Alkylation of 3-arylazetidin-2-ones by using Friedl Crafts reaction

M.S.Magtoof* and S.S.Bari**
**Chemistry Dept. , Science Coll. , Thiqar Univ., Iraq*
***emistry Dept. , Panjab Univ., Chandigarh, 160014, India*

Abstrac

3-phenylthio-4,4-diethoxy carbonylazetidin-2-ones 6 have been conveniently Synthesized by reacting phenylthioacetyl chloride 2 with aryl substituted aminomalonates 3 under mild basic conditions. Thus using sulfuryl chloride 3-phenylthioazetidin-2-ones were transformed to-3-α -chioro phenylthio azetidin-2-ones, Alternatirely ,C-3 alkylation's of azetidin -2-ones using anisole in stannic chloride($SnCl_4$)

الكلة 3-اريل ازديتين -2-ون باستخدام تفاعل فريدل كرافتس

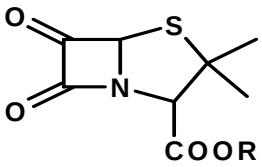
محمود شاكر مكطوف و شملير سنج باري *
قسم الكيمياء، كلية العلوم / جامعة ذي قار ، ناصرية / العراق
قسم الكيمياء، جامعة البنجاب ، جندكار / الهند

الملخص

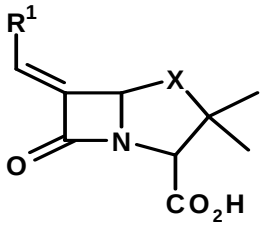
البيتالاكتام مركبات عضوية تتميز بوجود حلقة رباعية تحتوي على ذرة نـايتروجين غيـر متجانسة وهي الوحدة الاساسية للمضادات الحيوية .مركبات البحـث 4,4-ثنـائي ايثوكسـي كاربونيـل ازديتين-2-ون تحضر من تفاعل فنيل ثايو استيل كلوراميد مع امينو مالونيت بوجود البريدين كقاعدة ومن الكلة ذرة كاربون رقم -3 للمركب ازدتين-2-ون للمركب 7 مع الانيسول بوجـود ريـاعي كلوريـد القصدير تم تحضير مركبات البتالاكتام8 وشخصت بواسطة اطياف الاشعة تحت الحمراء والرنين النووي المغناطيسي ..

Introduction

Azetidine-2,3-diones 1 are importent starting materials for the introduction of alkylidene side chains at C3 poistion the β-lactam ring[1].the Wittig reaction[2], the Peterson olefination[3],and the Henry reaction[4] were the most widely employed methods to prepare en- β-lactam Antibiotics of type(2,3). However with expected of the Henry reaction[5],the expected products are often produced in very low yields together with concomitant formation of side products[6].

