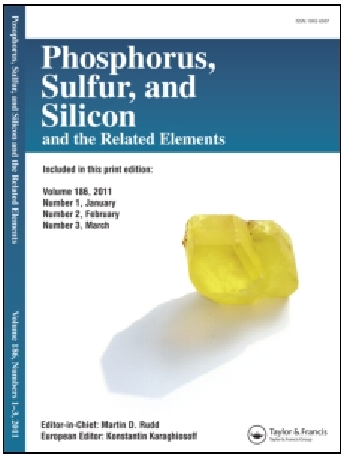

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Heterocyclic Synthesis with Thiophene-2-Carboxamide

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Heterocyclic Synthesis with Thiophene-2-Carboxamide

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*3-Amino-4-cyano-N-phenylaminothiophene-2-carboxamide (**2**) was prepared by reacting 2-(1,1-dicyanomethylene)-3-N-phenyl-1,3-thiazolidin-4-one (**1**) with ammonia. The carboxamide when reacted with benzaldehyde, formic acid, phenylisothiocyanate, cyclohexanone, cyclopentanone, ethylchloroformate and carbon disulfide yield. The pyrimidinone derivatives (**3**, **4**, **5**, **6**, **7**, **8**, and **9**), respectively. The biological activity of all synthesized compounds were studied as antibiotics and against Gram positive and Gram negative bacteria. The purpose of this article is synthesis of new antibiotic and antibacterial drugs.*

Keywords Tetrahydrothienopyrimidinone; dihydrothienopyrimidine; thienopyrimidinedione; oxazinone

INTRODUCTION

Thienopyrimidines still attract considerable attention of many research groups due to their wide applications in medicinal chemistry. Several of these compounds were used as analgecics,[1] antipyreties,[2] and anti-inflammatory agents.[3,4] In this part, preparation of thieno[3,2-d]pyrimidines was accomplished starting from thiophene. So, a number of thieno[3,2-d]pyrimidines were synthesized employing 3-amino-4-cyano-5-N-phenylaminothiophene-2-carboxamide **(2)**, which was in turn synthesized from 2-(1-dicyano)-3-phenylthiazolidin-4-ones **(1)**[5] and ammonia.

When compound **(2)**, was allowed to react with benzaldehyde, it afforded the 7-cyano-6-N-phenylamino-2-phenyl-1,2,3,4-tetrahydrothieno-[3,2-d]pyrimidin-4-one **(3)** in good yield (Scheme 1).

Also, compound **(2)** easily reacted with formic acid and gave the 7-carboxamide-6-N-phenylamino-3,4-dihydrothieno[3,2-d]pyrimidine (**4**). The structure of **(4)** was elucidated from its correct spectral data.

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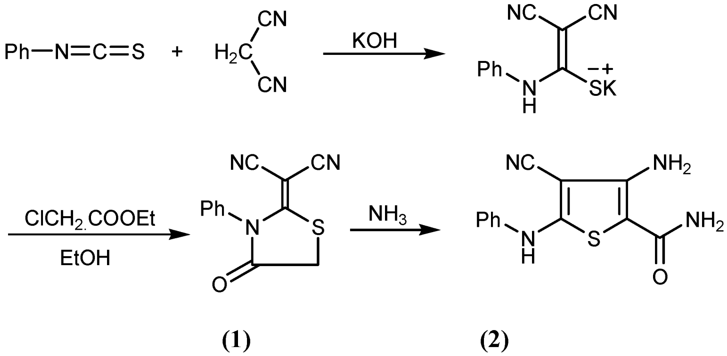


SCHEME 1

Furthermore, when compound **(2)** was allowed to react with phenyl isothiocyanate in refluxing acetic acid afforded the 7-cyano-2-mercapt-3-phenyl-6-N-phenylaminothieno[3,2-d]pyrimidin-4-one **(5)** (Scheme 2).

Compound **(2)** reacted with cyclohexanone and cyclopeantanone in refluxing acetic acid and yielded compounds **(6)** and **(7)** (Scheme 1). The structures of these compounds were confirmed from their correct analytical data.

Furthermore, compound **(2)** reacted with ethylchloroformate in refluxing acetic acid yielded the dione compound **(8)** (Scheme 2).

