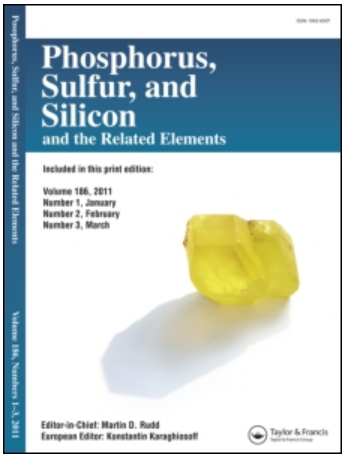


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Heterocyclic Synthesis Containing New Spiro, Isolated (β -Lactam and Thiazolidinone) 3-Cyano-2, 4- Diamino Thiophene Derivatives

H. A. Soleiman[a]; N. A. A. Elkanzi[a]
[a] Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt

To cite this Article Soleiman, H. A. and Elkanzi, N. A. A.(2008) 'Heterocyclic Synthesis Containing New Spiro, Isolated (β -Lactam and Thiazolidinone) 3-Cyano-2, 4- Diamino Thiophene Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 183: 7, 1679 — 1690
To link to this Article: DOI: 10.1080/10426500701724548
URL: http://dx.doi.org/10.1080/10426500701724548

Phosphorus, Sulfur, and Silicon, 183:1679–1690, 2008

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701724548

Taylor & Francis
Taylor & Francis Group

Heterocyclic Synthesis Containing New Spiro, Isolated (β-Lactam and Thiazolidinone) 3-Cyano-2, 4- Diamino Thiophene Derivatives

H. A. Soleiman and N. A. A. Elkanzi
Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt

The reaction of acetamide and malononitrile with elemental sulfur in ethanol containing piperidine catalyst afforded 3-cyano-2,4-diamino thiophene 1, which readily underwent condensation reaction with different aromatic aldehydes to yield Schiff bases ***(2a–c)*** *Cyclization of* ***(2a–e)*** *by refluxing with chloroacetyl chloride and/or mercaptoacetic acid afforded new (β-lactam* ***(3a–c)*** *and New thiazolidinone* ***(4a–c)*** *derivatives, respectively. In addition, 1 reacted with chloroacetyl chloride in presence of ethanol and triethylamine to give* ***6****. compound 6 react with different nitroso compounds to give Schiff bases* ***(7a–c)*** *which underwent cyclization with chloroacetyl chloride and/or mercaptoacetic acid to give spiro (β-lactam* ***(8a–c)*** *and spiro thiazolidinone derivatives* ***(9a–c)****, respectively. Also,* ***6*** *reacts with different aromatic amines in presence of ethanol and piperidine catalyst to give Schiff bases* ***(10a–c)****, cyclization of* ***(10a–c)*** *with chloroacety1chloride and/or mercaptoacetic acid afforded spiro β-lactam* ***(11a–c)*** *and Spiro thiazolidine derivatives* ***(12a–c)****.*

Keywords Thiophene derivatives

INTRODUCTION

β-lactams and related derivatives have been found to be active compounds having antibacterial activities. Some examples comprise the naturally occurring monobactams and nocardicins.[1] Contrary to penicillins, cephalosporins, or nocardicins, monobactams were not produced by fungi or actinomycetes, but from bacteria, for example Bacillus, pseudomonas.[2] Nocardicins proved the relationship with cephalosporins and penicillins via the corresponding Configuration at C_3, but they have no therapeutic significance. The synthetic oxamazins,[3–5] thiamazins,[6] and monosulfactams[7] showed some antibacterial activity, which raised again a major interest in the area of

Received 16 July 2007; accepted 4 August 2007.
Address correspondence to H. A. Soleiman, Chemistry Department, Faculty of Science, South Valley University, Aswan, Egypt. E-mail: hsoleiman2001@yahoo.com

2-azetidinone chemistry. Also thiazole derivatives such as penicillins which have fused thiazolidine and β-lactam rings were known and used as potent antibiotics.[8] Thiazole derivatives are also associated with a broad spectrum of biological properties, including anticonvulsant,[9,10] antimicrobial,[11,12] antituberculous,[13] and bacteriostatic activities,[14,15] Therefore, compounds containing (β-lactam ring, thiazolidinone are expected to possess potential biological activities. Our previous work aimed at developing new approaches to the synthesis of polyfunctionally substituted heterocyclic compounds of biological activity.[16–18]