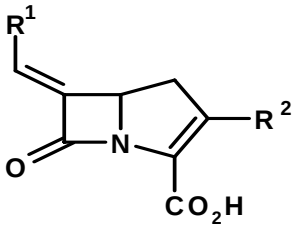


1



X = S, O, CH_2

2



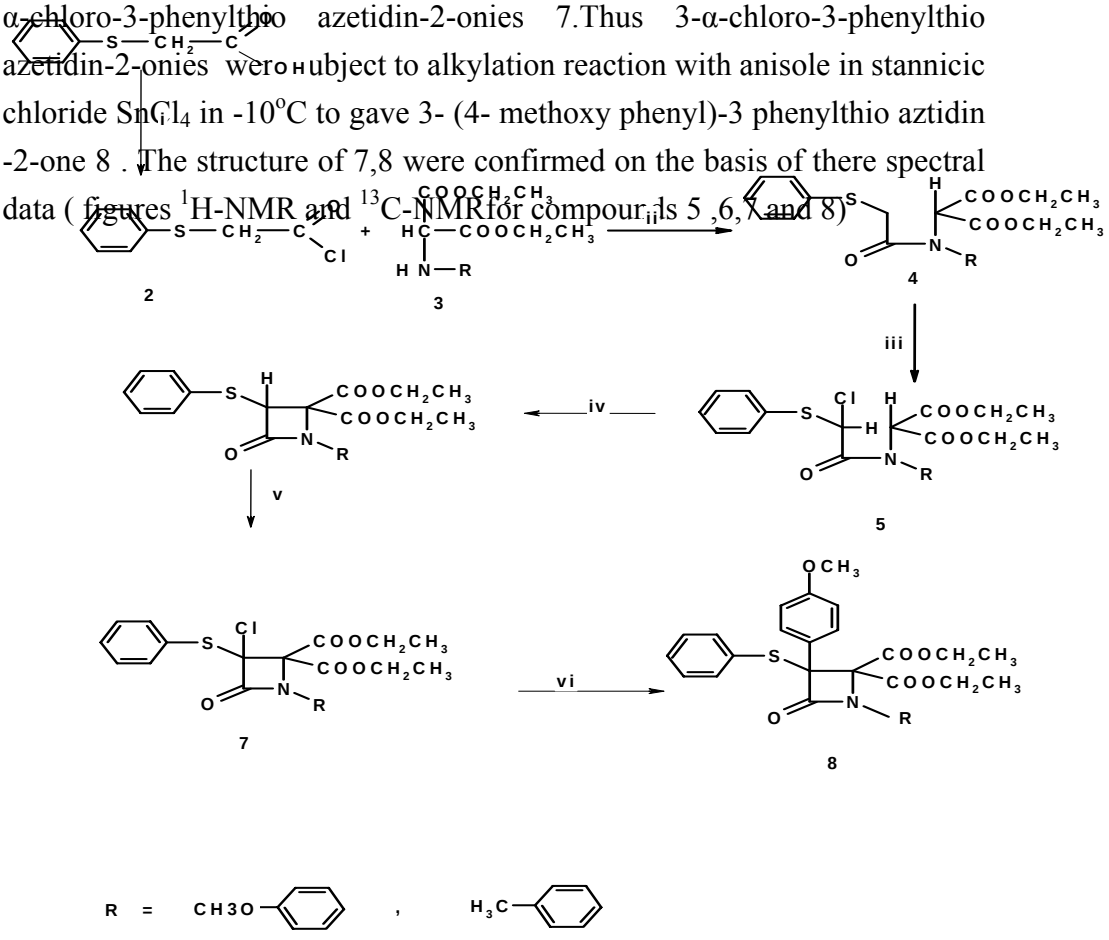
3

Recent discoveres of non classical β - lactams antibiotics such as nocardicines, Monobactams and thienamycin have stimulated much in terser [7,8,9] in the synthesis of monocyclic β -lactams. Besides this ,the unique feature of these straindes moleculesis that these heterocycles are becoming powerful building blocks for the synthesis of organic compounds[10,11,12,13], having different funetionalities such as α– amino acids,β-amino acids, α-hydroxy- β- amino acids[5],amino sugars and other heterocycles. A few methods of preporation of these 3-phenylthiozeidin -2-ones have been repoted[1] in the literature employing Staudinger reaction between appropriately substituted acid chlorides and imines. We repoort Herein a convenient and efficient synthesis of 3- phenylthio -4,4-diethoxy carbonyl Azetidin -2-ones 6 (R1=R2=$COOC_2H_5$) the strategy employs N-acylation of amino malonate followed by in situ C_3-C_4 bond formation as the key step (SCHEME I)

Result and Dissuasion

In an alternative approach (SCHEME I) substituted aminomlonate (3) on acylalation With phenylthioacetyl chloride(2) under basic conditions gave (4) in quantitative yield, The structure of compound 4 was confirmed .on the basis of spectral data (IR,^{1}H-NMR,^{13}C-NMR). This acylated aminomalonate when treated with SO_2Cl_2 in dry methylene chloride at 0^{o}C under N_2 fforded diethy1 1(4-methoxy phenyl)-1-(2-chloro)(phenylthioacety) aminoalonate 5in 90% yield whose structure was conformed through spectroscopic data (IR,^{1}H-NMR,^{13}C-NMR) cyclisation of 5 in pyridine at 50^{o}C gave 3-phenylthio-4,4-diethoxycarbonylazetidin-2-ones 6 in almost quantitative yield which had spectroscopic data (IR,^{1}H-NMR)