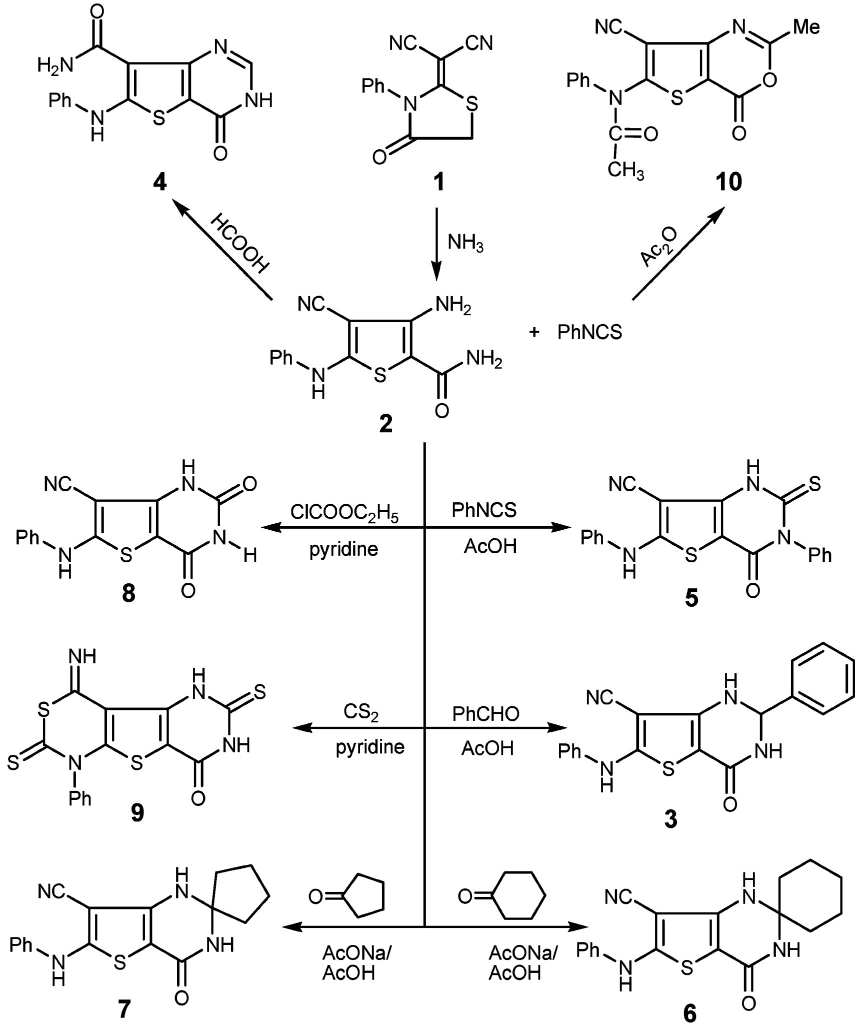
A very interesting reaction occurred when compound **(2)** was allowed to react with carbon disulphide in pyridine. This produce the tricyclic compound **(9)** (Scheme 2). The structure of compound **(9)** was confirmed from its correct spectral data.

Finally, 2-methyl-4-cyano-5-(N-acetyl-N-phenyl)aminothieno[3,2-d] oxazine-7-one **(10)** was obtained instead of the expected pyrimidinone, when the carboxamide **(2)** was allowed to react with acetic anhydride at reflux temperature (Scheme 2).

The biological activity of the tested compounds have been evaluated using filter paper disc method[6,7] (Table II).

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Unicam SP-1200 infrared spectrophotometer using KBr. ^1H NMR spectra were recorded on varianEM300 spectrometer at 60 MHz in DMSO-d_6, (chemical shift in ppm). ^{13}C NMR spectra were carried out on a Bruker Avance 75 MHz in DMSO-d_6 (chemical shift δ ppm).



SCHEME 2

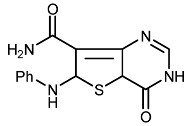
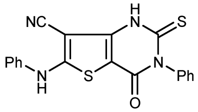
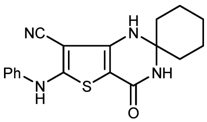
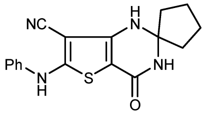
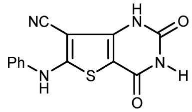
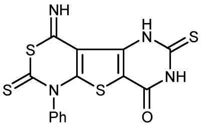
Synthesis of 2-(1,1-Dicyanomethylene)-3-N-phenyl-1,3-thiazolidin-4-one (1)

A solution of the ketene-N-S-acetyl (4.02 g, 0.02 mol) in distilled water (20 ml) was stirred at room temperature and ethylchloroacetate (2.44 g, 0.02 mol), in ethanol (25 ml) was added. The reaction mixture was heated at 60–80°C for about 2 h. The solid produced was collected and recrystallized from ethanol to give white powder,[5] yield 88%, m.p.: 271–273°C.