RESULTS AND DISCUSSION

Herein, we report the synthesis of heterocyclic compounds containing the aforementioned rings via readily available 3-cyano-2, 4-diamino thiophene **1**. Compound **1**, which reacts with different aromatic aldehydes to give new Schiff bases 3-cyano-2, 4-diarylazamethine thiophene **2a–c**. The proposed formulation of compound **2a–c** was confirmed by mass spectrum and elemental analysis (c.f. Table I), IR spectrum which revealed a characteristic band [KBr] at 1580 cm^{-1} (C=N) and ^1H NMR spectrum which showed signal at δ 7.12(s, 2H, 2N=CH). Schiff based 2a–c reacts with chloroacetylchloride and/or mercaptoacetic acid to afford β-lactam derivatives **3a–c** and thiazolidinone derivatives 4a–c. The proposed formulation of compounds **3a–c** and **4a–c** were confirmed by mass spectrum and elemental analysis (c.f. Table I), IR spectral which revealed characteristic peak [KBr] at 1760 cm^{-1} (C=O) and ^1H NMR spectrum of **4a** and **4a** as example which showed signal at δ 6.43(s, 1H, CH), 5.83(s, 2H, $2NCH_5$), 2.5(s, 4H, $2CH_2$) respectively. The activation exerted by the cyano group at C_3 on the exocyclic amino group at C_4 render it available for the condensation with chloroacetylchloride to give compound **5** or **6**. At first, our theoretical conception of the obvious cycloaddition reaction leads to the formation of compound **5**. But, the experimental evidence that depends on the different types of analysis to the reaction product proves that the cycloaddition reaction leads to the formation of compound **6** through the electronic cyclization according to the suggested mechanism (Scheme 2 illustrates the formation of compound **6**). The proposed formulation of compound **6** was confirmed by mass spectrum and elemental analysis (c.f. Table I); IR spectral that revealed characteristic peaks (KBr) at γ 3340 cm^{-1} 3160 cm^{-1}(NH and NH_2), 2217 cm^{-1}(CN), 1675 cm^{-1}(C=O), and ^1H NMR spectrum (DMSO-d6), which showed signal at δ 9.25(s, 1H, NH), 5.22(brs, 2H, NH_2), 4.65(s, 2H, CH_2). Reaction of compound **6** with different aromatic nitroso compounds to give the corresponding Schiff bases **(7a–c)**. The proposed formulation of **7a–c** were confirmed by mass spectrum and

TABLE I Characterization of Compounds (1–12)

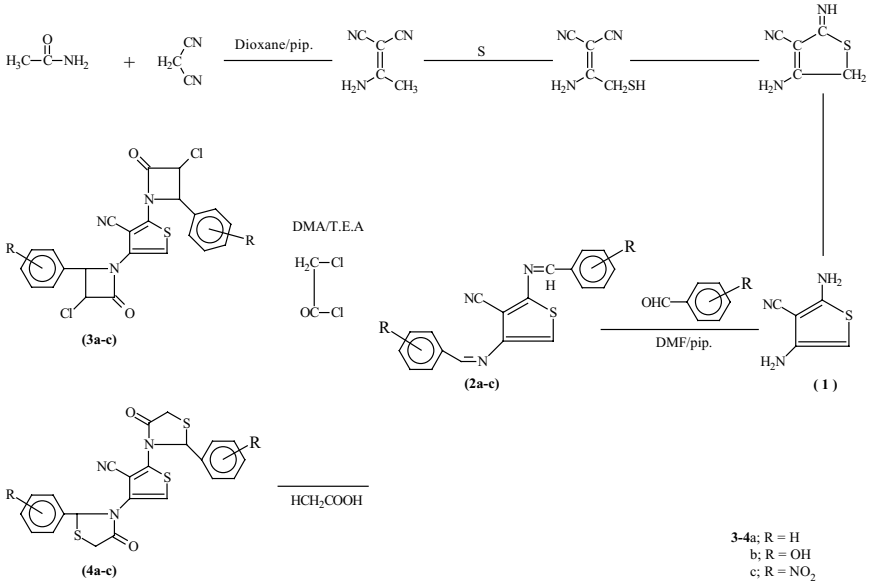
Comp. no.	M.P. C	Solvent of cryst.	Yield %	M.F. (M. Wt.)	Analysis % calcd. (found) C	H	N	M.S.
1a	227–229	Ether	80	$C_5H_5N_3S$ (139.17)	43.15 (43.25)	3.62 (3.53)	30.19 (30.16)	139
2a	244–246	Ethanol	67	$C_{19}H_{17}N_3S$ (319.42)	71.93 (71.96)	5.35 (5.23)	3.15 (13.05)	319
2b	249–251	Ethanol	70	$C_{19}H_{17}N_3O_2S$ (351.42)	64.93 (64.46)	4.88 (4.95)	11.96 (11.98)	351
2c	265–267	Ethanol	73	$C_{19}H_{17}N_5SO_4$ (411.44)	55.47 (55.50)	4.16 (4.15)	17.02 (17.00)	411
3a	284–286	Dioxane	68	$C_{23}H_{19}N_3O_2Cl_2S$ (472.39)	58.47 (58.28)	4.06 (4.01)	8.89 (8.36)	472
3b	289–291	Dioxane	66	$C_{23}H_{19}N_3O_4SCl_2$ (500.36)	55.21 (55.25)	3.02 (3.01)	8.40 (8.60)	500
3c	298–300	Dioxane	69	$C_{23}H_{17}N_5O_6SCl_2$ (558.35)	49.48 (49.40)	2.35 (2.40)	12.54 (12.54)	562
4a	252–254	Ethanol	73	$C_{23}H_{17}N_3O_2S_3$ (463.59)	59.59 (59.66)	3.70 (3.67)	9.06 (9.02)	463
4b	264–266	Ethanol	72	$C_{23}H_{17}N_3O_3S_3$ (479.59)	57.60 (57.50)	3.57 (3.64)	8.76 (8.80)	479
4c	271–273	Ethanol	70	$C_{23}H_{15}N_5O_4S_3$ (521.58)	52.96 (52.90)	2.90 (2.85)	13.43 (13.03)	521
6	239–241	Dioxane	78	$C_7H_5N_3OS$ (321.34)	26.16 (26.31)	1.57 (1.63)	13.08 (13.30)	321
7a	279–281	Methanol	68	$C_{17}H_{10}N_4O_2S$ (410.43)	38.04 (38.10)	1.96 (2.00)	13.65 (13.55)	410
7b	274–276	methanol	66	$C_{13}H_8N_4O_2S$ (284.00)	54.92 (54.82)	2.84 (2.89)	19.71 (19.59)	284
7c	285–287	Methanol	70	$C_{15}H_{13}N_5OS$ (345)	45.22 (45.25)	2.04 (2.15)	20.28 (20.35)	345
8a	289–291	Methanol	84	$C_{19}H_{11}N_4O_3SCl$ (344.78)	52.26 (52.30)	2.63 (2.50)	16.25 (16.30)	344
8b	295–297	Methanol	82	$C_{15}H_9N_4O_3SCl$ (360.77)	49.94 (49.79)	2.52 (2.59)	15.53 (15.46)	360
8c	297–299	Methanol	81	$C_{17}H_{14}N_5O_2SCl$ (395.82)	45.52 (45.55)	3.57 (3.57)	17.69 (17.73)	395
9a	252–254	Ethanol	73	$C_{18}H_{12}N_4O_3S_2$ (342.39)	52.62 (52.55)	2.49 (2.90)	16.36 (16.40)	342
9b	264–266	Ethanol	73	$C_{14}H_{10}N_4O_3S_2$ (358.39)	50.27 (50.16)	2.81 (2.70)	15.63 (15.60)	358
9c	271–273	Ethanol	70	$C_{16}H_{15}N_5O_2S_2$ (387.39)	46.51 (46.35)	2.34 (2.30)	18.08 (18.00)	387
10a	288–300	Methanol	68	$C_{13}H_{10}N_4S$ (254.31)	61.40 (61.46)	3.96 (3.97)	22.03 (22.01)	254
10b	289–291	Methanol	66	$C_{13}H_9N_5O_2S$ (412.45)	37.86 (37.80)	2.44 (2.40)	13.58 (13.58)	412

