6, which underwent thermal elimination to the isopropenyl pyrrolidine 7.



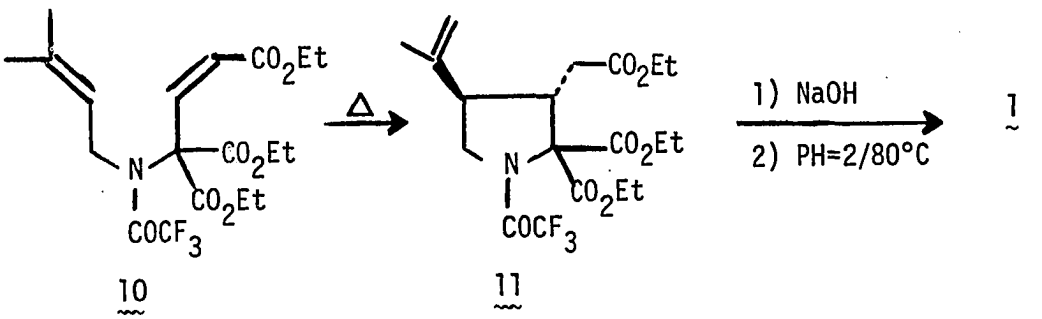
6 7

Saponification, decarboxylation, and epimerization were all accomplished with KOH in one step to give (±)α-allokainic acid (1). Several other syntheses by the same workers were reported which employed the same type of methodology (6,7,8).

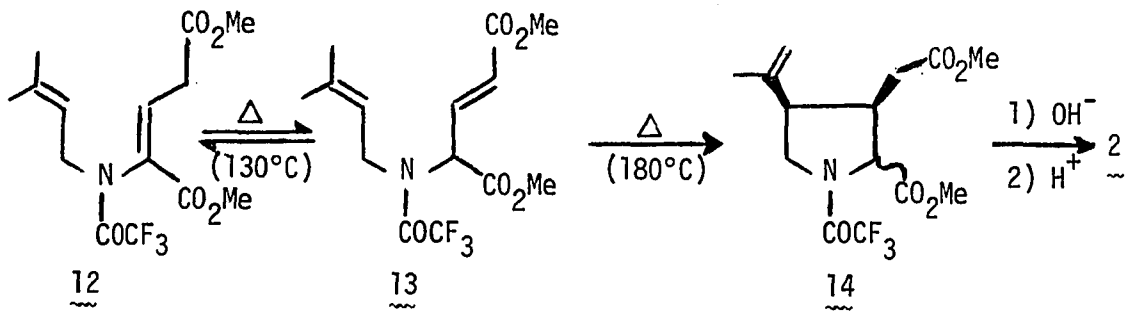
Honjo reported that a ring contraction of the α-bromo amide 8 produced the pyrrolidine system 9 which subsequently led to (±)α-allokainic acid (1) in six steps (9).



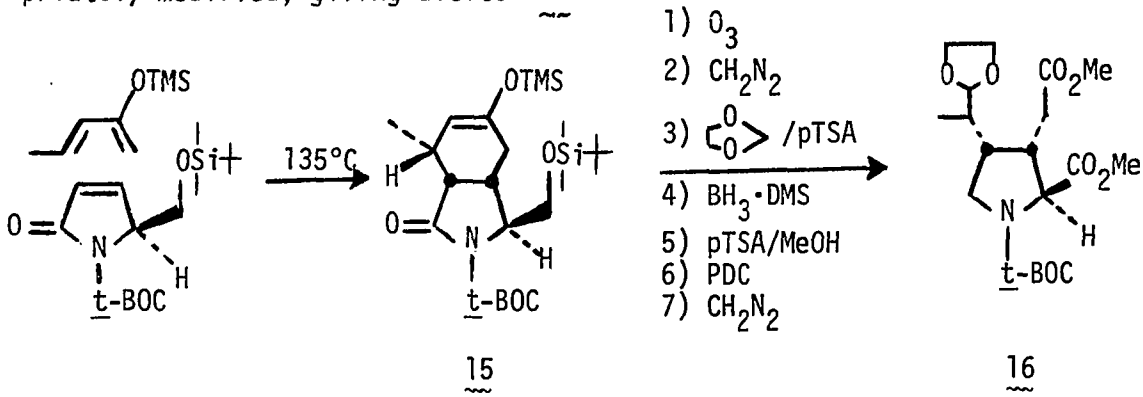
In a rather elegant synthesis, Oppolzer and Andres have synthesized 1, based on the utilization of an intramolecular ene reaction (10). They reported the thermal cyclization of their key intermediate 10 to produce pyrrolidine 11 in a 97% yield. Compound 1 was subsequently obtained in two steps with high overall yield.



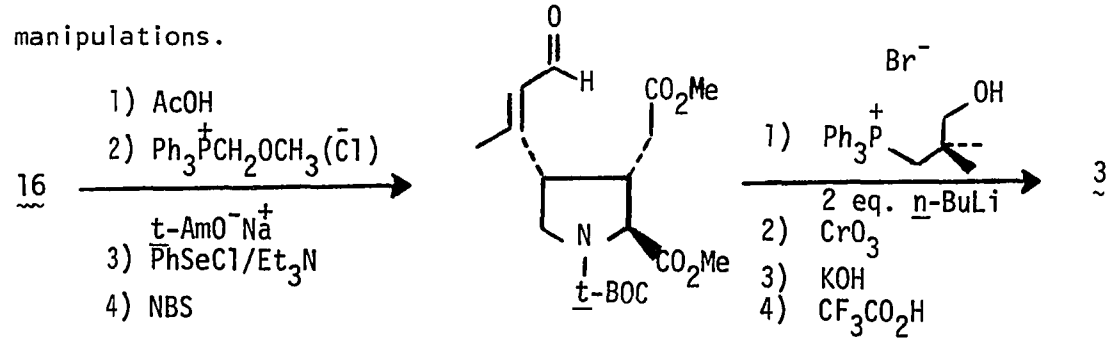
The same workers were able to produce α-kainic acid (2) by a similar intramolecular ene reaction (11). Key intermediate 12 was postulated to be in equilibrium with 13 under thermal conditions; compound 13 cyclized to 14 in high yield. Hydrolysis and epimerization were readily accomplished to yield 2.



At the time of writing this manuscript, domoic acid (3) had only once been synthesized. Ohfune and Tomita reported formation of the appropriate skeleton by a Diels-Alder reaction to a pyrrolone (12). The bicyclic system 15 was cleaved and the functional groups were appropriately modified, giving diester 16.



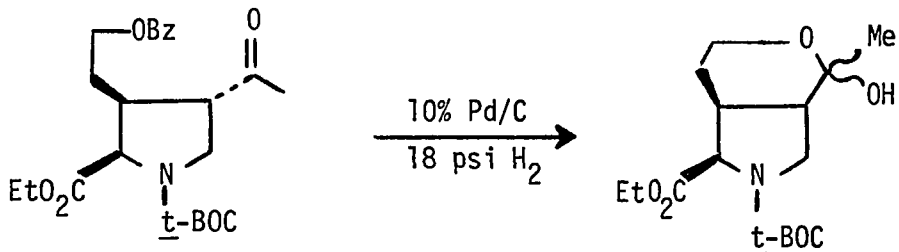
The side chain at the C-4 position was successfully appended by two sequential Wittig reactions on the aldehyde produced by removal of the acetal from 16. Compound 3 is obtained after several functional group manipulations.



