

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

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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)

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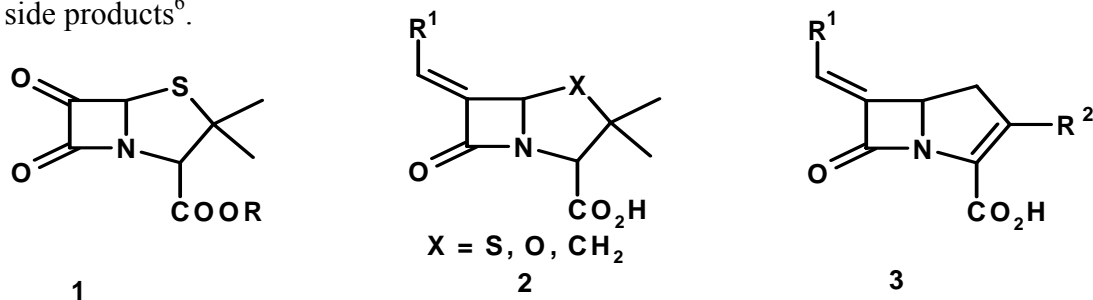
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Introduction

Azetidine-2,3-diones 1 are important starting materials for the introduction of alkylidene side chains at C3 position the β -lactam ring¹. The Wittig reaction², the Peterson olefination³, and the Henry reaction⁴ were the most widely employed methods to prepare en- β -lactam Antibiotics of type (2,3). However with expected of the Henry reaction⁵, the expected products are often produced in very low yields together with concomitant formation of side products⁶.

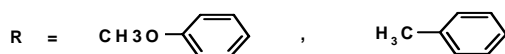
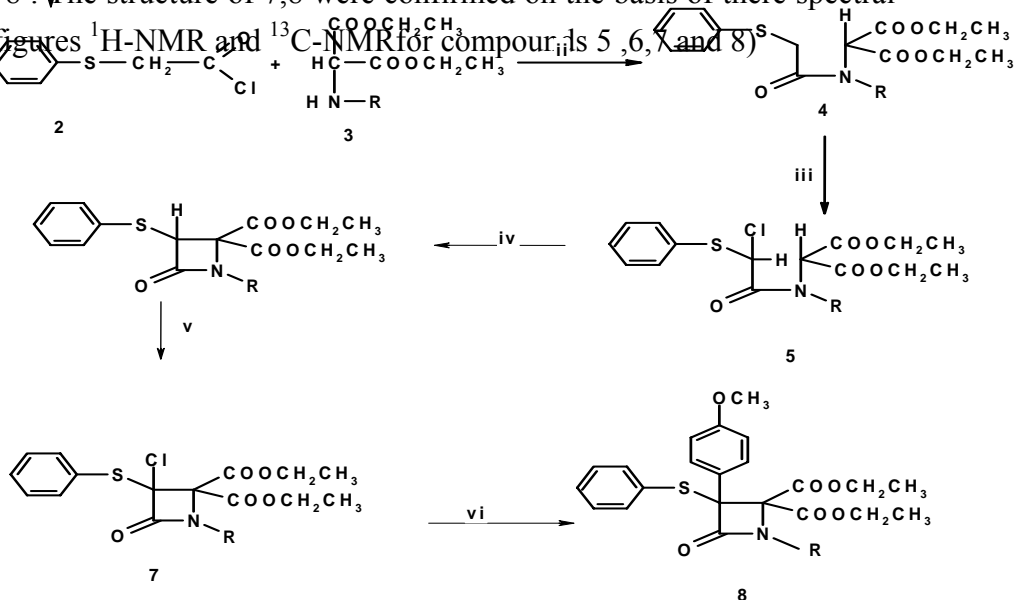


Recent discoveries of non classical β - lactams antibiotics such as nocardicines, Monobactams and thienamycin have stimulated much interest^{7,8,9} in the synthesis of monocyclic β -lactams. Besides this, the unique feature of these strained molecules is that these heterocycles are becoming powerful building blocks for the synthesis of organic compounds^{10,11,12,13}, having different functionalities such as α - amino acids, β -amino acids, α -hydroxy- β - amino acids⁵, amino sugars and other heterocycles. A few methods of preparation of these 3-phenylthiozeidin-2-ones have been reported¹ in the literature employing Staudinger reaction between appropriately substituted acid chlorides and imines. We report herein a convenient and efficient synthesis of 3- phenylthio -4,4-diethoxy carbonyl Azetidin-2-ones 6 ($R_1=R_2=COOC_2H_5$) the strategy employs N-acylation of amino malonate followed by in situ C₃-C₄ bond formation as the key step (SCHEME I)