(Continued on next page)

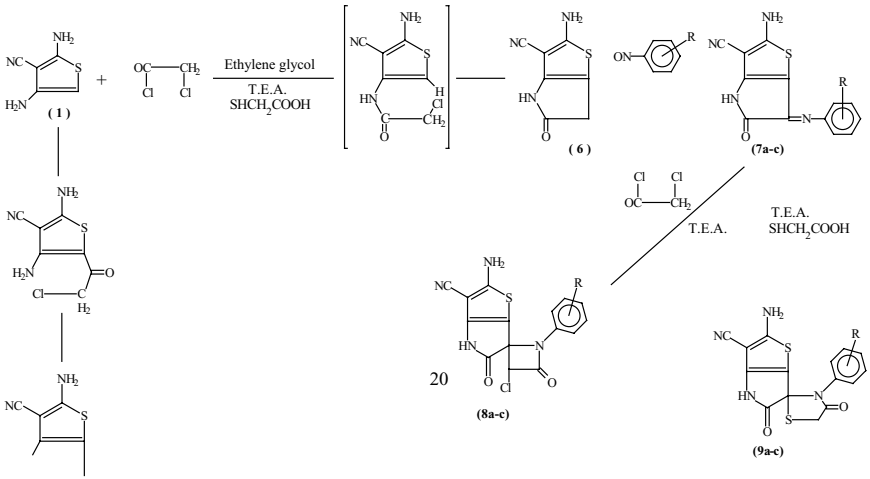
TABLE I Characterization of Compounds (1–12) *(Continued)*

