Asian Journal of Chemistry Vol. 3 No. 2 (1991), 225–231

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME 3-ACYLAMINO-2- AZETIDINONES

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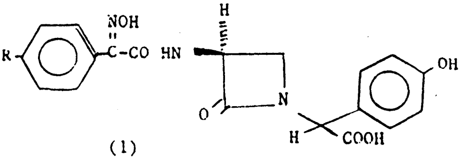
3-Amino and 3-acylamino 2-azetidinones were synthesized. Their antibacterial activity against gram negative, gram positive and β-lactamase producing bacteria were estimated. Compounds (16) and (17) with a –COOH group onto the N_1-phenyl substituent showed rather better activity against gram-negative and gram-positive bacteria.

INTRODUCTION

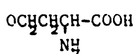
The discovery of the monocyclic β-lactam antibiotics (1)[1], 2(a)[2], 2(b)[3] and (3)[4] and their strong activity against gram negative bacteria and excellent stability against β-lactamase, extensive research has been reported aimed at obtaining new monocyclic β-lactams with improved antibacterial properties. In this study, the synthesis of 2-azetidinones bearing a vinyl-thioacetamido side chain and an α-ureidoacetyl group at C_3 side chain is reported as well as introduction of a –COOH group at N_1 substituent.

4-Fluorinated 3-acylamino-2-azetidinones were prepared which seemed particularly interesting because of their enhanced reactivity towards nucleophilic attack at the β-lactam ring[5].

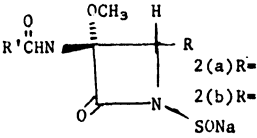


(1)

Nocardicin A

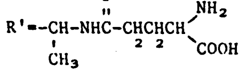
R = 

$$\mathrm{OCH_2CH_2\underset{NH_2}{C}H\text{-}COOH}$$

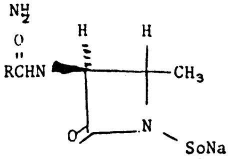


2(a)R=H sulfazecin

2(b)R=CH_3 MM42842



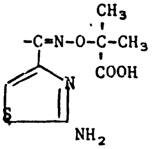
$$\mathrm{R'=\text{-}\underset{CH_3}{C}H\text{-}NH\overset{O}{C}\text{-}CH_2CH_2CH\lt^{NH_2}_{COOH}}$$



(3)

Aztreonam

R =

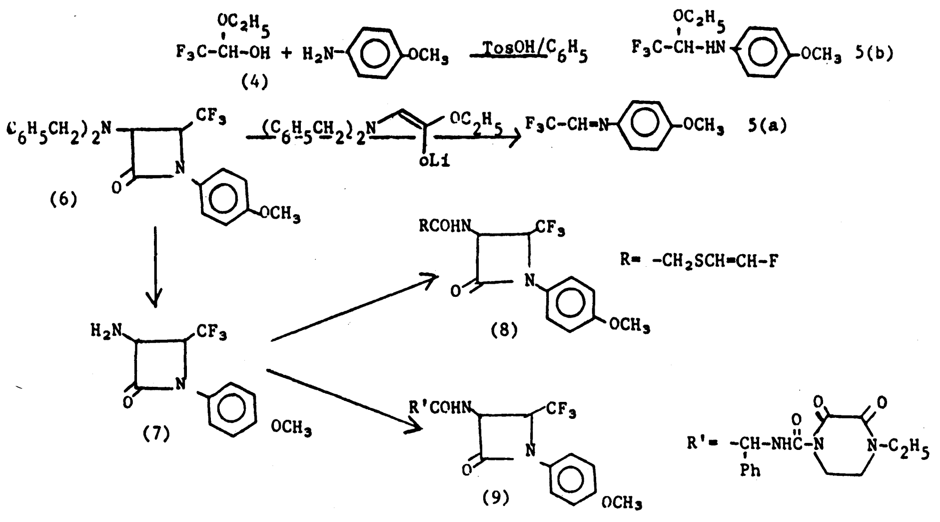


The 3-amino 2-azetidinones (7) and (13) were prepared by the routes shown in schemes (I) and (II). These compounds were acylated by fluorvinylthioacetic acid and 4-ethyl-2,3-dioxo-1-piperazinecarboxamide phenyl acetyl chloride respectively to give 3-acylamino β-lactams (8) and (9).

