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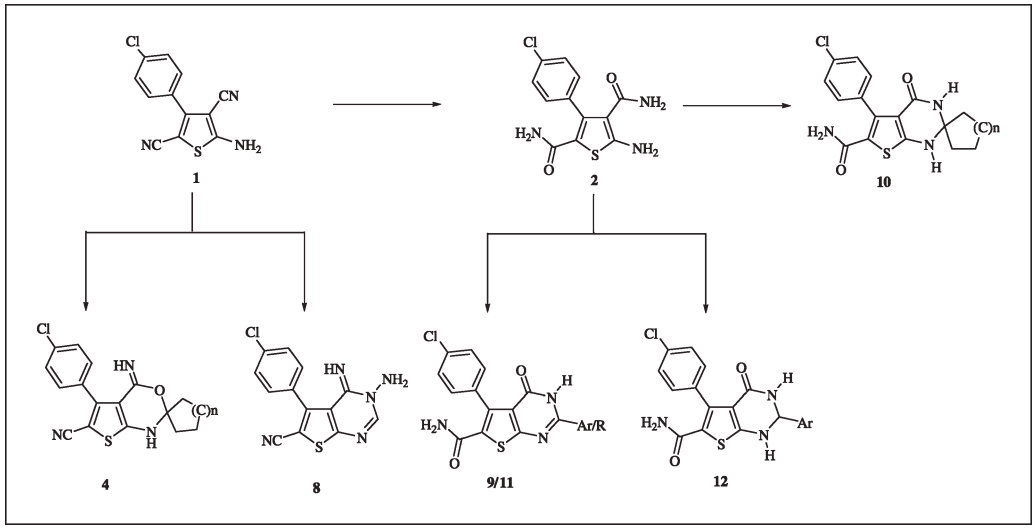
Received July 20, 2010
DOI 10.1002/jhet.748
Published online 31 December 2011 in Wiley Online Library (wileyonlinelibrary.com).



o-Aminothiophene dicarbonitrile **1** on neat reaction with cyclic ketones in anhydrous $ZnCl_2$ yielded mixture of fused aminopyridine **3** and iminospirooxazine **4** derivatives. Similarly, pyrimidine derivatives **5** and **8** were obtained by the reaction of this intermediate **1** with formic acid and DMF-DMA followed by hydrazine hydrate, respectively. The reaction of *o*-amino-thiophene dicarboxamide **2** at ambient temperature with cyclic ketones yielded spiropyrimidine **10** as a sole product in quantitative yield. The regioselective anellated pyrimidine **9**, **11**, and dihydropyrimidine **12** derivatives were also obtained by the reaction with aromatic aldehydes in presence of piperidine and iodine respectively.

J. Heterocyclic Chem., **49**, 363 (2012).

INTRODUCTION

The chemistry of 2-aminothiophenes has received much attention because of the convenient availability through most versatile synthetic method developed by Gewald [1]. 2-Amino-3-functionally substituted thiophene derivatives are useful precursor in the azo dye industry and as intermediates for the pharmaceutically important thieno[2,3-*d*]pyrimidines [2,3]. Previously, pharmacological studies of the thienopyridine and thienopyrimidine derivatives extensively showed variety of activities such as antibacterial [4,5], antimicrobial [6], anxiolytic [7], and psychotropic [8]. These thienopyridines are also useful as potential class of VEGFR-2 kinase inhibitors [9], IκB kinase inhibitors [10], gonadotropin releasing hormone antagonist [11–16], and anti-inflammatory agents, particularly for treating arthritis and bone resorption inhibiting agents [17]. Consequently, thienopyridines and thienopyrimidines have become well-sought privileged class of heterocyclic compounds in drug discovery programs.

In continuation of previous work aiming at the synthesis of different heterocycles from the readily obtainable nitrile intermediates [18–22], Kandeel *et al*. [23,24] and Vegh *et al*. [25] reported the synthesis of 5-amino-3-phenyl and 3-heteroarylthiophene-2,4-dicarbonitrile from phenyl- and heteroaryl-3-oxopropanenitriles, respectively. Encouraged with this work, we report here a facile and efficient route for the synthesis of some new thieno[2,3-*d*]pyrimidine and thieno[3,2-*e*]pyridine derivatives from 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile **1** and 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarboxamide **2**. These two precursors predominate the direction of ring growth and generally permits direct and regioselective introduction of substituents in newly formed heterocyclic ring. The required precursor 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile **1** was obtained