RESULTS AND DISCUSSION

Encouraged by the results of our dipolar additions of thiazolium ylides described in Part I, we embarked on a course to elaborate an adduct into a natural product system. Starting with N-t-butoxycarbonyl-3α-(2-benzyloxyethyl)-4β-acetyl-α-proline-ethyl-ester (see Part I trans-90), formed via the cycloaddition of 3-(2-ethoxy-2-oxoethyl)-5-(2-hydroxyethyl)-4-methylthiazolium bromide with 7-benzyloxy-3-hexene-2-one (see Part I adduct 73s), a few simple functional group manipulations and an epimerization were needed to produce (±)α-allokainic acid (1).

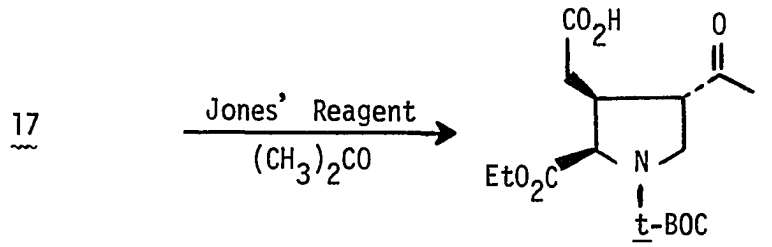
Removal of the benzyloxy protecting group of N-t-butoxycarbonyl-3α-(2-benzyloxyethyl)-4β-acetyl-α-proline-ethyl-ester with 10% palladium on carbon under a hydrogen atmosphere gave a diastereomeric mixture of hemiketals 17 as evidenced by the loss of the acetyl methyl in the proton NMR spectrum. The N-t-butoxycarbonyl group experiences hindered rotation with diastereomeric geometries at room temperature, giving rise to some fine splitting of signals especially in the C-13 NMR spectra (13).



17

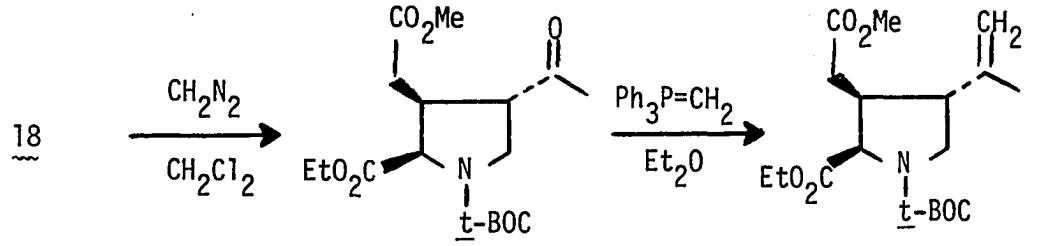
Jones oxidation of hemiketals 17 yielded the carboxylic acid (18) as a white, highly crystalline compound. Both a single crystal X-ray

structure, and an independent elemental analysis confirmed this as the correct structure.



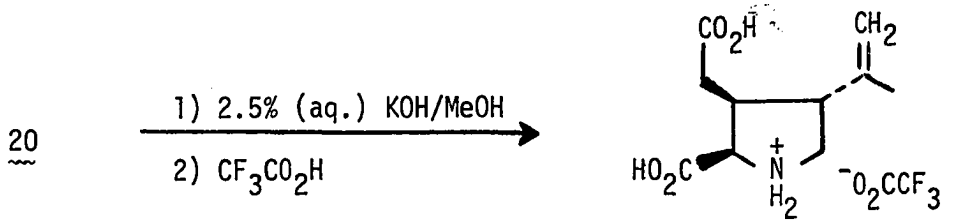
18

Conversion of the free acid into the methyl ester (19) with diazomethane, followed by addition of methylenetriphenylphosphorane, gave the isopropenyl compound (20).



19 20

Saponification of both esters and removal of the N-t-butoxycarbonyl group from 20 yielded amino diacid 21, which was isolated as the trifluroacetate salt (10,12).



21

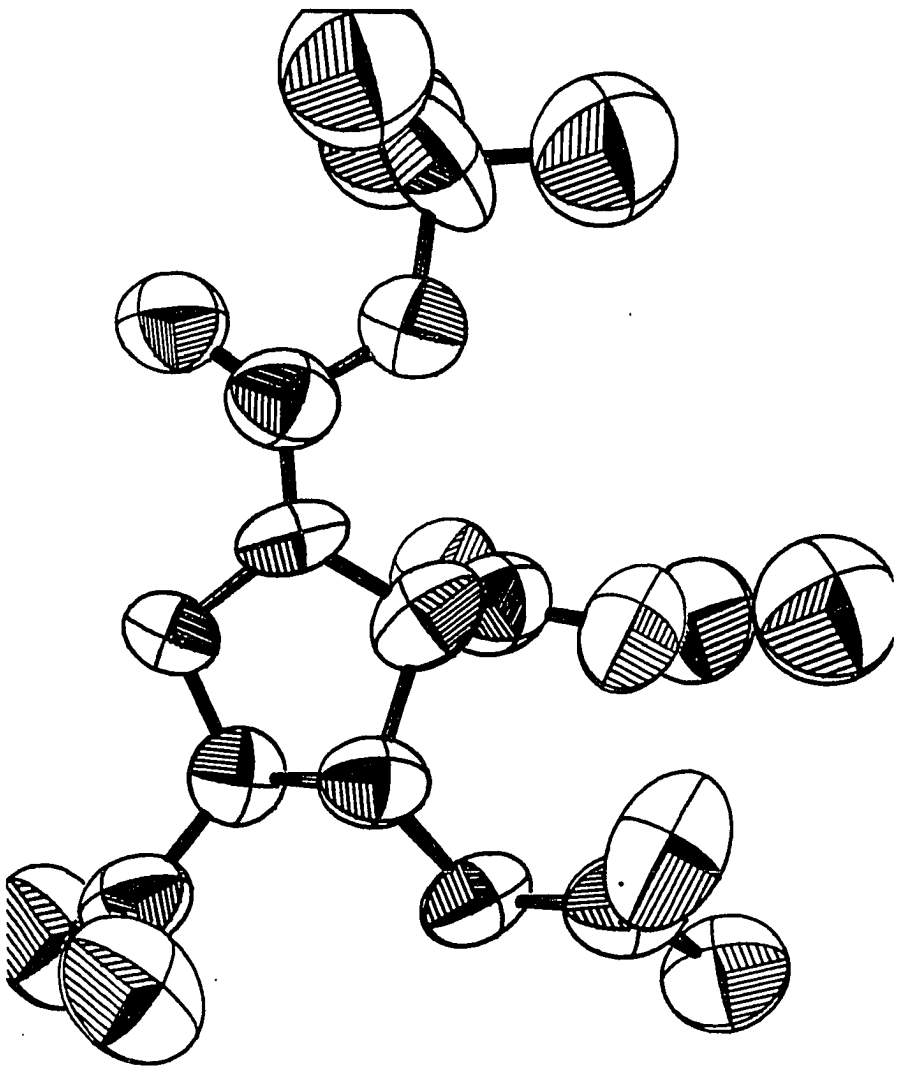


Figure 1. Molecular structure of N-t-butoxycarbonyl-3α-carboxymethyl-4β-acetyl-α-proline-ethyl-ester (18) as determined by a single crystal X-ray analysis

We anticipated that epimerization of the C-2 acid group to the trans-configuration of (1) might occur during the hydrolysis reaction, but this appeared not to be the case. A 300 MHz NMR spectrum showed significant differences between our synthetic material and that of an authentic sample supplied to us by Dr. Y. Ohfune. Our initial attempts to epimerize 20 or 21 with either equilibrating bases (DBU, t-butoxide/t-butanol), or strong bases (lithium-2,2,6,6-tetramethyl piperidine, lithium diisopropylamide) were unsuccessful.

We found that L-proline was almost completely racemized by the action of 0.5N aqueous sodium hydroxide at a temperature of 175-180°C in a sealed tube. This result indicated to us that moderately high temperatures in very polar media were required to form the dianion of proline.