TABLE I Physical and Spectral Data of the Synthesized Compounds (3–10)

No.	M.p./yield%	IR cm^{-1}	^{1}H NMR ppm	^{13}C NMR ppm
3	350–352 66	3314 (νNHCO-), 3252 (νNH), 3162 (νNH-Ph), 2220 (νCN), 1624 (νC=O)	δ 5.7(s, 1H, pyrimidone), 7.8 (s, 1H, NH), 8.1 (s, 1H, NH-Ph), 10.2–10.5 (broad, 1H, NH-CO-), 7.2–7.6 (m, 10H, two phenyl)	164, 160, 150, 141, 140, 113, 90, 79, 120-129 (two phenyl groups, C-Ar)
4	360 85	3377 (νNHCO-), 3300-3190 (νNH), 3100 (νNH-Ph), 1674 (νC=O)	δ 11.8(s, NH-CO-), 10–10.2 (broad NH-Ph), 7.7 (s, 2H, amide), 7.8–8.4 (m, 5H, phenyl)	163, 160, 156, 147, 145, 139, 130, 125, 130, 125, 121, 107, 105
5	230 76	3350 (νNH), 3300 (νNH-Ph), 2205 (νCN), 1706 (νC=O), 1456 (νC=S)	δ 6.7(s, 1H, NH-CS-), 7.1–7.5 (m, 10H, two phenyl), 10 (s, 1H, NH-Ph)	
6	260 74	3373 (νNHCO-), 3114 (νNH-Ph), 3257 (νNH), 2211 (νCN), 1678 (νC=O)	δ 1.2–2.6(m, 10H, aliphatic), 7.1 (s, 1H, NH), 7.4 (1H, NH-Ph), 7.2–7.5 (m, 5H, phenyl), 10.1 (broad, 1H, NH-CO-)	163, 160, 150, 113, 90, 80, 78, 70, 22, 21.8
7	230 70	3413 (νNHCO-), 3353 (νNH-Ph), 2213 (νCN), 1693 (νC=O), 3211 (νNH)	1.2–2.6 (m, 8H, aliphatic), 6.8 (1H, NH), 7.1–7.5 (m, 5H, aromatic), 7.6 (1H, NH-Ph), 10.2 (1H, NH-CO-)	
8	177 88	3342 (νNHCO-), 3413 (νNH), 3200 (νNH-Ph), 2213 (νCN), 1691 (νC=O)	δ 7.1 – 7.4(m, 5H-aromatic), 7.8 (1H, NH.Ph), 10–10.2 (broad 1H, NH-CO), 12.1 (1H, -CO-NH-CO-)	
9	350 85	3329 (νCO-NH-CS), 3150 (νNH-CS-), 3126 (νNH), 1636 (νC=O), 1453 (νC=S), 1208 (ν-C(S)=S)	δ 13.1(broad, 1H, -CO-NH-CS-), 12.4 (s, 1H, NH-CS), 11 (s, 1H, =NH), 7.2-7.6 (m, 5H aromatic)	
10	296–298 75	1696 (νCO-O), 1680 (νCO-CH$_3$), 2217 (νCN)	3.6 (s, 3H, COCH$_3$), 2.4 (s, 3H, CH$_3$), 7.3-7.8 (m, 5H phenyl)	

TABLE II Antimicrobial Activity of the Tested Thienopyrimidinone Derivatives

			Diameter of inhibition zone				
No.	Compound	Solvent	*S. aureus*	*E. coli*	*P. are*	*K. spp*	*Pr. Vul*
4		MeOH	−ve	+ve	++ve	+++ve	++ve
5		CH_3COOEt	+ve	−ve	++ve	+++ve	+++ve
6		Acetone	+ve	−ve	+++ve	+ve	++ve
7		Acetone	+ve	+ve	+ve	++ve	+++ve
8		Acetone	+ve	−ve	++ve	++ve	+++ve
9		Acetone	++ve	+ve	+ + +ve	+++ve	+++ve

+ve = 8 mm; ++ve = 12 mm; +++ve = 18 mm; S. aureus = staphylococcus aureus; E. coli = Escherichia; P. aer = Pseudomonas arugonosa; K. spp = Klebsiella Spp.; Pr. Vul = Proteus Vulgaris.