by Gewald reaction [23,26] of 3-(4-chlorophenyl)-3-oxopropanenitrile [27,28], malononitrile, and elemental sulfur. It is well known [29,30] that the nitrile on reaction with acid yielded carboxylic acid or amide depending on reaction conditions. Here, we observed that the reaction of dicarbonitrile compound **1** with conc. H_2SO_4 afforded dicarboxamide compound **2** in quantitative yield, which is our second vital precursor. In this article, the active *o*-aminocarbonitrile **1** and *o*-aminocarboxamide **2** moieties have found wide applicability for annulation of heterocyclic ring systems and hence were successfully utilized for syntheses of new class of thieno[3,2-*e*]pyridine, thieno[2,3-*d*]pyrimidine, and thieno-[2,3-*d*][1,3]oxazine derivatives in good yields. Acid hydrolysis of compound **1** at ambient temperature furnished dicarboxamide **2**, which showed three broad singlets at δ 4.82, 6.84, and 7.69 for amide NH_2 and free NH_2, respectively. ^{13}C NMR spectrum showed strong peak at δ 162.99 and 163.04 for two primary amide carbons. Neat reaction of 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile **1** with cyclopentanone and/or cyclohexanone in anhydrous $ZnCl_2$ afforded mixture of fused thienopyridines **3a–b** and spirothienooxazines **4a–b**, which were separated by column chromatography eluting with chloroform: methanol (9:1) in 20–25% and 68–70% yields, respectively. The formation of major spirothienooxazine products **4a–c** can be explained by the mechanism [31,32]. This mechanism actually assigned based on the IR and ^1H NMR spectra. IR of spirooxazine **4a** showed strong absorption bands at 3168 cm^{-1} for NH, 2935 cm^{-1} for CH_2, and 2205 cm^{-1} for CN groups. ^1H NMR of **4a** showed two broad singlets at δ 6.50 for imine NH and δ 4.93 for free NH, whereas, IR of **3b** showed strong absorption at 3500, 3392 cm^{-1} for primary amine NH_2, and ^1H NMR showed broad singlet for two protons at δ 4.37 for the same amine. The structures of all new compounds were assigned based on the spectroscopic and analytical characterization given in the ''Experimental'' section. (Scheme 1)

An extremely convenient, environmentally benign spirocyclization under solventless conditions for the preparation of spiro[cycloalkane-1,2′-thieno-[2,3-*d*]pyrimidine]-6′-carboxamide **10a–b**, has been successfully utilized by stirring cyclopentanone and/or cyclohexanone with *o*-aminodicarboxamide **2**. Compound **10b** showed strong IR absorption bands at 3381–3213 cm^{-1} and 1654 cm^{-1} for secondary amide and carbonyl groups, respectively, and 3288 cm^{-1} for primary amide group. ^1H NMR showed two broad singlets at δ 5.37 and 8.30 for two NH protons, and ^{13}C NMR showed quaternary carbon at δ 70.33 and secondary amide carbon at δ 163.09. The reaction of acid chloride with compound **2** afforded dihydropyrimidines **11a–d** in 62–70% yields. The regioselective reaction of aldehydes with *o*-aminocarboxamide **2** in presence of acetonitrile and slight excess of molecular iodine furnished thienopyrimidine **9a–c** in 65–68% yield, whereas the same reaction in ethanol and catalytic amount of piperidine afforded tetrahydropyrimidines **12a–c** in 50–55% yield. All new compounds were well characterized by IR, NMR, and mass spectrometry (MS) given in ''Experimental'' section. (Scheme 2)