We cautiously subjected 21 to similar conditions and observed that substantial amounts of highly insoluble polymeric material were formed above 155°C. A 300 MHz NMR spectrum of the soluble portion of the reaction mixture showed approximately 20% of a material having an identical spectrum to the authentic compound 1. Repeating the reaction keeping the temperature slightly below 155°C caused only small amounts of polymer to form and the conversion of 21 to 1 occurred in 30 to 50% yield based on 300 MHz NMR spectra peak ratios.

In our synthesis, two of the three asymmetric centers are correctly set by the initial dipolar cyclization, making this method superior to the earlier nonstereoselective routes. Only Oppolzer and Andres' synthesis offers the advantage of stereospecific molecular construction.

EXPERIMENTAL

General

Diethyl ether was distilled from lithium aluminum hydride. All organic extracts were dried over Na_2SO_4. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman Acculab 2 spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 instrument or a Bruker WM 300 MHz instrument in $CDCl_3$ with absorptions recorded in ppm downfield from internal Me_4Si. Carbon-13 NMR spectra were recorded on a JOEL FX-90Q Fourier Transform Spectrometer, with absorptions expressed in ppm relative to the chemical shift of $CDCl_3$. Elemental analyses were performed by Galbraith Laboratories, Inc.

Hemiketal 17

N-t-Butoxycarbonyl-3α-(2-benzyloxyethyl)-4β-acetyl-α-proline-ethyl-ester (see Part I) (0.45 g, 1.08 mmoles) was dissolved in 95% ethanol (3 ml) containing a suspension of 10% Pd/C (0.5 g). A hydrogen pressure of 18 psi was applied on a Parr shaker apparatus. The reaction was shaken for approximately one hour and followed to completion by TLC analysis (silica gel, hexane:ethyl acetate, 2:1). The solution was filtered through Celite, and the solvent removed, leaving 0.26 g (0.80 mmoles, 79%) of 17 as a mixture of diastereomers: IR (film) 3500, 2990, 1740, 1700, 1400, 1380, 1190 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H), 1.45 (s, 9 H), 1.46 (s, 3 H), 2.0-2.4 (m, 4 H), 3.1-3.8 (m, 4 H), 4.1-4.5 (m, 1 H), 4.20 (q, J = 7 H, 2 H); 90 MHz C-13 MNR ($CDCl_3$)

(major isomer) δ 14.11, 15.09, 22.83, 28.09, 38.37, 46.30, 47.86, 55.41, 60.48, 61.97, 79.60, 97.74, 153.73, 171.09.

N-t-Butoxycarbonyl-3α-carboxymethyl-4β-acetyl-α-proline-ethyl-ester (18)

Hemiketal 17 (0.129 g, 0.39 mmoles) was dissolved in acetone (5 ml). A solution of Jones reagent (0.5 ml, 8N dissolved in 7 ml acetone) was added dropwise until a red-brown color persisted for 15 minutes. Two drops of isopropanol were added to discharge the color. The solution was diluted with ether (10 ml) and filtered through paper. The solvents were removed by evaporation, the residue was taken up in ether and extracted four times with 1N Na_2CO_3. The aqueous extract was made acidic with conc. HCl, extracted four times with CH_2Cl_2, and the extract dried over Na_2SO_4. Evaporation gave 0.081 g (0.24 mmoles, 63%) of 18 as a fine white crystalline solid: MP 132-133°C (CCl_4); IR (in CH_2Cl_2) 3020, 2990, 1735, 1705, 1400, 1365, 1255, 1195, 1160, 1140 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 3 H), 1.41 (s, 9 H), 2.2-2.6 (m, 3 H), 2.19 (s, 3 H), 2.9-3.4 (m, 3 H), 4.15 (q, J = 7 Hz, 2 H), 4.4-4.6 (m, 1 H), 7.8 (bs, 1 H); 90 MHz C-13 NMR ($CDCl_3$) (major isomer) δ 14.18, 28.29, 34.40, 39.41, 48.12, 52.67, 53.58, 61.32, 62.04, 80.70, 153.47, 171.55 (2C), 206.47. Anal. calcd. for $C_{16}H_{25}NO_7$: C, 55.97; H, 7.34. Found: C, 56.16; H, 7.63.

N-t-Butoxycarbonyl-3α-methoxycarbonylmethyl-4β-acetyl-α-proline-ethyl-ester (19)

Acid 18 (0.077 g, 0.22 mmoles) was dissolved in CH_2Cl_2 (3 ml) and excess CH_2N_2 (0.5N in Et_2O) was added dropwise until a yellow color

persisted. The solvents and excess reagent were removed by evaporation leaving 0.078 g (0.22 mmoles, 100%) of 19 as colorless oil: IR (film) 2980, 1735, 1700, 1390, 1360, 1250, 1190, 1160, 1125 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3 H), 1.43 (s, 9 H), 2.1-2.5 (m, 3 H), 2.19 (s, 3 H), 2.8-3.5 (m, 3 H), 3.66 (s, 3 H), 4.15 (q, J = 7 Hz, 2 H), 4.2-4.6 (m, 1 H); 90 MHz C-13 NMR ($CDCl_3$) (major isomer) δ 14.18, 28.22, 33.75, 39.41, 48.06, 51.76, 52.54, 61.06, 61.71, 61.91, 80.51, 153.34, 171.29, 171.42, 205.87.

N-t-Butoxycarbonyl-3α-methoxycarbonylmethyl-4β-isopropenyl-α-proline-ethyl-ester (20)

A solution of diester 19 (0.030 g, 0.085 mmoles) in dry Et_2O (1 ml) was added to a cooled (0°C) solution of methylenetriphenylphosphorane (0.053 g, 0.13 mmoles triphenylmethylphosphonium iodide and 0.11 mmoles of n-butyl lithium) in Et_2O (4 ml), under nitrogen. The initial rust-red colored solution turned white and gave a precipitate upon addition. The solution was allowed to stir for two hours, then the mixture was allowed to rise to ambient temperature. Filtration, followed by removal of the solvent, gave a yellow oil, which was flash chromatographed (silica gel: 230-400 mesh, hexane:ethyl acetate, 10:1). Isolation gave 0.017 g (0.048 mmoles, 57%) of 20, as a clear oil: 60 MHz NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3 H), 1.43 (s, 9 H), 1.80 (s, 3 H), 2.1-2.4 (m, 2 H), 2.4-2.9 (m, 2 H), 3.0-3.4 (m, 1 H), 3.5-3.8 (m, 1 H), 3.67 (s, 3 H), 4.13 (q, J = 7 H, 2 H), 4.3-4.6 (m, 1 H), 4.84 (bs, 2 H); 90 MHz C-13 NMR ($CDCl_3$) (major isomer) δ 14.24, 18.60, 28.35, 33.36, 40.64, 48.38, 49.36, 51.70, 60.93, 61.84, 80.12, 114.65, 141.31, 153.60, 171.55, 172.07.

3α-Carboxymethyl-4β-isopropenyl-α-proline (21)

Diester (20) (0.017 g, 0.048 mmoles) was dissolved in aqueous KOH (3 ml, 2.5%) and methanol (0.5 ml), and brought to reflux (66°C) for two hours. A TLC analysis (silica gel, hexane:ethyl acetate, 5:1) indicated none of the starting material (20) was present in the mixture. The solution was acidified with conc. HCl (∿3 on pH paper), and evaporated to dryness. Excess trifluoroacetic acid (0.5 ml) was added and the solution was allowed to stir for 15 min. at room temperature. The excess CF_3CO_2H was removed by vacuum, yielding a white solid, 21 (along with some KCl): 300 MHz NMR (D_2O, Ref: TMS cap.) δ 1.71 (s, 3 H), 2.42, 2.48 (dd, J = 9.8 Hz, 1 H), 2.66, 2.72 (dd, J = 4.9 Hz, 1 H), 2.76-2.83 (m, 1 H), 2.89-3.00 (m, 1 H), 3.25-3.33 (m, 1 H), 3.67, 3.71 (dd, J = 8.3, 1 H), 4.68 (d, J = 8.6 Hz, 1 H), 4.96 (s, 2 H), 5.00 (bs, 4 H).