Comp. no.	M.P. C	Solvent of cryst.	Yield %	M.F. (M. Wt.)	Analysis % calcd. (found) C	H	N	M.S.
10c	285–287	Methanol	70	$C_{13}H_9N_4SCl$ (299.31)	52.17 (52.24)	3.03 (3.10)	23.40 (23.36)	299
11a	295–297	Methanol	84	$C_{15}H_{11}N_4OSCl$ (329.78)	54.63 (54.70)	3.06 (3.15)	16.99 (16.90)	329
11b	290–292	Methanol	82	$C_{15}H_{10}N_5O_3SCl$ (346.79)	51.95 (51.80)	3.20 (3.25)	16.16 (16.20)	346
11c	278–280	Methanol	81	$C_{15}H_{10}N_4OSCl_2$ (507.38)	47.94 (48.00)	2.68 (2.60)	18.64 (18.70)	375
12a	262–264	Ethanol	73	$C_{15}H_{12}N_4OS_2$ (628.69)	28.70 (28.60)	1.77 (1.84)	8.93 (8.88)	628
12b	274–276	Ethanol	272	$C_{15}H_{11}N_5O_3S_2$ (344.41)	52.31 (52.52)	3.51 (2.70)	16.27 (16.38)	344
12c	269–271	Ethanol	170	$C_{15}H_{11}N_4OS_2Cl$ (373.40)	48.25 (48.37)	2.97 (3.03)	18.76 (18.67)	373

elemental analysis (c.f. Table I), IR spectral which revealed a characteristic peaks (KBr) at 3398(OH), 3345–3170 cm^{-1}(NH and NH_2), 2210 cm^{-1}(CN), 1680 cm^{-1} (C=O) and ^1H NMR spectrum (DMSO-d6) at δ 9.88(s, 1H, NH), 8.45–7.32 (m, 5H, Ar-H^+, OH), 5.55 (brs, 2H, NH_2).



SCHEME 1

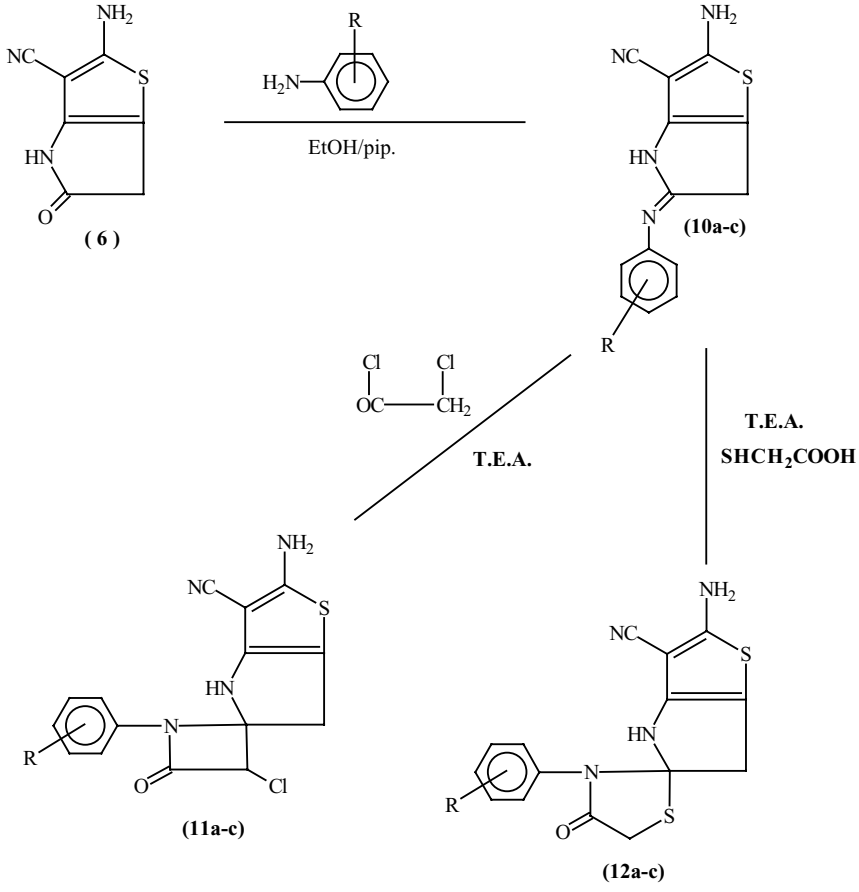


SCHEME 2

Treatment of an ethanolic solution of 7a-c with chloroacetylchloride and/or mercaptoacetic acid in the presence of triethylamine afforded the corresponding new Spiro β-lactam **(8a–c)** and new Spiro thiazolidinone **(9a–c)**. The proposed formulations of **8a–c** and **9a–c** were confirmed by mass spectrum and elemental analysis (c.f. Table I); IR spectral, which revealed a characteristic peaks of **8a** and **9a** as example (KBr) at 3396 cm^{-1} (OH), 3346, 3177 cm^{-1}(NH, NH_2), 2216 cm^{-1}(CN), 1765 cm^{-1}(C=O), and 3396 cm^{-1}(OH), 3190, 3186 cm^{-1} (NH, NH_2), 2215(CN), 1765 cm^{-1}(C=O), respectively. ^{1}H NMR spectrum of **8a** and **9a** as example which showed signals at δ 9.75(s, 1H, NH), 8.45–7.33(m, 8H, ArH^+; β-lactam H^+), 5.42(brs, 2H, NH_2), and at δ 9.86(s, 1H, NH), 8.23–7.12(m, 8H, Ar-H^+), 6.23(s, 1H, CH), 5.42(brs, 2H, NH_2), 2.58(s, 2H, CH_2), respectively.