The imine N-(trifluoroethylidene)-4-methoxyaniline (5a) required for the β-lactam cyclization was obtained by the reaction of the commercially available trifluoroacetaldehye ethyl hemiacetal and 4-methyoxyaniline[6]. The reaction of (5a) with lithium enolate of ethyl dibenzylamino acetate[7] afforded the β-lactam (6) which upon reductive cleavage gave the amino β-lactam (7) (Scheme I). The synthesis of N_1-carbethoxyphenyl-3-amino 2-azetidinones (13) has been achieved by a reported method using azidoacetyl chloride[8] (12) (Scheme II).

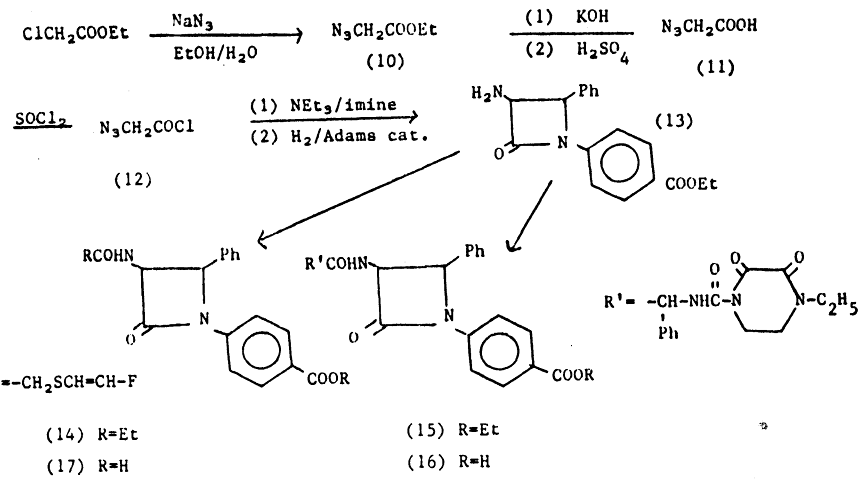
Methyl-2-fluoroethylthio acetate (19) was obtained by treatment of the tosylate (18) with methyl thioglycolate and NEt_3 in N,N-DMF. Chlorination followed by oxidation with m^- chloroperbenzoic acid afforded the sulfoxide (2) which was treated with trifluormethane sulfonic anhydride to give the dichloroacetate (21). Treatment with Zn/AcOH and NaOH afforded (22)[9] (Scheme III).

SCHEME 1



The 3-fluorovinylthio 2-azetidinones were obtained by coupling the carboxylic acid (22) and the 3-amino-2-azetidinones in presence of phosphorous oxychloride in pyridine. The 3-amino-2-azetidinones were also acylated with α-(ureido) phenyl acetylchloride to afford the corresponding acylamino derivatives. Deprotection of the ethyl ester of the N-carbethoxy aryl azetidinones (14) and (15) by hydrogenation was a slow process leading to the destruction of the β-lactam ring. The ester was readily cleaved by treatment with aluminium trichloride.[10]

SCHEME II



SCHEME III

$$\mathrm{FCH_2CH_2OTS} \xrightarrow{\mathrm{HSCH_2COOCH_3/NEt_3}} \mathrm{FCH_2CH_2SCH_2COOCH_3}$$

(18) (19)

$$\xrightarrow[\text{(2) McPBA}]{\text{(1) } \mathrm{Cl_2/M}} \mathrm{FCH{=}CH_2SO{-}CCl_2COOCH_3}$$

$$\mathrm{FCH{=}CHSCCl_2COOCH_3} \xrightarrow[\text{(2) in NaOH}]{\text{(1) Zn/ACOH}} \mathrm{FCH{=}CH{-}SCH_2COOH}$$

(21) (22)

BIOLOGICAL RESULTS AND DISCUSSION

The MICs of the monocyclic b-lactams prepared are summaried in Table I. Compounds (16) and (17) showed poor activity against gram-negative and gram-positive organisms (MIC $\geq$ 20 μg/ml). Although the trifluoro substitution is expected tto enhance the reactivity of the β-lactam ring and its susceptibility to nucleophillic attack and ring cleavage, compounds (8) and (9) are inactive against both gram-negative and gram-positive bacteria (MIC $\geq$ 300μg/ml).