CONCLUSION

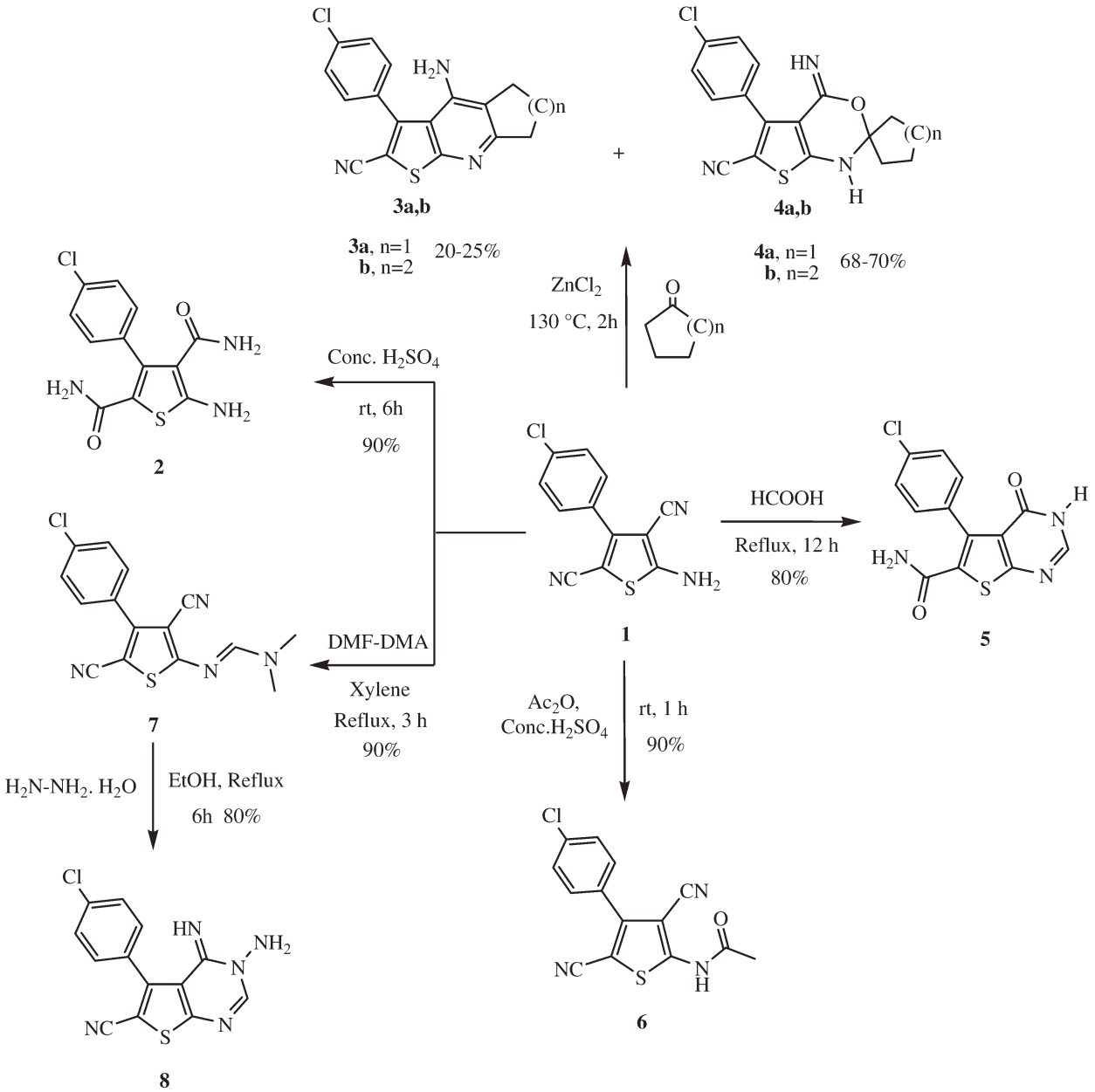
Acid hydrolysis of *o*-aminothiophenedicarbonitrile at ambient temperature afforded *o*-aminothiophenedicarboxamide in excellent yield, which is successfully utilized for the synthesis of regioselective annelated thienopyrimidine derivatives. A new category of thieno[2,3-*d*]pyrimidines, thieno[3,2-e]pyridines and thieno[2,3-*d*][1,3]oxazines were obtained in good yields from 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile **1** and 5-amino-3-(4-chlorophenyl)thiophene-2,4-dicarboxamide **2** with simple work up and clean products.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus. The ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane, and multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Infrared spectra were recorded as KBr pellets on a Shimadzu FTIR-408 spectrophotometer. Mass spectra were recorded on a Shimadzu LC-MS: EI QP 2010A mass spectrometer with an ionization potential of 70 eV. Elemental analyses were performed on Thermo Quest Flash 1112 Series EA analyzer. Reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection, and compounds were purified by column chromatography by using silica gel of 5–20 μm (Merck, 60–120 mesh). Column dimension is 39 × 2 cm, and elution volume used is about 200–400 mL for each product where necessary. Common reagent-grade chemicals are either commercially available and were used without further purification or were prepared by standard literature procedures.