Also, the reaction of **6** with different aromatic amines in ethanol in the presence of piperidine catalyst gives the corresponding new Schiff bases **(10a–c)**. The structure of **10 a–c** was confirmed by mass spectrum and elemental analysis (c.f. Table I) and IR spectral which revealed a characteristic bands (KBr) of **12 a** as example at 3345, 3176 cm^{-1}(NH, NH_2), 2217 cm^{-1}(CN), 1225 cm-1(C=N), and ^{1}H NMR spectrum of **10a** as example (DMSO-d6) which showed signal at δ 9.17(s, 1H, NH), 8.45–7.32(m, 5H, Ar-H^+), 5.36(brs, 2H, NH_2), 2.58(s, 2H, CH_2).

Reaction of **10a–c** with chloroacetylchloride and/or mercaptoacetic acid in presence of ethanol as solvent and triethylamine as a catalyst give the corresponding Spiro β-lactam **(11a–c)** and Spiro thiazolidinone **(12a–c)**.



10-12: a; R = H
b; R = 4-NO_2
c; R = 4-Cl

SCHEME 3

The proposed formulations of **11a–c** and **12a–c** were confirmed by mass spectral and elemental analysis (c.f. Table I) and IR spectrum which revealed a characteristic peaks (KBr) of **11a** and **12a** as examples at 3356, 3177 cm^{-1}(NH, NH_2), 2214 cm^{-1}(CN), 1766 cm^{-1}(C=O), 1226 cm^{-1}(C=N) and 3100–3189 cm^{-1}(NH, NH_2), 2219 cm^{-1}(CN), 1765 cm^{-1}(C=O), 1226 cm^{-1}(C=N), respectively, and ^{1}H NMR spectrum, which showed signals of **11a** and **12a** as examples (DMSO-d6) at δ 9.78(s, 1H, NH), 8.45–7.32(m, 5H, Ar-H^+), and β-lactam-H^+), 5.47(brs, 2H, NH_2), 2.22(s, 2H, CH_2), and at δ 9.88(s, 1H, NH), 8.23–7.12(m,

5H, Ar-H^+), 6.24(s, 1H, CH), 5.47(brs, 2H, NH_2), 2.25(s, 4H, $2CH_2$), respectively.

EXPRIMENTAL

All melting points are uncorrected; IR spectra were measured as KBr pellets on a Pye Unicam sp 1000 spectrophotometer. ^{1}H NMR spectra were recorded in DMSO- d6 at 200 MHz on a Varian Gemini NMR spectrometer, using TMS as internal reference; the chemical shifts are expressed as δ Values (ppm). Mass spectra were obtained on a Shimadzu GCMS- Qp 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the micro analytical center of Cairo University.

Synthesis of 2, 4-Diamino 3-Cyano Thiophene (1)

A solution of appropriate amount of acetamide (0.59 g, 1 mmol) and malononitrile (0.66 g, 1 mmol) was added with sulfur (0.32 g, 1 mmol) in presence of (0.5 ml) of piperidine catalyst and dioxane as solvent. The reaction mixture was heated under reflux for 12 h, concentrated in vacuum, cooled, and diluted with ice water acidified by concentrated hydrochloric acid. The precipitate obtained was filtered, washed with ice water, dried, and recrystallized from diethyl ether to afford **1**.

Synthesis of 2,4 Diarylazamethine Phenyl-3-Cyano Thiophene (2a–c)—General Procedures

To a stirred solution of 2,4-diamino-3-cyano-thiophene **1** (I.39g, 1mmol) in DMF (20 ml), different aromatic aldehydes (2.22 g, 2 mmol; 2.44 g, 2 mmol; 3.02 g, 2 mmol, respectively) in presence of (0.5 ml) of piperidine catalyst. The reaction mixture was heated on a boiling water bath for 7 h, then left to cool until it reached 25°C. The reaction mixture diluted with ice water (40 ml) and neutralized with hydrochloric acid. The solid product formed on standing overnight was filtered, washed thoroughly with cold water, and dried, recrystallization from ethanol to yield the corresponding **(2a–c)**, (c.f. Tables I, II).