Result and Dissuasion

In an alternative approach (SCHEME I) substituted aminomalonate (3) on acylation 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, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$). This acylated aminomalonate when treated with SO_2Cl_2 in dry methylene chloride at 0°C under N_2 afforded diethyl 1(4-methoxy phenyl)-1-(2-chloro)(phenylthioacety) aminoalonnate 5 in 90% yield whose structure was conformed through spectroscopic data (IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$) cyclisation of 5 in pyridine at 50°C gave 3-phenylthio-4,4-diethoxycarbonylazetidin-2-ones 6 in almost quantitative yield which had spectroscopic data (IR, $^1\text{H-NMR}$)

Thus β -lactams treated to SO_2Cl_2 in dry methlene chloride at 0°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 stannic chloride SnCl_4 in -10°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 $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ for compounds 5, 6, 7 and 8)



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

Experimental section:

Melting points reported are uncorrected IR spectra were recorded on Pekin Elmer 1430 spectrophotometer (V max in cm^{-1}) . $^1\text{HNMR}$ and $^{13}\text{CNMR}$ 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 gently warmed and stirred in dry flask fitted with condenser and gura tube . The reaction mixture turned into aclear solution and stirring continued at 50°C 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 $112-115^\circ\text{C}$ gave pure phenyl thioacetyl chloride 2 (3.4g 95%) IR: 1820; $^1\text{HNMR}$: 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 method¹⁴ by reacting diethyl bromamalonate (2.38g ,10 mmole) with *p*-anisidine (2.46g,20mmole)in dry benzene in 56% (1.82g) yield,m.p. : $49-50^\circ\text{C}$,IR:3390,1765,1735,1520, $^1\text{HNMR}$:1.27(t,6H,J=7.2Hz,2XCOOCH₂CH₃) ,3.71(s,3H,OCH₃) ,4.20 (q,4H,j=7.2Hz , 2XCOOCH₂CH₃) , 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*-toluidine (2.14g,20 mmole)as reported earlir in 67% (1.77g) yield m.p. 45°C ,IR :3350,1760,1735, $^1\text{HNMR}$:1.20 (t,6H,2XCOOCH₂CH₃),2.3(s,3H, -

CH₃), 4.21(q,2H,2XCOOCH₂CH₃),4.55(bs,1H,-NH-) .4.71(s,1H,-CH-),6.88(m,4H,aromatons).

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

A solution of phenylthioacetyl chloride 2.(1.86g,10mmole)in methylene 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°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; ¹H-NMR : 1.2(t,6H,2XCOOCH₂CH₃), 3.51 (s,2H,-S-CH₂-CO-),3.81 (s,3H,OCH₃), 4.15(q,4H, 2XCOOCH₂CH₃) , 5.52(s,1H,HC-),6.8-7.4 (m,9H,aromatic protons);¹³CNMR (CDCl₃): 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: ¹HNMR : 1.19 (t ,6H, 2XCOOCH₂CH₃), 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°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) afforded the α- Chlorinated derivative 5a (2.19,94%)as an oil ; IR : 1720,1700; ¹HNMR1.22(t,6H, 2XCOOCH₂CH₃), 3.78(s,1H,-SCH(Cl)CO-),3.82(s,3H,OCH₃),4.35(m,4H, 2XCOOCH₂CH₃),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 literature¹⁵.

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° C , was added a solution of sulfuryl Chloride (SO₂Cl₂) (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 ,¹HNMR (CDCl₃) δ 1.26 (t,6H, 2XCOOCH₂CH₃),3.78(s,3H,OCH₃), 4.35(q,4H, 2XCOOCH₂CH₃), 6.83-7.73 (m,9H,aromatic protons) . ¹³CNMR(CDCl₃) 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 prepared as reported in 7a . IR: 1758, 1722 cm⁻¹ ,¹HNMR(CDCl₃) δ :1.24(t 6H, 2XCOOCH₂CH₃), 2.35(s,3H,-CH₃)4.13(q,4H, 2XCOOCH₂CH₃) 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 of α -chloro- β - lactam 7a (85mg , 0.2mmole) in dry methylene chloride (10ml) was added anisole (30 mg, 0.24mmole) 0.03ml) at -10°C under N₂ 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° C IR: 1765,1725 cm⁻¹ ¹HNMR (CDCl₃) δ : 1.26 (t ,6H, 2XCOOCH₂CH₃), 3.75 (s,3H,-OCH₃) 3.78

(s,3H,-OCH₃)4.43 (q,4H, 2XCOOCH₂CH₃),, 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°C , IR: 1760,1730cm⁻¹.¹HNMR (CDCl₃) δ : 1.25(t ,6H, 2XCOOCH₂CH₃),2.30(s ,3H, -CH₃) , 3.76(s,3H,-OCH₃), 4.41(q , 4H, 2XCOOCH₂CH₃), 6.71-7.45 (m, 13H, aromatic protons).

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