Synthesis of 3-Amino-4-cyano-5-phenylaminothiopene-2-carboxamide (2)

Ammonia solution (30 ml) was added to **(1)** (2.41 g, 0.01 mol) and the reaction mixture was stirred at room temperature for 24 h. The solid produced was collected by filtration and recrystallized from chloroform to give brown powder, yield 75%, m.p.: 198–200°C.(5)

Synthesis of 7-Cyano-6-N-phenylamino-2-phenyl-1,2,3, 4-tetrahydro-thieno[3,2-d]pyrimidin-4-one (3)

To a solution of (**2**), (2.58 g, 0.01 mol) in glacial acetic acid (20 ml), benzaldehyde (1.06 g, 0.01 mol) was added. The reaction mixture was refluxed for 6 h, the solid produced was collected, dried, and recrystallized from the chloroform, to give brown powder of (**3**), yield 66%, m.p.: 350–352°C.

Synthesis of 7-Carboxamide-6-N-phenylamino-3, 4-dihydrothieno[3,2-d]-pyrimidine (4)

In a round-bottom flask with a reflux condenser a mixture of (**2**), (2.58 g, 0.01 mol) and formic acid (20 ml), were refluxed for 6 h. The precipitate produced was collected and recrystallized from ethanol to give a yellow powder of (**4**), yield 85%, m.p.: 360°C.

Synthesis of 7-Cyano-2-mercapto-3-phenyl-6-N-phenylaminothieno[3,2-d]-pyrimidin-4-one (5)

To a solution of (**2**) (2.58 g, 0.01 mol), phenylisothiocyanate (1.35 g, 0.01 mol), was added, the reaction mixture were refluxed for 5 hours in acetic acid (20 ml). The precipitate was collected and recrystallized from ethanol, to give light brown powder of (**5**), yield 76% m.p.: 230°C.

Synthesis of 7-Cyano-6-phenylamino-1,3,4-trihydrospyro-cyclohex-ane-(1′, 2)-thieno-[3,2-d]pyrimidin-4-one (6)

In a round-bottom flask with a reflux condenser a mixture of compound (**2**) (2.58 g, 0.01 mol), cyclohexanone (0.98 g, 0.01 mol) and sodium acetate (3 gm) were refluxed for 5 h in glacial acetic acid (20 ml); the reaction mixture was concentrated by evaporation under vacuum, the solid product was collected and recrystallized from chloroform, to give dark gray crystal of compound (**6**), yield 74%, m.p.: 260°C.

Synthesis of 7-Cyano-6-phenylamino-1,3,4-trihydrospyro-cyclopent-ane(1′,2)-thieno-[3,2-d]pyrimidin-4-one (7)

In a round-bottom flask with a reflux condenser a mixture of compound (**2**) (2.58 g, 0.01 mol), cyclopentanone (0.84 g, 0.01 mol) and sodium acetate (3 g) were refluxed for 5 h in glacial acetic acid (20 ml), the reaction mixture was concentrated by evaporation under vacuum, the solid product was collected and recrystallized from acetic acid, to gave light gray crystal of compound (**7**), yield 70%, m.p.: 230°C.

Synthesis of 7-Cyano-6-phenylamino-1,2,3,4-tetrahydrothieno[3,2-d]-pyrimidin-2,4-dione (8)

In a round-bottom flask with a reflux condenser a mixture of compound **(2),** (2.58 g, 0.01 mol) and ethylchloroformate (1.08 g, 0.01 mol), were refluxed for 4 h in pyridine (10 ml) and then allowed to cool. The solid product formed upon pouring onto ice/hydrochloric acid was collected by filtration and recrystallized from acetic acid, to give red crystals of **(8)**, yield 88%, m.p.: 177°C.

Synthesis of 4-Imino-1-phenyl-2,6-dithia-5,6,7,8-tetrahydropyrimido[5,4-b]-thieno-[5,4-d]-1,3-thiazine-8-one (9)

A mixture of **(2)**, (2.58 g, 0.01 mol), carbon disulfide, (1.56 g, 0.02 mol) and dry pyridine (20 ml), were refluxed until the evolution of hydrogen disulphide ceased (20 h), (until no more yellow coloration of lead acetate impregnated filter paper took place). The reaction mixture was allowed to cool, the solid product formed upon pouring in ice cold water containing few drops of hydrochloric acid (pH = 6) was collected and recrystallized from DMF, to give yellow powder of compound (**9**), yield 85%, m.p.: 350°C.

Synthesis of 2-Methyl-4-cyano-5-(N-acetyl-N-phenyl)aminothieno[3,2-d]-oxazin-7-one (10)

In a round-bottom flask with a reflux condenser a mixture of **(2)**, (2.58 g, 0.01 mol) and acetic anhydride (20 ml) were refluxed for 6 h. The precipitate was collected and recrystallized from ethanol to give yellow crystals of compound (**10**)[5], yield 75%, m.p.: 296–298°C.

CONCLUSION

This article enabled us to synthesize a new biologically active heterocyclic compounds against Gram (+ve) and Gram (–ve) bacteria.

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