Synthesis of 2, 4-Dimono Substituted β-Lactam Arylazamethine Phenyl 3 Cyano Thiophene (3a–c)—General Procedures

A mixture of **(2a–c)** (3.19 g, 1 mmol; 3.51 g, 1 mmol; 4.11 g, 1 mmol respectively) and chloroacetylchloride (1.13 g, 2 mmol) in DMF in presence of (0.5 ml) of triethylamine was refluxed in water bath for

TABLE II IR, ^{1}H NMR Spectral Data of Compound

Comp. no.	IR $(cm)^{-1}$	^{1}H NMR (δ-ppm)
1	3350-3340(NH_2), 2220(C≡N).	5.35(brs, 4H, $2NH_2$), 6.41(s, 1H, CH).
2a	2216(C≡N), 1580(C=N).	6.35(s, 1H, CH), 7.12(s, 2H, CH=N), 7.32–8.45(m, 10H, Ar–H^+).
2b	3450(OH), 2212(C≡N), 1585(CH=N).	6.25(s, 1H, CH), 7.13(s, 2H, 2CH=N), 7.33–8.42(m, 10H, Ar–H^+).
2c	1596(CH=N), 2206(C≡N).	6.45(s, 1H, CH), 7.13(s, 2H, 2CH=N), 7.33–8.45(m, 8H, Ar–H^+).
3a	1222(C-N), 1760(C=O), 2218(C≡N).	6.43(s, 1H, CH), 7.35-8.45(m, 8H, Ar–H^+& β–lactam H^+).
3b	1226(C-N), 3440(OH), 1765(C=O), 2213(C≡N), 3440(OH).	6.38(s, 1H, CH), 7.33-8.45(m, 8H, Ar–H^+& β–lactam H^+).
3c	1224(C-N), 1763(C=O), 2216(C≡N).	6.36(s, 1H, CH), 7.32-8.45(m, 6H, Ar-H^++ β–lactam H^+).
4a	1675(C=O), 2213(C≡N).	2.51(s, 4H, $2CH_2$), 6.23(s, 1H, CH), 5.83(s, 2H, $2NCH_5$), 7.12–8.22(m, 10H, Ar–H^+).
4b	1680(C=O), 2210(C≡N), 3945(2OH).	2.55(s, 4H, $2CH_2$), 6.33(s, 1H, CH), 5.86(s, 2H, $2NCH_5$), 7.12-8.33(m, 10H, Ar–H^+).
4c	1685(C=O), 2206(C≡N).	2.58(s, 4H, $2CH_2$), 6.36(s, 1H, CH), 5.88(s, 2H, $2NCH_5$), 7.12-8.23(m, 8H, Ar–H^+).
7a	3398(OH), 3345–3170(NH, NH_2), 1680(C=O), 2210(C≡N).	5.35(brs, 2H, NH_2), 9.69(s, 1H, NH), 7.3–8.45(m, 7H, Ar–H^+ +OH-H^+).
7b	3395–3176(NH, NH_2), 1685(C=O), 2216(C≡N)	5.55(brs, 2H, NH_2), 9.88(s, 1H, NH), 7.32-8.45(m, 5H, Ar–H^+ +OH).
7c	3350-3175(NH, NH_2), 1686(C=O), 2206(C≡N).	1.35(s, 6H, $2CH_3$), 5.33(brs, 2H, NH_2), 9.67(s, 1H, NH), 7.30-8.45(m, 4H, Ar–H^+).
8a	1223(C-N), 1765(C=O), 2216(C≡N), 3396(OH), 3346–3177(NH, NH_2).	5.42(brs, 2H, NH_2), 9.75(s, 1H, NH), 7.33–8.45(m, 8H, Ar–H^+ + β-lactam-H^+)
8b	1225(C-N), 1766(C=O), 2213(C≡N), 3395(OH), 3341-3180(NH, NH_2).	5.46(brs, 2H, NH_2), 9.85(s, 1H, NH), 7.35–8.45(m, 6H, Ar–H^+ + β-lactam-H^+)
8c	1228(C-N), 1768(C=O), 2210(C≡N), 3340-3170(NH, NH_2).	1.22(s, 6H, $2CH_3$), 5.56(brs, 2H, NH_2), 9.78(s, 1H, NH), 7.35–8.45(m, 6H, Ar–H^+ + β-lactam-H^+)
9a	1675(C=O), 2215(C≡N), 3396(OH), 1228(C-N), 3186(NH, NH_2).	5.42(brs, 2H, NH_2), 9.86(s, 1H, NH), 7.12–8.23(m, 8H, Ar–H^+), 2.58(s, 2H, CH_2), 6.23(s, 1H, CH).
9b	1680(C=O), 2208(C≡N), 3398(OH), 1224(C-N), 3180(NH, NH_2).	5.45(brs, 2H, NH_2), 9.88(s, 1H, NH), 7.32–8.45(m, 4H, Ar–H^+), 2.58(s, 2H, CH_2), 6.35(s, 1H, CH).
9c	1675(C=O), 2210(C≡N), 1224(C-N), 3187(NH, NH_2).	1.23(s, 6H, $2CH_3$), 5.36(brs, 2H, NH_2), 9.80(s, 1H, NH), 7.32–8.45(m, 4H, Ar–H^+), 2.58(s, 2H, CH_2), 6.33(s, 1H, CH).