5-Amino-3-(4-chlorophenyl)thiophene-2,4-dicarbonitrile (1). This compound was synthesized by the known literature method [18,21]. This compound was recrystallized from water/DMF (4:2) to afford faint yellow amorphous solid, mp 292–294°C; IR: 3383s, 3304s, 2208m, 2198m, 1630s, 1506w, 1485w, 1421w cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.57 (d, J = 8.4 Hz, 2H, Ar-H), 7.62 (d, J = 8.4 Hz, 2H, Ar-H), 8.37 (bs, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 85.7, 85.8, 114.9, 115.0, 129.5, 130.5, 135.2, 150.9, 198.3; ms: *m/z* 259 (M^+, 100%), 261 (M+2, 33%). *Anal*. Calcd. for $C_{12}H_6ClN_3S$ (259.00): C, 55.50; H, 2.33; N, 16.18. Found: C, 55.38; H, 2.15; N, 16.32.

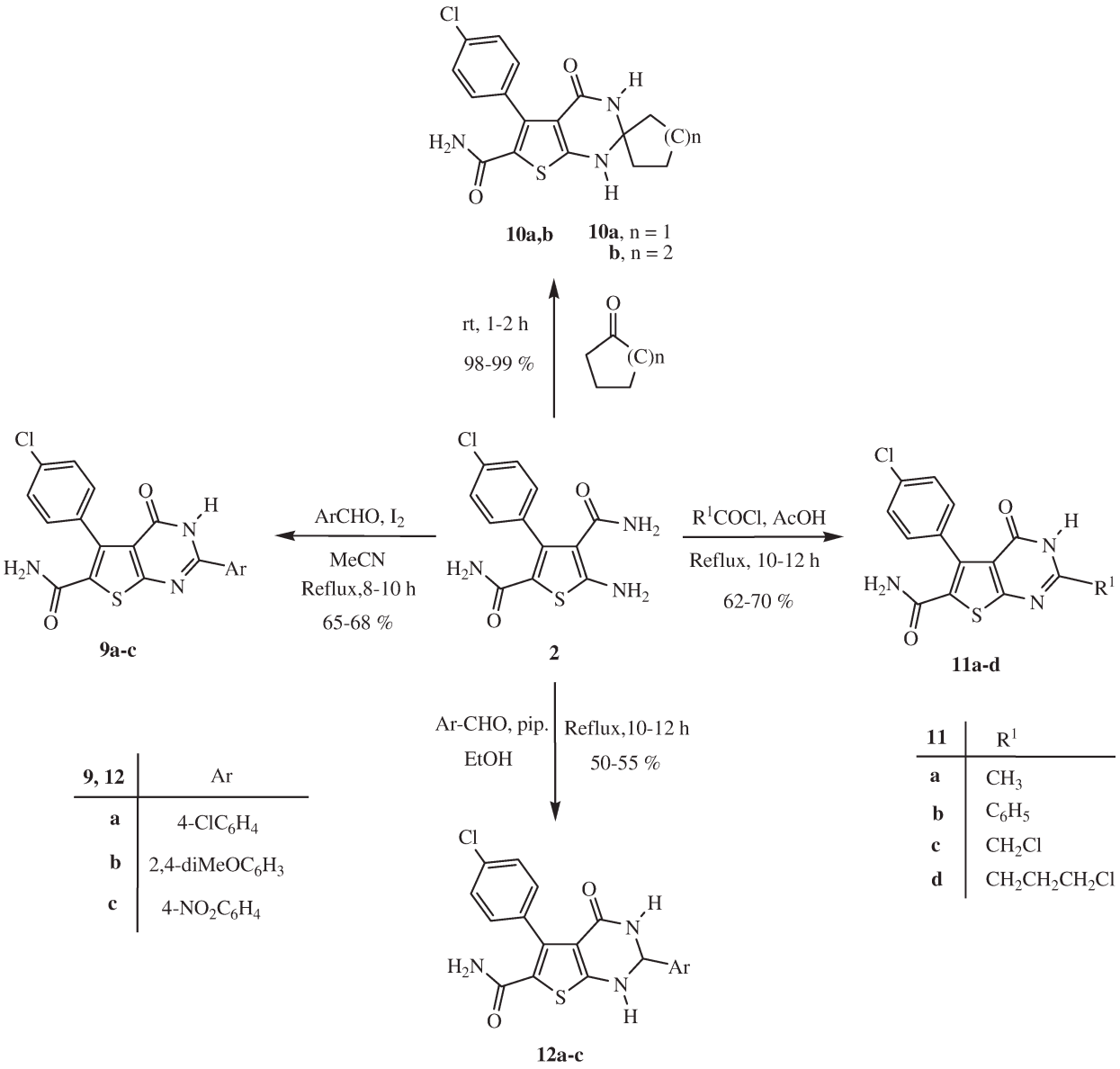
Scheme 1



5-Amino-3-(4-chlorophenyl)thiophene-2,4-dicarboxamide (2). Compound **1** (2.59 g, 0.01 mol) was stirred in conc. H_2SO_4 (10 mL) at room temperature for 6 h (TLC check, chloroform: methanol, 8:2). The reaction mass was then added to crushed ice (250 mL) and neutralized with saturated $NaHCO_3$ (30 mL). The crude solid separated was filtered, washed with water, dried, and recrystallized from ethanol: DMF (8:2) afforded pale yellow crystals, 2.65 g (90%), mp 200–202°C; IR: 3327s, 3306s, 3252m, 3169m, 3475m, 3345m, 1668s, 1672s cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.82 (bs, 2H, amide NH_2), 6.84 (bs, 2H, amide NH_2), 7.38 (d, J = 8.3 Hz, 2H, Ar-H), 7.56 (d, J = 8.3 Hz, 2H, Ar-H), 7.69 (bs, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 109.3, 114.7, 129.2, 131.1, 133.6, 134.3, 139.0, 162.9, 163.0, 166.8; ms: m/z 295 (M^+, 100%), 297 (M+2, 33%). *Anal*. Calcd. for $C_{12}H_{10}ClN_3O_2S$ (295.02): C, 48.73; H, 3.41; N, 14.21. Found: C, 48.82; H, 3.62; N, 14.12.