Thus β-lactams treated to SO_2CL_2 in dry methlene chloride at 0^{o}C to gave 3-α-chloro-3-phenylthio azetidin-2-onies 7.Thus 3-α-chloro-3-phenylthio azetidin-2-onies were subject to alkylation reaction with anisole in stannicic chloride $SnCl_4$ in -10^{o}C to gave 3- (4- methoxy phenyl)-3 phenylthio aztidin -2-one 8 . The structure of 7,8 were confirmed on the basis of there spectral data (figures ^{1}H-NMR and ^{13}C-NMRfor compour ls 5 ,6, 7 and 8)



Scheme I-Reagents (i) PCl_3,(ii) py,CH_2Cl_2 ,0^oC (iii) SO_2Cl_2,CH_2Cl_2,0^oC (iv) py,CH_2Cl_2 , reflux ; (v) SO_2Cl_2,CH_2Cl_2,0^oC ,(vi) anisole , $SnCl_4$, CH_2Cl_2 , -10^oC , N_2 atm .

Experimental section:

Melting points reported are uncorrected IR spectra were recorded on Pekin Elmer 1430 spectrophotometer (V max in cm $^{-1}$) . ^{1}HNMR and ^{13}CNMR spectra recorded on a Varin EM390, 90 MHz spectrometer or Bruker WP300 SY , 300 MHz spectrometer in CCl_4 or $CDCl_3$ with TMS as internal refrence (chemical shift in δ ppm) Chromatographic separation was carried out using silica gel 100-200 mesh (Acme).

Phenylthioacetyl chloride 2

A mixture of Phenylthioacetic acid (2.3g ; 20mmol) and phosphorus trichloride (2.75g ,20mmoles)was gentyl warmed and stirred in dry flask fitted with condenser and gurad tube . The reaction mixture turned into aclear solution and stirring continued at 50^oC for 30 min .

A greenish sticky material deposited on the sides of the flask indicating the completion of reaction . There after , the contents were diluted with dry methylene chloride (100ml) and transferred into another dry flask. The residue on distillation at 112-115 ^oC gave pure phenyl thioacetyl chloride 2 (3.4g 95%) IR: 1820; 1HNMR: 3.62 (s 2H, -SCH2-) , 6.8-7.3(m, 5H, aromatic protons).

Diethyl- N-(4-merhoxy phenyl) aminomalonate 3a.

It was prepared according to literature method[14] by reacting diethyl bromamalonate (2.38g ,10 mmole) with *p*-anisidine (2.46g,20mmole)in dry benzene in 56% (1.82g) yield,m.p. :49-50^oC,IR:3390,1765,1735,1520, ^{1}HNMR:1.27(t,6H,J=7.2Hz,2XCOOCH$_2$CH$_3$) ,3.71(s,3H,OCH$_3$) ,4.20 (q,4H,j=7.2Hz , 2XCOOCH$_2$CH$_3$) , 4.61 (bs, 1H , -NH-).

4.71(s,1H,-CH-).6.7(m,4H,aromatic protons).

Dethyl- N-(4-methyl phenyl) aminomalonate 3b.

This was prepared from diethylbromo malonte (238g,10 mmole) and *p*-toludine (2.14g,20 mmole)as reported earlir in 67% (1.77g) yield m.p. 45^oC,IR :3350,1760,1735,^{1}HNMR:1.20 (t,6H,2XCOOCH$_2$CH$_3$),2.3(s,3H, -

CH_3), 4.21(q,2H,2XCOOCH$_2$CH$_3$),4.55(bs,1H,-NH-) .4.71(s,1H,-CH-) ,6.88(m,4H,aromatons).

Diethyl- N-(4-methoxy phenyl)-1- pheny-thioacetlaminomalonate 4a.