Replacement of $-OCH_3$ moiety by a hydrophillic group (–COOH) onto the N_1-phenyl substituent afforded compounds with better activity. The –COOH group at N_1 of the β-lactam of (16)and (17) is biological equivalent to the –COOH at C_3 of penicillins. However, compounds (14) and (15) which share similar chemical structures with (16) and (17) respectively, except for the ethyl ester protecting group, have lower antibacterial activity. Compound a (15) and (16) with a-ureidoacetyl side chain showed slightly better activity than (14) and (17) which have a vinyl thioacetamido side chain on C_3 instead. While the nature of the acetamido side chain at C_3 remains unpredictable, a free –COOH group seems an essential structural feature of monocyclic β-lactams. Taking the overall data into account, (16) and (17) are selected for further antibacterial evaluation against b-lactamase producing organisms.

TABLE 1
MIC VALUES (μg/ml) of 3-AMINO AND 3-ACYLAMINO-2-AZETIDINONES

	Compounds								
Test Strain	7	8	9	13	14	15	16	17	Aztreonam
Escherichia coli NCTC 9012	–	500	500	–	120	100	30	35	0.4
Escherichia coli EC-14	–	500	500	–	90	80	20	20	0.3
Staphylococcus aureus NCTC 8532	–	–	–	–	280	280	280	180	200
Psudomonas aeruginosa 1 FO-3445	–	500	300	–	110	100	100	20	4.5

(–) No inhibition.

EXPERIMENTAL

IR spectra were obtained with a Perkin Elmer 783 infrared spectrophotometer, ^{1}H NMR spectra were recorded on a Varian T-60A spectrometer. Kieselgel 60 (63-200 μm Merk) was used as the adsorbent for column chromatography at normal pressure. Melting point was recorded on a Metler F.P. 80 instrument.

Antibacterial activity

All the antibacterial activities are given as the MIC in μg/ml required to prevent growth of bacterial culture. MICs were determined by the agar cup plate method after incubation at 37°C for 24-30 hrs with an inoculum size of about 10^6 cells/ml.

N-(2,2-2-Trifluoroethyledine)-4-methoxy aniline (5a)

Trifluoroacetaldehyde ethyl hemiacetal (14 mmol) and 4-methoxyaniline (13 mmol) were refluxed in dry benzene (50 ml) for 3 h. A catalytic amount of *p*-toluene sulfonic acid was added. On completion the reaction mixture was treated with aqueous $NaHCO_3$ solution (20 ml). The aqueous layer was washed with ether. After evaporation of the solvent the organic extract gave a liquid which on distillation afforded a pale yellow liquid of a mixture of (5a) and (5b) (yield 85%)[11,12].

A solution of this mixture of (5a) and (5b) is treated with 0.4N lithium diisopropylamide and 2,2-bipyridyl. After 30 mins. the solution is treated with 1% $NaHCO_3$. Extraction with ether, evaporation and distillation of the product gave pure (5a); (yield 72%).
^{1}HNMR ($CDCl_3$) : $\delta = 3.69$ (s,3H,OCH_3); 6.8-7.3(m,4H); 7.84 ppm (dq,1H,J=3.72Hz), 1.2Hz, CH-CF_3).