(±)α-Allokainic acid (1)

The white solid 21 was dissolved in aqueous NaOH (0.5N, 1 ml) and freeze-thaw degassed four times. The mixture was sealed in a thick-walled glass tube under N_2. The temperature was raised to 130-140°C for five hours. A very slightly discolored solution along with a small amount of white precipitate were obtained. The solution was filtered and and evaporated to dryness, yielding a mixture of 21 and 1. The 300 MHz NMR spectrum of 1 compared exactly to the authentic sample of (±)α-allokainic acid: 300 MHz NMR (D_2O, Ref.: TMS cap.) (disodium salt)

δ 1.65 (s, 3 H), 2.11-2.30 (m, 1 H), 2.4-2.8 (m, 1 H), 2.47-2.56 (m, 2 H), 2.84-2.87 (m, 2 H), 3.03 (d, $\underline{J}$ = 7.8 Hz, 1 H), 4.72 (s, 3 H); 300 MHz NMR (D_2O, Ref.: TMS cap.) (trifluroacetic acid salt) δ 1.69 (s, 3 H), 2.72-2.78 (m, 2 H), 2.8-3.0 (m, 1 H), 3.31 (t, $\underline{J}$ = 11.3 Hz, 1 H), 3.5-3.6 (m, 2 H), 4.24 (d, $\underline{J}$ = 9.2 Hz, 1 H), 4.7 (bs, 4 H), 5.0 (bs, 2 H). The mixture of $\underset{\sim\sim}{21}$ and $\underset{\sim}{1}$ has been separated by an ion exchange resin (Dionex DC-6A) with a Durrum model D-400 amino acid analyzer, and their ninhydrin derivatives detected by a 440nm UV detector. With a flow rate of approximately 31 ml per hour over a 30 cm column (0.9 cm inner diameter), $\underset{\sim\sim}{21}$ eluted with a retention time of 49.5 (±0.5) min. and $\underset{\sim}{1}$ eluted with a retention time of 56.4 (±1.2) min. with a pH 3.1 buffer (0.67 M sodium citrate). Injection of a mixture of our synthetic $\underset{\sim}{1}$ and authentic α-allokainic acid showed identical retention times.

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PART III. CYCLOADDITION REACTIONS OF 1,2-BENZOQUINONEDIAZIDES

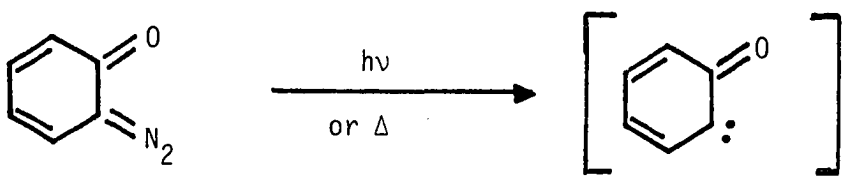
INTRODUCTION

Cyclizations of 1,2-benzoquinonediazides are a relatively unexplored area of carbene addition reactions. Compounds of this class are important precursors to a wide variety of 1,2-dihydrobenzofurans and other heterocyclic systems. At the time this work was initiated, the literature contained only a small number of examples of cycloadditions occurring with the carbenes generated from 1,2-benzoquinonediazides (1,2,3,4,5). This manuscript will detail the results of our efforts in the investigation of some of the aspects of 1,2-benzoquinonediazide cyclizations (6).

HISTORICAL

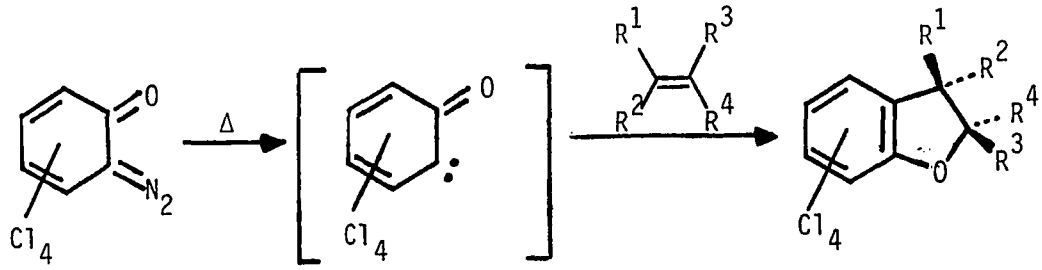
1,2-Benzoquinonediazides 1 have been known for almost a century. Since their initial detection by Hantzsch and Davidson (7) in 1896, a wide variety of reactions have been reported for these interesting compounds. A recent book on the subject describes at length the many facets of their known chemistry (8). This literature review will focus on only the cycloaddition reactions that have been reported.

Through the loss of nitrogen, these systems become exceedingly prone to thermal and photochemical decomposition. Unlike aromatic diazonium salts, which decompose to the aryl carbonium ion upon loss of nitrogen, 1,2-benzoquinonediazides give a cyclic carbene, 3,5-cyclohexadien-2-onylidene (2).



1 2

Huisgen and co-workers were the first to report addition of the carbene so generated to carbon-carbon multiple bonds (1,2). They trapped the 3,4,5,6-tetrachloro-3,5-cyclohexadien-2-onylidene (3) with dimethylmaleate and dimethylfuarate to produce dihydrobenzofurans (4a + 4b) in approximately 50% yields. The reaction is shown to be stereospecific, since a trans-geometry about the olefin results in a trans-configuration on the dihydrofuran moiety.