(Continued on next page)

TABLE II IR, ^{1}H NMR Spectral Data of Compound *(Continued)*

Comp. no.	IR $(cm)^{-1}$	^{1}H NMR (δ-ppm)
10a	3345-3176(NH, NH_2), 2217(C≡N), 1225(C≡N).	5.36(brs, 2H, NH_2), 9.71(s, 1H, NH), 2.58(s. 2H, CH_2), 7.32–8.45(m, 5H, Ar—H^+).
10b	3340-3186(NH, NH_2), 2221(C≡N), 1223(C=N).	5.46(brs, 2H, NH_2), 9.73(s, 1H, NH), 7.31-8.45(m, 4H, Ar—H^+).
10c	3355-3178(NH, NH_2), 2245(C≡N), 12228(C-N).	5.39(brs, 2H, NH_2), 9.69(s, 1H, NH), 7.31-8.45(m, 4H, Ar—H^+).
11a	1226(C-N), 2214(C≡N), 3356-3177(NH, NH_2), 1766(C=O).	5.47(brs, 2H, NH_2), 9.78(s, 1H, NH), 7.32–8.45(m, 5H, Ar—H^+ + β-lactam-H^+).
11b	1224(C-N), 1770(C=O), 2210(C≡N), 3345-3180(NH, NH_2).	5.46(brs, 2H, NH_2), 9.85(s, 1H, NH), 7.35–8.45(m, 6H, Ar—H^+ + β-lactam-H^+).
11c	1221(C-N), 1768(C=O), 2206(C≡N), 3340-3170(NH, NH_2).	5.56(brs, 2H, NH_2), 9.78(s, 1H, NH), 7.35–8.45(m, 6H, Ar—H^+ + β-lactam-H^+).
12a	1765(C=O), 2219(C≡N), 1226(C-N), 3189(NH, NH_2)	5.47(brs, 2H, NH_2), 9.88(s, 1H, NH), 7.12–8.23(m, 8H, Ar—H^+), 2.25(s, 4H, $2H_2$), 6.24(s, 1H, CH).
12b	1766(C=O), 2214(C≡N), 1224(C-N), 3187(NH, NH_2)	5.55(brs, 2H, NH_2), 9.88(s, 1H, NH), 7.32–8.45(m, 4H, Ar—H^+).
12c	1765(C=O), 2210(C≡N), 1226(C-N), 3187(NH, NH_2)	5.46(brs, 2H, NH_2), 9.82(s, 1H, NH), 7.32–8.45(m, 4H, Ar—H^+), 2.15(s, 4H, $2CH_2$), 6.33(s, 1H, CH).

15 h. After removal the DMF under reduced pressure, the resulting solid product was filtered and washed with water. The crude product was recrystallized form dioxane to yield the corresponding **(3a–c)**.

Synthesis of 2, 4-Dithiazolidinone Arylaza Methine Phenyl-3-Cyano Thiophene (4a-c)—General Procedures

A mixture of **(2a–c)** (3.19 g, 1 mmol; 3.51 g, 1 mmol; 4.11 g, 1 mmol respectively) and mercaptoacetic acid (1.84 g, 2 mmol) was refluxed in dry benzene (30 ml) in presence of triethylamine (using a Dean–stark water separator). The excess benzene was evaporated in vacuum. The resulting residue was triturated with ice water naturalized by concentrated hydrochloric acid and was allowed to stand overnight. The solid thus obtained washed with water, dried, and recrystallized from ethanol to yield the corresponding **(4a–c)**.

Synthesis of Compound (6)

A solution of **1** (1.39 g, l mmol) in ethylene glycol (30 ml) and chloroacety1chloride (l.13 g, 1 mmol) in presence of (0.5 ml) of triethylamine was heated under reflux for 12–15 h (TLC control). After removal of the ethylene glycol under reduced pressure, the resulting solid product was filtered and washed with water. The crude product was recrystallized from dioxane to yield the **6**.

Synthesis of New Schiff Bases (7a–c)—General Procedures

To a solution of **6** (1.79 g, 1 mmol) in ethanol (25 ml), different aromatic nitroso compound (1.73 g, 1 mmol; 1.73 g, 1 mmol; 1.23 g, 1 mmol, respectively) in presence of piperidine (0.5 ml) as catalyst. The reaction mixture was heated under reflux for 4–5 h; the solvent was then evaporated under reduced pressure. The residue treated with ice water was neutralized by concentrated hydrochloric acid. The solid product so formed was collected by filtration and recrystallized from methanol to yield the corresponding **(7a–c)**.

Synthesis of Spiro β-Lactam (8a–c)—General Procedures

A mixture of **7a–c** (4.1 g, 1 mmol; 2.84 g, 1 mmol; 3.45 g, 1 mmol respectively) and chloroacetylchloride (l.13 g, 1 mmol) in dioxane in presence of (0.5 ml) of triethylamine was heated under reflux for 13 h. The solvent removed under reduced pressure, the resulting solid product was filtered and washed with water. The crude product was recrystallized from methanol to yield the corresponding **8a–c**, (c.f. Table I, II).