1-(4-Methoxyphenyl)-3-dibenzylamino-4-trifluoromethyl-2-azetidinone(6)

Ethyl dibenzylaminoacetate (8mmol) in dry THF (20ml) was added dropwise to 0.5N solution of lithium diisorpoylamide containing few crystals of 2,2′ bipyridyl. The reaction was stirred for 30 min. at 60°C then lithium diisopropylamide was added until the solution became red. The reaction mixture was then treated with 30% NH_4Cl solution (10ml). After extraction with ether the organic layer was evaporated and the crude product chromatographed on a column to give a white solid, M.P. 132- 135°C; yield 48%.
^{1}H NMR ($CDCl_3$): δ = 3.78(s,3H,OCH_3; 3.72, 3.82(m,4H,J=13.6Hz,N-CH_2-C_6H_5); 4.32 (dq.1H,J=5.6Hz, 2 Hz, CH-CF_3); 4.48 (d,1H,J=2Hz, CH-N); 6.79 (d,2H,J=8.7 Hz,2H); 7.1-7.3 ppm (m,10H+4H).

N-(4-Methoxyphenyl)-3-amino-4-trifluoromethyl-2-azetidinone(7)

A solution of the 2-azetidinone(6) (8.0mmol) in dry ethyl acetate (100ml) was hydrogenated over 10% palladium on charcoal (0.5mmol) for 2 days at room temperature. Removal of the catalyst and purification[13] gave a white solid m.pt. 105-107°C.

N-(4-Carbethoxyphenyl)-3-amino-4-phenyl 2-azetidinone(13)

Azido acetyl chloride (12) (0.1 mmol) was added to a stirring solution of benzylidene *p*-carbethoxy aniline (0.1 mml) and equimolar amount of NEt_3 in dichloromethane (50 ml) at 0°C. The reaction was stirred for 2 hrs. and then washed with water. The organic layer was evaporated and the crude product chromatographed over silica gel to give 40% yield of (13).
^{1}H NMR: δ = 1.94(S,2H); 4.58(d,1H); 1.27(t 3H,J=7.2Hz); 2.81(m,2H); 6.85(d,J=8.7Hz,2H); 6.8- 7.78ppm(m,5H+4H).

Methyl-fluorovinylthio dichloroacetate (21)

Methyl thioglycolate (12.3mmol), 3.2N $NaOCH_3$(10mmol), and the tosylate (18) (10mmol) were stirred in DMF (20ml) for 1.5 hrs. The reaction mixture was extracted with ether, evaporated and distilled to give methyl-(2-fluoroethylthio) acetate, a solution of chlorine (1M in CCl_4, 10ml) was added to the sulphide (19) in CCl_4. After 30 min, the dichloride was obtained. The reaction mixture was washed with aqueous Na_2SO_3, aqueous $NaHCO_3$ and brine and dried to give the sulfoxide (2)

Trifluoromethanesulfonic anhydride (22.3mmol) was slowly added to a mixture of (20) and 2,6-di-*tert*-butyl-4-methyl pyridine (57.2mmol) in 100 ml of CH_2Cl_2 at -30°C. After stirring for 30 min. the precipitated product was filtered, washed with water and dried.

Fluorovinylthio acetic acid (22)

To the dichloride (18.3 mmol) in CH_2Cl_2 methanol zinc was added in portions at 0°C. After 30 min. the reaction mixture was filtered, washed and dried to yield an ester, 2N NaOH (20mmol) was added to the ester at 0°C. After 20 min. the reaction mixture was washed with ether. The aqueous layer acidified and extracted with ethylacetate. The extracts dried and evaporated to give the acid(22)[14]. ^1H NMR ($CDCl_3$) d = 3.42(2H,S) 5.50(1H dd J=38 and 4Hz), 6.72(1H,dd,J=8.1 and 4Hz).

N-(4-Methoxyphenyl)-3Fluorovinylthio acetamido-4- trifluromethyl-2-azetidinone (8)

A solution of 3-amino-2-azetidinone (7) (18mmol) in CH_2Cl_2 (100 ml) is added at 30°C to the carboxylic acid(22) (20mmol) and $POCl_3$ (19 mmol) in pyridine(12ml). After 30 min. the reaction mixture was washed with water and dilute HCl, dried, evaporated to dryness and recrystallized from CH_2Cl_2 -ether to afford (8).
M.pt. 153°-155°C. ^{1}HNMR ($CDCl_3$) δ = 3.42(s,2H); 5.20(s,2H); 5.75(d,1H); 6.88(s,1H); 4.35(dq,1H,J=5.6Hz); 3.79(s,3H); 6.8-7.70 ppm (m,4H).