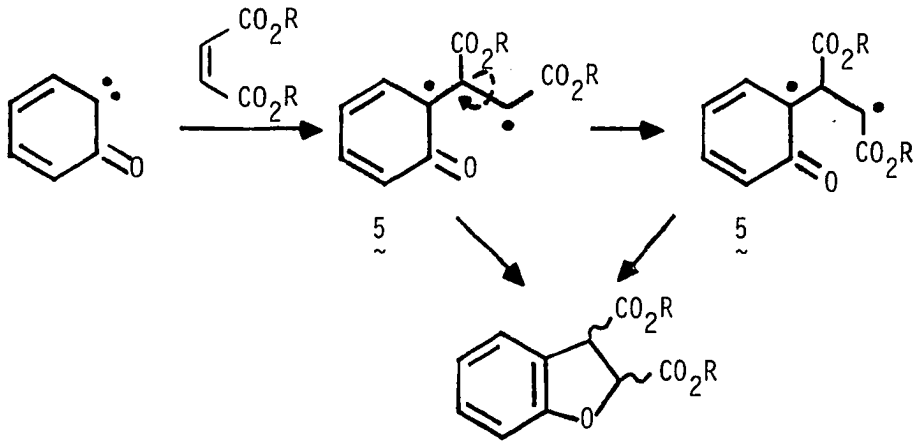
3

4a, 4b

a: $R^1 = R^3 = H$
$R^2 = R^4 = CO_2Me$

b: $R^1 = R^4 = H$
$R^2 = R^3 = CO_2Me$

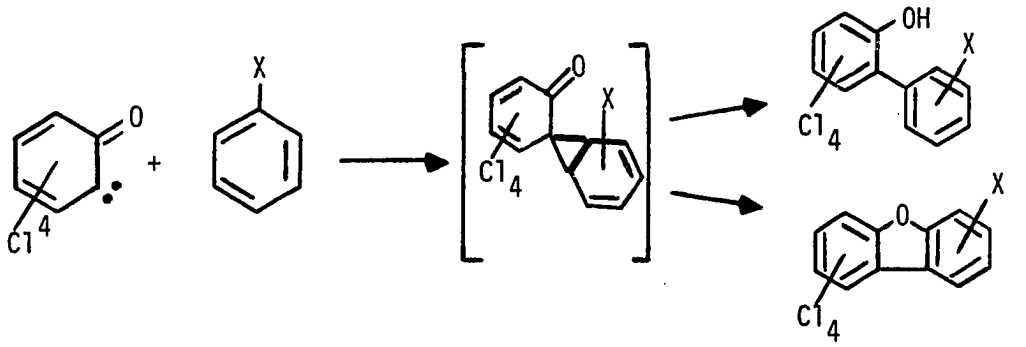
The ground state, calculated with the LCAO-MO method using the Hückel approximation (9), was found to be the triplet for the analogous 2,5-cyclohexadien-4-onylidene. But, it is the singlet excited state that is generally thought to be responsible for the stereospecificity in the additions to 1,2-disubstituted olefins (10). Addition of the triplet form carbene is postulated to give an intermediate 1,3-biradical (5), which may rotate before closure. The observation of retention of stereochemistry in the product is taken as evidence for addition of the singlet form of the carbene.



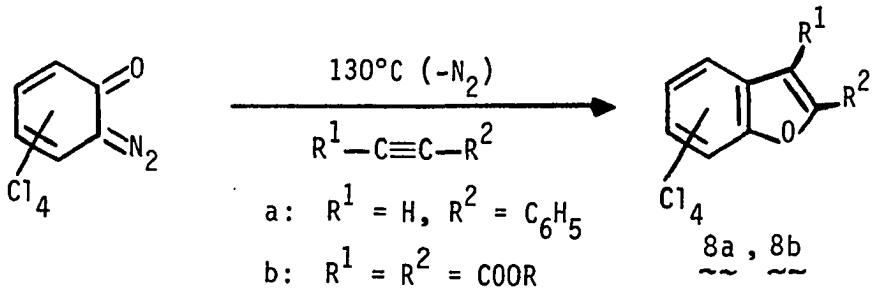
The formation of 1,2-dihydrobenzofurans from 3,4,5,6-tetrachloro-3,5-cyclohexadien-2-onylidene (3) addition to olefins may involve an intermediate cyclopropane which undergoes a rapid isomerization at the reaction temperature. Although no experimental evidence is overly compelling for this mechanism, in the analogous 2,5-cyclohexadien-4-onylidene (6) (generated from 1,4-benzoquinonediazide), trapping by olefins gives high yields of spirocyclopropanes (7) (11).

If the α-keto-carbene is trapped by a substituted benzene derivative, two unique products are formed depending on the nature of X

(4,12). This is believed to be due to a preferred direction of opening of the postulated cyclopropane intermediate.



Acetylenes, acting as the trapping agent, have been reported to add satisfactorily to the fully halogenated carbene 3, yielding benzofurans (8) (1,3,5). In the case of a product arising from addition to an unsymmetrical acetylene (8a), only one regioisomer is observed. This is again believed to be due to a preferred direction of cyclopropane ring opening.

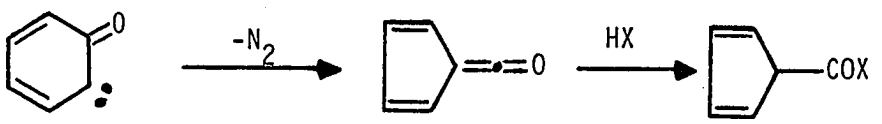


8a , 8b

Carbon-heteroatom multiple bonds in a wide variety of systems have been reported to trap the carbene which results from decomposition of 1,2-

benzoquinonediazides. Table 1 gives a listing of adducts and their corresponding heterocyclic products resulting from addition of carbene 3.

The isomerization of a divalent carbon adjacent to a carbonyl group into a ketene is well-known in the chemical literature as a Wolff rearrangement (13). This structural reorganization is seen as a major by-product for carbenes generated from 1,2-benzoquinonediazides but not from their 1,4-isomers. The resulting ketene, 9, is rather unstable and usually reacts with the solvent or another molecule of starting material (14,15).

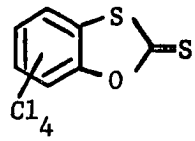
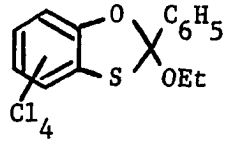
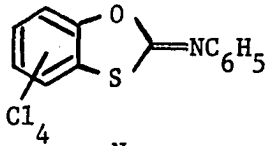
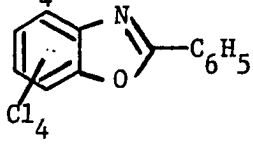
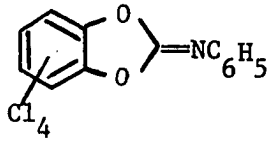
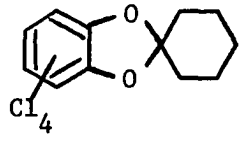
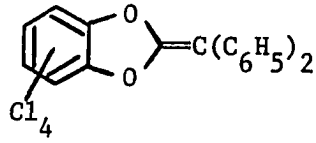
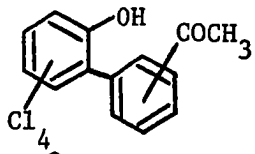
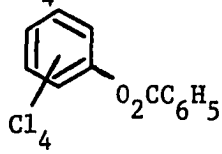


9

There is some debate as to whether an actual carbene intermediate is involved or whether ketene formation is concurrent with nitrogen elimination (16). It has been shown that transformation of α-keto-carbenes into ketenes is a dark process, making the free carbene mechanism of the Wolff rearrangement seem more preferable (17).

As the stability of the carbene center is decreased, the formation of the Wolff-rearranged products increases. The carbene can in some cases be so exceedingly reactive that no products of bimolecular additions are seen. This trend was noted by Huisgen, where a steady decrease in the yield of addition products with carbonbisulfide was observed as chlorine atoms were sequentially replaced by hydrogen atoms

Table 1. Heterocyclic products from additions to carbene 3

Adduct	Product	Yield %	Method of Gener.	Ref.
S=C=S		80	hν, Δ	4
$C_6H_5C(S)OEt$		58	Δ	4
$C_6H_5N=C=S$		57 61	Δ hν	4, 5
$C_6H_5C\equiv N$		36 25	Δ hν	1, 4
$C_6H_5N=C=O$		32	Δ	4
		~30	hν	4
$(C_6H_5)_2C=CO$		50	Δ	4
$C_6H_5COCH_3$		~30	hν	4
C_6H_5COH		~36	Δ	4

in the 1,2-benzoquinonediazide system (4). The tetrachloro derivative, being the most stable added in a yield of 80%, while the monochloro analogue yielded only a 9% yield of cycloaddition product. The halogens are believed to increase the electrophilicity of the carbene moiety, favoring addition rather than rearrangement (18,19). The Wolff-rearrangement of 1,2-benzoquinonediazides has been developed into a useful synthetic transformation called the Süs reaction, and has been carried out on a wide variety of systems (8).

This survey summarizes all the known cycloadditions of the carbenes generated from 1,2-benzoquinonediazides to carbon-carbon and carbon-heteroatom multiple bonds. There are many aspects of this relatively untouched field of research that need to be investigated. 1,2-Benzoquinonediazides appear to be exceedingly useful intermediates in multistep syntheses of complex heterocycles. Once their reactivity is bracketed and stereo and regiospecificity understood, their general utility may become widespread.