A solution of phenylthioacetyl chloride 2.(1.86g,10mmole)in methytene chloride (10ml) was added dropwise to a stirred solution of diethyl N-(4-methoxypheny aminomalonate 3a (2.5g,9mmoles) and pyridine (10ml) in methylene chloride (50 ml) at 0^{o}C . The progress of the reaction was checked by TLC and stirring continued at room temperatuer for 5h . Thereafter ,the reaction mixture was washed with water (2X20ml) , brine (30ml) and ethylacetate – hexanes (3:7)to afford the acylated aminomalonate 4a as an oil

(3.39 g,87%) ;IR: 1750 , 1695; ^{1}H-NMR : 1.2(t,6H,2XCOOCH$_2$CH$_3$), 3.51 (s,2H,-S-CH$_2$-CO-),3.81 (s,3H,OCH$_3$), 4.15(q,4H, 2XCOOCH$_2$CH$_3$) , 5.52(s,1H,HC-),6.8-7.4 (m,9H,aromatic protons);^{13}CNMR ($CDCl_3$): 13.78,13.82,38.93 ;93;55.39, 61.99 64-77, 114.47, 126.59 ,128.80, 129.95,130-71,131.99,135.47,159.81, 165.59, 169.39 .

Diethyl- N-(4- methyl phenyl) -1- phenyl thioacetyl amionmalonate 4b.

This was prepared as reported in 4a . IR: 1749, 1694 cm^{-1}: ^{1}HNMR : 1.19 (t ,6H, 2XCOOCH$_2$CH$_3$), 5.42(s,1H, CH-) 7.15-7.36 (m, 9H, aromatic protons).

Diethyl -N-(4- methyl phenyl)-N- (2- chloro)- phenyl thioacetyl amionmalonate5a.

A solution of sulfuryl Chloride (0.68 g , 0.48ml , 5.02 mmoles) in methylene chloride (10ml) was added dropwise to a stirred solution of acylated aminomalonate 4a (2.15g , 5mmoles)in methylene chloride (50ml) at 0^{o}C under nitrogen .The progress of reaction was checked by TLC and stirred continued . There after , the solvent was evaporated under vacuum and the residue on chromatographic purification on silica gel (hexanes-ethyl actate , 10:1) affored the α- Chlorinated derivative 5a (2.19,94%)as an oil ; IR : 1720,1700; ^{1}HNMR1.22(t,6H, 2XCOOCH$_2$CH$_3$), 3.78(s,1H,-SCH(Cl)CO-),3.82(s,3H,OCH$_3$),4.35(m,4H, 2XCOOCH$_2$CH$_3$),5.51(s,1H,-CH-),6.9-7.3(m,9H,aromatic protons).

1-(4-Methoxyphenyl)-3-phenylthio -4,4-diethoxycarbonyl,azetidin -2-one 6a.

This was prepared according to the procedure as reported in the litature[15].

1-(4-Methoxyphenyl)-3-Chloro-3-phenylthio-4,4-diethoxycarbonylazetidin -2-one 7a.

To a well stirred solution of α- phenylthio-β-lactam 6a (0.9g, 2mmoles) in 50 ml dry methylene Chloride , under nitrogen at 0^o C , was added a solution of sulfuryl Chloride (SO_2Cl_2) (0.39g , 2mmol,0.2ml) in 10 ml dry methylene Chloride in 10 minutes contents were stirred for additional half hour . The progress of reaction was monitored by TLC. Solvent evaporation followed by column chromatography on silica gel using ethylacetate : hexanes(1:10) yielded pure

β- lactam 7a (1.0g , 75%) ,IR: 1760,1720 cm^{-1} ,^{1}HNMR ($CDCl_3$) δ1.26 (t,6H, $2XCOOCH_2CH_3$),3.78(s,3H,OCH_3), 4.35(q,4H, $2XCOOCH_2CH_3$), 6.83-7.73 (m,9H,aromatic protons) . ^{13}CNMR($CDCl_3$) δ:13.94, 29.70 ,55.459 , 63.37 , 113.97, 120.99 121.32 ,127.36, 128.96, 129.15, 129.32, 130.31, 130.47, 136.42 , 157.35, 159.15, 163.55.

1- (4-Methylphenyl)-3- α- Chloro-3- phenylthio4,4-diethoxycarbonylazetidin -2-one 7b.

This was prepoared as reported in 7a . IR: 1758, 1722 cm^{-1} , ^{1}HNMR($CDCl_3$) δ:1.24(t 6H, $2XCOOCH_2CH_3$), 2.35(s,3H,-CH_3)4.13(q,4H, $2XCOOCH_2CH_3$) 6.83-7.73 (m,9H,aromatic protons) .