N(4-Carbethoxyphenyl)-*cis* fluorovinylthio acetamido-4-phenyl-azetidinone(14)

Acylation of 3 amino-2-azetidinone (14) is achieved using the previous method used for preparation of (8). Recrystallization from ether and CH_2Cl_2 afforded (14).
^1H NMR($CDCl_3$) δ = 1.27(t,3H,J=2Hz); 2.8(m,2H), 3.42(s,2H); 5.20(s,2HO; 5.75(dd,1H); 6.88(s,1H), 4.35(dq,1H,J=6.7Hz); 7.10-7.30 ppm(m,5H+4H).

N-(4-Methoxyphenyl)3-(α-ureido)acetamido-4-trifluoromethyl-2-azetidinone(9)

To a mixture of 3-amino-2-azetidinone(7) (2mmol) in CH_2Cl_2 was added Et_3N (4.5mmol) at –30°C. α-(4-Ethyl-2,3-dioxo-1-piperazinecarboxamido)phenyl acetyl chloride (2.3mmol) was added to the solution at the same temperature. The mixture was stirred for 1 hr. at –15°C and further 1 hr. at room temperature. The solvent was evaporated and the residue purified to afford(9) in 45% yield. m.p. 114°-116°.
^1H NMR ($CDCl_3$) δ = 2.8(t,2H); 3.76(s,6H) 2.3(d,1H,J=8.7Hz); 5.13(d,4H), 5.54(d,2H,J=7.5Hz), 4.51(d,1H,J=7.5Hz) 7.9-8.4ppm (m,4H).

N-(4-Carbethoxy ethyl)-3-(α-ureido) acetamido-4- phenyl-2-azetidinone(15)

3-Amino-2-azetidinone(13) is acylated by -(4-ethyl-2,3-dioxo-1-piperazinecarboxamido) phenyl acetyl chloride using the same method as for (8). Purification of the crude product afforded (15), yield 42%.
^1H NMR = ($CDCl_3$) δ = 4.51(d,1H j=7.5Hz); 5.54(d,1H J=7.5Hz); 7.5(S,10H), 5.13(t,4H); 2.3(d,1H); 4.58(d,1H J=8.7Hz); 7.6-8.1 ppm(m,5H+4H).

ACKNOWLEDGEMENT

This work is sponsored in part by the Research Centre, King Saud University, Kingdom of Saudi Arabia.

REFERENCES

1. A. Ackietal, *J. Antibiotics,* **29**, 492 (1976).
2. M. Asai, K. Haibara, M. Muroi, K. Kintaka and T. Kishi, *J. Antibiotics* **34**, 42, 7–12 (1988).
3. S.J. Box, A.G. Brown, M.L. Gilpin, M.N. Gwynn and S.R. Spear, *J. Antibiotics,* **41**, 7–12 (1988).
4. C.M. Cinarusti, *Tetrahedron* **39**, 2577 (1983).
5. K. Yoshioka, *J. Org. Chem.* **49**, 1427 (1984).
6. H. Newman and E.L. Moon, *J. Org. Chem.* **29**, 2063 (1964).
7. G. Guanti, L. Banfi and E. Narisano, C. Scolastico, *Tetradendron Lett.* **25**, 4693 (1984).
8. M.S. Manhas, H.P.S. Chawla, S.G. Amin and A.K. Bose, *Synthesis,* 407 (1977).
9. M. Zrihen, R. Labia and M. Wakselman, *Eur. J. Med. Chem. Chin. Ther.,* **18**, 307 (1983).
10. Teruji Tsuji, *Tetrahedron lett.* **30**, 2793 (1979).
11. H. Newman and E.L. Moon, *J. Org. Chem.,* **29**, 2063 (1964).
12. Giuseppe Ganuti, Luca Banfi and Enrica Narisano, *Synthesis,* 610 (1985).
13. W.C. Still, H. Khan and A. Mitra, *J. Org. Chem.* **43**, 2923 (1978).
14. Yasuhira Nishitani, *J. antibiotics,* **3**, 332 (1988).

(Received 28 February 1990; Accepted 12 May 1990) AJC-174.