RESULTS AND DISCUSSION

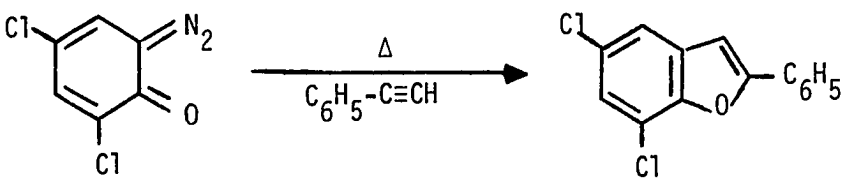
We decided to undertake a study of the cycloaddition reactions of carbon-carbon multiple bonds to the carbenes generated from decomposition of 1,2-benzoquinonediazides. Our goal was threefold: 1) to determine the regiochemistry of addition to unsymmetrical olefinic and acetylenic molecules; 2) to investigate which chemical groups, either on the adduct or carbene-bearing molecule, enhance the reactivity towards addition rather than Wolff rearrangement, and 3) to attempt to apply the addition product toward an intermediate in a synthesis of a biologically interesting natural product.

Intrigued by the results of Huisgen (see Historical section) with the successful addition of the carbene generated from the 3,4,5,6-tetrachloro-1,2-benzoquinonediazide to olefins and acetylenes, we first proceeded to determine the minimum number of halogens attached to the ring that are needed to promote any addition reaction. While the fully halogenated example is mechanistically interesting, the products are not especially useful in natural product synthesis. Few naturally occurring compounds contain fully halogenated aromatic rings as subunits.

In our first attempt, we prepared the nonhalogenated system—1,2-benzoquinonediazide by the method of Kikot' (20). All attempts to add the carbene (generated via thermal decomposition at 135°C in a sealed tube with the trapping agent as solvent) to olefins failed. In all cases uncharacterizable dark, tarry matter was recovered.

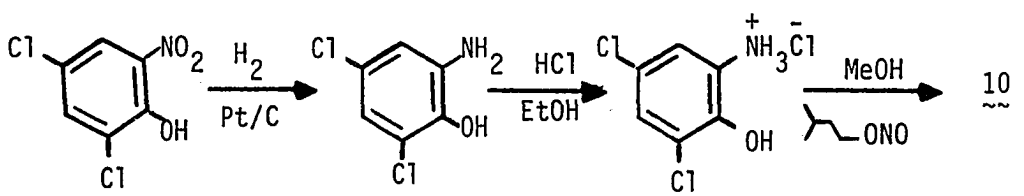
The 4,6-dichloro-1,2-benzoquinonediazide (10) has been thermally decomposed to the carbene in the presence of phenylacetylene, to give

adduct 11 (3). Although the yield of 11 was reported to be only 13% for this cycloaddition, we decided to explore its reactivity toward other systems.



10 11

A simple three-step procedure from readily available 2,4-dichloro-6-nitrophenol was employed. This is a slightly modified version of the reported preparation (21,22). Catalytic hydrogenation of the nitro group to the amine (12) followed by acidification with hydrochloric acid gave the anilinium salt 13. Treatment with isoamyl nitrite in methanol at 0°C gave an almost instantaneous orange-yellow precipitate. This solid was characterized by ^{1}H NMR, IR, and ^{13}C NMR as 4,6-dichloro-1,2-benzoquinonediazide (10).

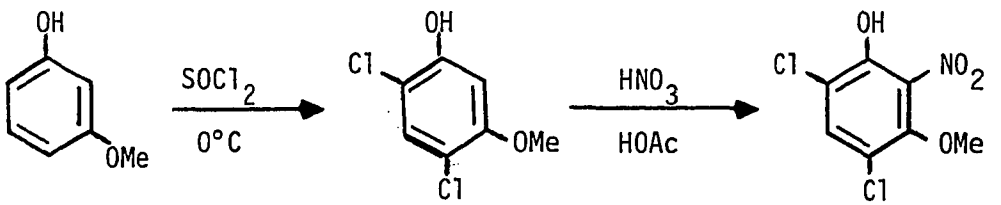


12 13

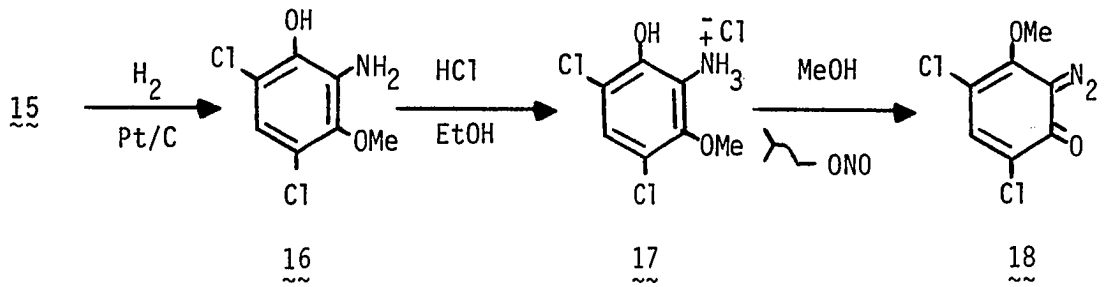
In the synthesis of 1,2-benzoquinonediazide (1), the precursor is o-diazoniumphenol, an isolable salt which, upon treatment with base,

isomerizes to the product. Unlike the parent system (1), no diazonium salt is isolable with the 2,4-dichloro analogue (10). The 1,2-benzoquinonediazide is formed spontaneously by diazotization of the anilinium salt.

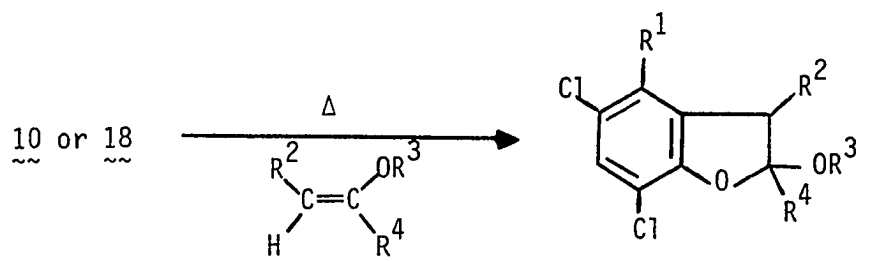
The 5-methoxy derivative of 4,6-dichloro-1,2-benzoquinonediazide (18) has been concomitantly synthesized. Starting with commercially available m-methoxyphenol, chlorination according to the literature procedure (23) gave 2,4-dichloro-5-methoxyphenol (14) which crystallized upon standing. Treatment of 14 under nitration conditions (HNO_3/HOAc) gave 2,4-dichloro-5-methoxy-6-nitrophenol (15) as a light yellow solid. Catalytic reduction of 15 with platinum on carbon (10%) under 90 psi of H_2 in ethanol gave amine 16 which was not isolated due to the fear of suspected instability, as reported for similar systems (24). This aniline was instead converted to the hydrochloride salt (2N HCl in ethanol) and isolated as a tan solid (17). The purified anilinium salt (17) was dissolved in methanol and was exposed to the diazotizing agent, isoamylnitrite, at 0°C. Evaporation of the solvent gave an orange solid which was identified by ^1H, NMR, IR, and ^{13}C NMR as 4,6-dichloro-5-methoxy-1,2-benzoquinonediazide (18).



14 15



Compounds 10 and 18 were thermolyzed in the presence of a variety of olefins to give substituted dihydrobenzofurans or benzofurans (see footnote c, Table 2) (19). The results of this study are compiled in Table 2 (6).