1-(4-Methoxyphenyl)-3-(4-methoxyphenyl)-3-phenylthio-4,4-diethoxycarbonyl azetidin-2-one 8a.

To a well stirred solution ofα-chloro- β- lactam 7a (85mg , 0.2mmole) in dry methylene chloride (10ml) was added anisole (30 mg, 0.24mmole) 0.03ml) at -10^oC under N_2 atmosphere. To this mixture stannic chloride (70 mg, 0.3mmole ,0.3mL)was added rapidly via a syringe . The reaction mixture was stirred for 2h. The progress was cheked by TLC. Solvent evaporation followed by silica gel using ethyl acetate :hexanes (1:10)to yielded pure β- lactam 8a (40mg ,45%) m.p. 141-142^o C IR: 1765,1725 cm^- ^{1}1HNMR ($CDCl_3$) δ: 1.26 (t ,6H, $2XCOOCH_2CH_3$), 3.75 (s,3H,-OCH_3) 3.78

(s,3H,-OCH_3)4.43 (q,4H, 2X$COOCH_2CH_3$),, 6.75-7.48 (m, 13H, aromatic protons) .

1-(4-Methylphenyl)-3-(4-methoxyphenyl)-3-phenylthio-4,4-diethoxycarbonyl azetidin-2-one 8b.

This was prepared as reported in 8a.

m.p. 140-142^oC , IR: 1760,1730cm^{-1}. ^{1}HNMR ($CDCl_3$) δ : 1.25(t ,6H, 2X$COOCH_2CH_3$),2.30(s ,3H, -CH_3) , 3.76(s,3H,-OCH_3), 4.41(q , 4H, 2X$COOCH_2CH_3$), 6.71-7.45 (m, 13H, aromatic protons).

Acknowledgement :-

We are gratefyll to the Department of science and Tehnology (DST), NEW Delhi for providing financial support for this work. We also thank the Regional sophisticated Instrumentation Center (RSIC) , Panjab University , Chandigarh for spectral facilities.

References

Bari, S.S.; Tetehan, I,R.; Sharma,A.K.; Manhas, M.S, 1992, Synthesis, 439.

Bari, S.S; Madan, S.; Sethi, M.K. , 1999 , Indian J.Chem.38B,10.

Bari, S.S;Sharma,A.K;Sethi,M.K. 1998 , Indian. J.Chem.37B,1114.

Berenner,D.G., 1985, J. org.chem.,50,18.

Brown ,A.GRoberts, S.M(Eds), Recent Adrances in the chemistry of β-lactam Antibiotics ; The Royal society of chemistry ; Burlington House London , 1984.

Chandrassekaran ,s.; Kluge, A.F;Edwards, J.A.1977, J.org.chem.,42,3972

Georg , G.I; Ravikumar ,V.T in the organic chemistry of β-lactams, edited by Georg ,G.I, VCH, New York,1992.

Hesse, M, , In Ring Enlargement in organic chemistry edited by weller , M.G(VCH, New York) 1991,97.

Manhas, M.S.; Wagle, D.R. ; Chiang, J.; Bose ,A.K., 1988,Hetrocycles, 27,1755.

Manhas, M.S.;Bari,S.S;Bhawal, B.M; Bose, AK, 1984 , Tetrahedron lett., 25,4733.

Palomo,C.; Aizpurua , J.M.; Cossio , F.P.; Garcia ,J.M.; Lopez, M.C.;Oiarbide, M. 1990 , J. org.chem.,55,2070.

Palomo,C.; Aizpurua , J.M.;Aurrekoetxea,N.; Lopez, M.C. 1990 , Tetrahedron lett. ,31,2205.

Sammes,P.G(ED),Topics in Antibiotics chemistry , Eills Harwood; New York. 1980.

Sheehan ,J.C;Lu, Y.S., 1973 , J.org.chem.,38,3227.b) Habich,D .; Metzger,K. Herterocycles.1986.24, 289.c)chen.,Y.L.;Chang,c.W.; Hedberg,k.Tetrahedron lett.1988,27,3449.

Vandervan ,J.M; Bari, S.S; Krishnan, L.; Manhas , M.S,Bose ,A.K. ,1989 , J.org.chem.,54,5758.

Wasserman ,H.H. 1987 , Alderichimic acta., 20, 63.