Synthesis of Spiro Thiazolidinone 9a–c—General Procedures

A mixture of **7a–c** (4.1 g, 1 mmol; 2.84 g, 1 mmol; 3.45 g, 1 mmol respectively) and meracaptoacetic acid and (0.92 g, 1 mmol) was refluxed in dry benzene (30 ml) in presence of triethylamine using a Dean-stark water separator. The excess of benzene was evaporated in vacuum. The resulting residue was triturate with ice water neutralized by concentrated hydrochloric acid and was allowed to stand overnight the solid was recrystallized from ethanol to yield corresponding **9a–c**, (c.f. Tables I, II).

Synthesis of New Schiff Bases (10a–c)—General Procedure

To a solution of **6** (1.79 g ,1 mmol) in ethanol (25 ml) , different aromatic amino compound (0.92 g, 1 mmol; 1.38 g, 1 mmol; 1.57 g, 1 mmol,

respectively) in presence of piperidine (0.5 ml) as catalyst. The reaction mixture was heated under reflux for 4–5 h; the solvent was then evaporated under reduced pressure. The residue treated with ice water neutralized by concentrated hydrochloric acid. The solid product so formed was collected by filtration and recrystallized from methanol to yield the corresponding **10a–c**, (c.f. Tables I, II).

Synthesis of Spiro β-Lactam (11a–c)—General Procedure

A mixture of **10a–c** (2.54 g, 1 mmol; 4.12 g, 1 mmol; 2.99 g, 1 mmol, respectively) and chloroacetyl chloride (1.13 g, 1 mmol) in dioxane in presence of (0.5 ml) of triethylamine was heated under reflux for 13 h. The solvent removed under reduced pressure, the resulting solid product was filtered and washed with water. The crude product was recrystallized from methanol to yield the corresponding **11a–c** (c.f. Table I, II).

Synthesis of Spiro Thiazolidine (12a–c)—General Procedure

A mixture of **10a–c** (2.54 g, 1 mmol; 4.12 g, 1 mmol; 2.99 g, 1 mmol ,respectively) and mercaptoacetic acid (0.92 g, 1 mmol) was refluxed in dry benzene 30 ml in presence of triethylamine using a Dean stark water separator the excess of benzene was evaporated in vacuum. The resulting residue was triturated with ice water neutralized by concentrated hydrochloric acid and was allowed to stand overnight. The solid was recrystallized from ethanol to yield the corresponding **12a–c** (c.f. Tables I, II).

REFERENCES

[1] W. Darkheimer, J. Bumbach, R. Lattrell, and K. H. Scheanemann, *Angew. Chern.*, **97,** 183 (1985).
[2] C. Cimarustic, and R. Sykes, *Chern. Br.*, **19,** 302 (1983).
[3] S. R.Woulfe, and M. Miller, *Tetrahedron Lett.*, **25,** 3293 (1984).
[4] S. R.Woulfe, and M. Miller, *J. Med. Chern.*, **28,** 1447 (1985).
[5] H. Breure, H. Straub, D. Treuner, J. M. Drossard, H. Hoehn, and J. Lindlerk., *Antibiot.*, **38,** 813 (1985).
[6] S. R.Woulfe, and M. Miller, *J. Org. Chern.* **51,** 3133 (1986).
[7] M.J. Miller, A. Biswas, and M. A. Krook, *Tetrahedron*, **93,** 2571 (1983).
[8] W.O. Foye, Principles of Medicinal Chemistry, (Lea and Febiger, Philadelphia, 1981), 2nd ed.
[9] P.J. Coornu, C. Pernin, B. Dumaitre, G. Streichenberher, Can CA 1231950; *Chem. Abstr.*, **109,** 149544g (1988).
[10] M. Yamamoto, S. Morooka, M. Kosshiba, S. Inaba, H. Yamamoto, Japenese Patent 76100098, 1976; *Chern. Abstr.*, **86,** 12364f (1977).

[11] T. Denzel and H. Hoem, Ds Patent 3981 801, 1976; *Chern. Abstr.*, 8616675k (1977)..
[12] A. Brucato, A. Coppola, S. Glanaguzza, and P. M. Provenzano, *Bull. Soc. Ital. BioI. Sper.*, **54,** 1051 (1978).
[13] D. L. Coffen, and R. I. Fryer, Ds Patent 3349434, 1974.
[14] L. Mir, and M. T. Siddiqui, *Tetrahedron*, m **26,** 5235 (1970).
[15] A. Gaslo, V. Mortyarini, and E. Reyaund, *Farmaco Ed. Sci.*, **28,** 624 (1973).
[16] A. K. Kalafallah, R. M. Abdel-Aal, and N. A. A. EI-Kanzi, *J. Chin. Chem. Soc.*, **51,** 769–774 (2004).
[17] A. K. Kalafallah, R. M. Abdel-Aal, and N. A. A. EI-Kanzi, J. *Chin. Chern. Soc.*, 49 (3), (2002).
[18] N. A. A. El-Kanzi, H. A. Soleiman, and A. K. Khalafallah, *Phosphorus, Sulfur, and Silicon*, **182,** 1459–1473 (2007).