We found the highest yields of adducts were obtained with electron-rich olefins, such as vinyl ethers and acetates. Little or no addition was observed with acetylenes, electron-poor olefins such as dimethylmaleate, conjugated dienes, quinones, or unactivated olefins such as 1-hexene. This seems reasonable based on the calculations indicating carbenes of this type are electrophilic in nature (9). The major

Table 2. Benzoquinonediazide cyclizations

Entry[a]	1,2-benzoquinonediazide	R^2	R^3	R^4	% Yield[b]	19
1	10	H	Et	H	55	a
2	10	H	$COCH_3$	H	47[c]	b[c]
3	10	H	$COCH_3$	CH_3	50[c]	c[c]
4	18	H	Et	H	46	d
5	10	H	CH_3	$CH=CH_2$	--	e
6	10	H	$COCH_3$	Ph	52[c]	f[c]
7	10	$-CH_2CH_2-$		H	55	g
8	18	$-CH_2CH_2-$		H	45	h

[a]The reactions denoted by entries 1-6 were run by Mr. Jim DeLano, an undergraduate working in our group, 1982-1983.

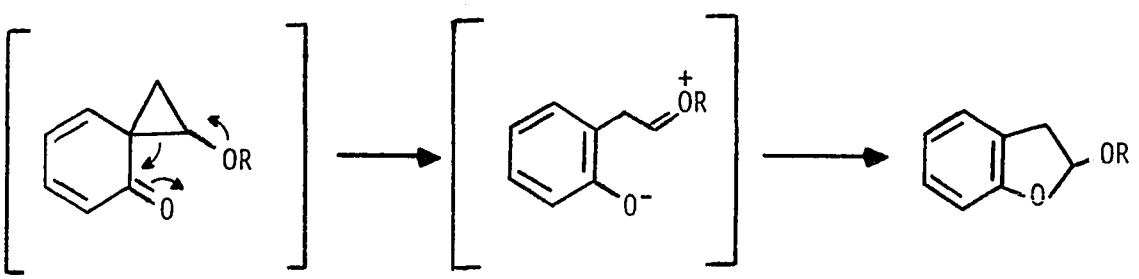
[b]The yields were all based on chromatographically separated compounds.

[c]These yields are based on the conversion of the addition products into benzofurans by elimination of acetic acid.

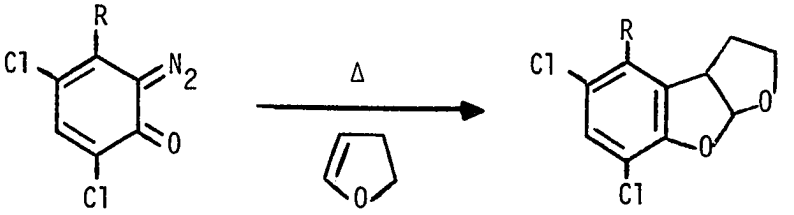
by-product seems to be that resulting from Wolff-rearrangements and dimerizations. No further characterization of the highly colored resin by-products has been attempted.

Entries 2, 3, and 6 showed a tendency to partially eliminate acetic acid during the course of the cyclization reaction, giving mixtures of benzofurans and 1,2-dihydrobenzofurans. It was found that complete elimination to benzofurans could be accomplished by simply treating the resulting mixture with a catalytic amount of p-toluenesulfonic acid in benzene at reflux overnight.

The additions to unsymmetrical olefins are observed to give only one regioisomer, that which has the activating group adjacent to the 1,2-dihydrofuran oxygen. This can be rationalized in terms of the adduct oxygen assisting in opening of the cyclopropane to the zwitter-ionic resonance form.



The reactions denoted by entries 7 and 8 yielded highly interesting tricyclic molecules, 19g and 19h. Only one regioisomer is formed, as in the earlier examples. This tricyclic skeleton was recognized as a major subunit in various classes of natural products such as aflatoxins and the versicolorins (25).



10 R = H

18 R = OMe

19g R = H

19h R = OMe

EXPERIMENTAL

General

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined on a Beckman Acculab 2 IR spectrometer. Nuclear magnetic resonance spectra were determined on a Varian EM 360 A or EM 360 L with absorptions recorded in ppm downfield from internal $(CH_3)_4Si$. Carbon nuclear magnetic resonance spectra were determined on a Joel FX 90-Q spectrometer with an internal reference of $CDCl_3$ and/or $(CH_3)_4Si$. High resolution mass spectra were recorded on an AEI MS-902 high resolution mass spectrometer.

2-Amino-4,6-dichlorophenolhydrochloride (13)

The literature procedure (21) was modified slightly for our purposes, allowing for an easier isolation of product on a large scale.

Commercially available 2,4-dichloro-6-nitrophenol (Aldrich Chem. Co.) (52 g, 0.250 moles) was carefully hydrogenated with 10% platinum on carbon (2 g) in ethanol at ambient temperature. A hydrogen pressure of 90 psi was applied with a Parr apparatus and the reaction followed by TLC. Periodic cooling of the pressure bottle was necessary in order to prevent overheating due to the exothermic reaction. When complete, the mixture was filtered through Celite to give a dark solution of 12 which was not isolated. Acidification with excess ethanolic HCl (2N) gave the crude aniliniumhydrochloride, 13. The solution was evaporated in-vaccuo to give a brown solid, which was recrystallized from methanol-

ether, yielding 32 g (0.18 moles, 72%) of 13 as a white solid: 60 MHz NMR ($D_2O/(CD_3)_2CO$) δ 7.40 (d, J = 2Hz, 1 H), 7.49 (d, J = 2 Hz, 1 H); 90 MHz C-13 NMR ($D_2O/(CD_3)_2CO$) δ 122.87, 123.90, 125.26, 125.91, 129.16, 146.22.

4,6-Dichloro-1,2-benzoquinonediazide (10)

The literature procedure (22) was again modified for easy isolation on a large scale.

A cooled (0°C), methanolic solution of 12 (10.0 g, 46.6 mmoles in 150 ml) was treated with neat isoamylnitrite (25 ml) which was added over 30 min., with the reaction protected from light. The mixture very quickly became turbid and gave a fluffy, bright orange precipitate. The solution was warmed to ambient temperature, filtered, and the solid washed with ether-hexane (1:1). The collected mass was dissolved in methylene chloride and washed four times with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated, without heating above room temperature to give 10. The fluffy, yellow-orange solid (decomposes above 115°C) is light-sensitive, but can be stored indefinitely if cooled to 10°C in the dark. IR (film $CDCl_3$) 2160, 1620, 1610 cm^{-1} (lit. (22) 2128, 1630 cm^{-1}); 60 MHz NMR ($CDCl_3$) δ 7.12 (br d, 1 H), 7.50 br d, 1 H); 90 MHz C-13 NMR ($(CD_3)_2CO$) δ 100.80, 116.21, 122.84, 131.75, 139.88, 172.53.

2,4-Dichloro-5-methoxy-6-nitrophenol (15)

2,4-Dichloro-5-methoxyphenol 14 (9.95 g, 51.5 mmoles) was dissolved in glacial acetic acid (55 ml) and cooled to 10°C in a water bath.

Nitric acid (4 ml, 70%) was added slowly with stirring, so as to keep the temperature below 14°C, over a period of approximately 15 min. After 1 hour, the reaction was allowed to warm to ambient temperature and stirred overnight. Approximately 40 ml of water was then added and a light yellow precipitate formed. The solid was washed with water, then dissolved in CH_2Cl_2. The residual aqueous layer was separated and the organic layer was dried over Na_2SO_4. Evaporation gave 15, a yellow solid, recrystallizable from hexane: (11.03 g, 46.35 mmoles, 90%) mp 90-92°C; IR (film, $CDCl_3$) 1595, 1540, 1470, 1210 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 3.85 (s, 3 H), 7.38 (s, 1 H), 8.50 (br s, 1 H); 90 MHz C-13 NMR, δ 62.54, 118.45, 120.45, 134.21 (2C), 147.54, 149.65.

3,5-Dichloro-2-hydroxy-6-methoxyanilinium hydrochloride (17)

Compound 15 (7.59 g, 31.9 mmoles) was dissolved in 100% ethanol (60 ml) containing 10% platinum on carbon (0.5 g). The solution was shaken on a Parr hydrogenation apparatus for two hours under a hydrogen pressure of 90 psi. Periodic cessation of shaking was necessary to keep the temperature from rising excessively due to the exothermic reaction. The reaction was followed to completion by TLC, at which time the solution was filtered through Celite. The free amine 16 was not isolated, but was treated with HCl in ethanol (2N) until a pH paper test indicated an acidic solution. Evaporation gave 5.4 g of 17 (22.0 mmole, 69%) as a white solid: 60 MHz NMR ($(CD_3)_2CO$) δ 3.90 (s, 3 H), 7.60 (s, 1 H); 90 MHz C-13 NMR ($D_2O/(CD_3)_2CO$) δ 61.93, 117.73, 118.48, 119.68; 127.10, 145.84, 148.17.

4,6-Dichloro-5-methoxy-1,2-benzoquinonediazide (18)

To a solution of 17 (3.7 g, 15.1 mmoles) in methanol (50 ml) at 0°C, neat isoamylnitrite (7 ml) was added with constant stirring over a period of 20 min. The resulting orange colored solution was allowed to warm to ambient temperature and was stirred for two hours. It was always protected from light. Removal of the solvent (without heating above ambient temperature) caused an orange solid to form. Reprecipitation from ether-hexane gave 1.79 g (8.2 mmoles, 54%) of 18: mp 75°C; IR (film, $CDCl_3$) 2160, 2130, 1625, 1570, 1515, 1150 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 3.89 (s, 3 H), 7.02 (s, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 61.91, 85.90, 103.92, 125.44, 138.64, 147.68, 170.77.

General Procedure for 1,2-Benzoquinonediazide Cyclizations

1,2-Benzoquinonediazide 10 or 18 was slurried into a sealable, thick-walled glass tube with trapping agent as solvent (approximately 0.5 to 1 ml agent per 1 mmole 1,2-benzoquinonediazide). The tubes were freeze-thaw degassed several times and sealed under nitrogen. Thermolyses were carried out in an oil bath heated to 135°C (±4°C) for 80 min. The resulting dark-colored solutions were then evaporated and flash chromatographed over 230-400 mesh silica gel for purification.

6,8-Dichloro-2-ethoxy-2,3-dihydrobenzofuran (19a)

IR (film) 2940, 1590, 1465, 1105 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 2.9-3.9 (m, 4 H), 5.49 (dd, J = 2 Hz, 1 H), 6.80

(br d, $\underline{J}$ = 4 Hz, 2 H); 90 MHz C-13 NMR ($CDCl_3$) δ 15.02, 37.39, 64.77, 107.04, 115.62, 123.43, 127.91, 128.56, 152.82, 153.15.

6,8-Dichlorobenzofuran (19b)

IR (film) 2940, 1580, 1445, 1410 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 6.8 (br d, $\underline{J}$ = 1 Hz, 1 H), 7.30 (br d, $\underline{J}$ = 1 Hz, 1 H), 7.45 (d, $\underline{J}$ = 1 Hz, 1 H), 7.70 (d, $\underline{J}$ = 1 Hz, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 106.96, 117.47, 119.42, 124.46, 128.63, 129.72, 146.89, 149.44.

6,8-Dichloro-2-methylbenzofuran (19c)

IR (film) 2920, 1575, 1440, 1175 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 2.50 (s, 3 H), δ 6.35 (br s, 1 H), δ 7.20 (br d, $\underline{J}$ = 1 Hz, 1 H), δ 7.35 (br d, $\underline{J}$ = 1 Hz, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 14.11, 103.14, 116.42, 118.43, 123.23, 128.24, 131.49, 149.18, 158.09.

6,8-Dichloro-2-ethoxy-5-methoxy-2,3-dihydrobenzofuran (19d)

IR (film) 2980, 1600, 1470, 1440, 1110, 1060 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.21 (t, $\underline{J}$ = 5 Hz, 3 H), 3.30 (dd, $\underline{J}$ = 4 Hz, 2 H), 3.85 (q, $\underline{J}$ = 5 Hz, 2 H), 3.85 (s, 3 H), 5.80 (dd, $\underline{J}$ = 4 Hz, 1 H), 7.15 (s, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 15.03, 36.16, 60.00, 64.82, 107.18, 110.16, 118.61, 118.72, 129.23, 151.22, 154.20.

6,8-Dichloro-2-phenylbenzofuran (19f)[1]

IR (nujol mull) 1610, 1580, 1440, 1418, 1180, 915, 845, 765, 750, 690, 665 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 6.97, (s, 1 H), 7.27-7.60 (m, 5 H), 7.8-8.0 (m, 2 H); 90 MHz C-13 NMR ($CDCl_3$) δ 101.19, 117.18, 119.07, 124.34, 125.25 (3C), 128.89 (2C), 129.41 (2C) 131.56, 149.31, 158.22.

6,8-Dichlorofuro[2,3b]-2,3-dihydrobenzofuran (19g)

IR (film) 2990, 1585, 1455, 1075, 1030 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.8-2.6 (m 2 H), δ 3.4-4.3 (m, 3 H), δ 6.40 (d, J = 6 Hz, 1 H), δ 7.0-7.3 (m, 2 H); 90 MHz C-13 NMR δ 33.17, 47.21, 67.31, 111.92, 114.78, 123.23, 125.83, 128.43, 130.76, 154.12.

6,8-Dichloro-5-methoxyfuro[2,3b]-2,3-dihydrobenzofuran (19h)

IR (film) 2995, 2950, 1595, 1470, 1430, 1060; 60 MHz NMR ($CDCl_3$) δ 1.8-2.6 (m, 2 H), δ 3.6-4.3 (m, 3 H), δ 3.90 (s, 3 H), δ 6.28 (d, J = 6 Hz, 1 H), δ 7.08 (s, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 31.93, 46.34, 60.54, 67.58, 112.33, 121.81, 130.10, 131.56, 135.73, 151.39, 155.07.

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[1] α-Acetoxystyrene was prepared according to the procedure of D. S. Noyce and R. M. Pollack, J. Amer. Chem. Soc. 1969, 91, 119.

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OVERALL SUMMARY

Part I describes the successful utilization of the 1,3-dipolar cycloaddition reaction of an activated thiazolium ylide to create highly stereospecific tricyclic systems which can be modified to produce substituted pyrrolidines and Δ^1- or Δ^2-pyrrolines. The key steps are the cycloaddition reaction to activated olefins and cleavage of the products by either silver ions or tri-n-butyltin hydride followed by acid.

Part II describes the successful modification of one of the pyrrolidines (from Part I) into a biologically interesting natural product, α-allokainic acid. Two of the three asymmetric centers are correctly set by the 1,3-dipolar addition; the last step in the synthesis involves an epimerization with base at an elevated temperature to obtain the correct stereochemistry of the natural product.

Part III describes the additions of the carbene thermally generated from two 1,2-benzoquinonediazides followed by in situ rearrangements to give 1,2-dihydrobenzofurans. Two tricyclic systems are rapidly and elegantly created which are major subunits of compounds of the highly biologically active aflatoxin and versicolorin family.

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