General procedure for the synthesis of compounds 3a–b and 4a–b. A mixture of **1** (0.259 g, 0.001 mol) and cyclohexanone/cyclopentanone (0.001 mol) was stirred at 120–130°C in an oil bath in presence of anhydrous $ZnCl_2$ (0.136 g, 0.001 mol) for 2–3 h (TLC check, chloroform: methanol, 9:1). The residue was dispersed in cold water and titrated to pH 12–13 by adding 20% NaOH (5 mL). The solid product separated was filtered, washed with water, dried, and purified by column chromatography eluting with chloroform: methanol (9:1) gave **3a–b** and **4a–b** in 20–25% and 68–70% yields, respectively.

Scheme 2



9, 12	Ar
a	4-ClC_6H_4
b	2,4-di$MeOC_6H_3$
c	4-$NO_2C_6H_4$

11	R^1
a	CH_3
b	C_6H_5
c	CH_2Cl
d	$CH_2CH_2CH_2Cl$

4-Amino-3-(4-chlorophenyl)-6,7-dihydro-5H-cyclopenta[b]-thieno[3,2-e]pyridine-2-carbonitrile (3a). This compound was obtained as faint brown amorphous solid, 0.081 g (25%), mp 249–251°C; IR: 3540m, 3430m, 2210m, 1626s cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (m, 2H, CH_2), 2.73–2.98 (m, 4H, $2CH_2$), 5.92 (bs, 2H, NH_2), 7.62 (d, J = 7.8 Hz, 2H, Ar-H), 7.69 (d, J = 7.8 Hz, 2H, Ar-H); ms: m/z 325 (M^+, 100%), 327 (M+2, 33%). *Anal.* Calcd. for $C_{17}H_{12}ClN_3S$ (325.04): C, 62.67; H, 3.71; N, 12.90. Found: C, 62.53; H, 3.60; N, 12.76.

4-Amino-3-(4-chlorophenyl)-5,6,7,8-tetrahydrothieno[2,3-b]-quinoline-2-carbonitrile (3b). This compound was obtained as an off white amorphous solid, 0.068 g (20%), mp 260–261°C; IR: 3500m, 3392m, 2937s, 2208m, 1624m cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.83–1.98 (m, 4H, $2CH_2$), 2.41 (t, J = 5.3 Hz, 2H, CH_2), 2.95 (t, J = 5.3 Hz, 2H, CH_2), 4.37 (bs, 2H, NH_2), 7.43 (d, J = 8.2 Hz, 2H, Ar-H), 7.57 (d, J = 8.2 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 22.3, 22.4, 22.8, 33.4, 102.5, 111.4, 114.3, 114.5, 129.6, 130.5, 131.9, 136.1, 144.4, 148.0, 159.4, 160.6; ms: m/z 339 (M^+, 100%), 341 (M+2, 33%). *Anal.* Calcd. for $C_{18}H_{14}ClN_3S$ (339.06): C, 63.62; H, 4.15; N, 12.36. Found: C, 63.50; H, 4.24; N, 12.18.

5′-(4-Chlorophenyl)-4′-imino-1′,4′-dihydrospiro[cyclopentane-1,2′-thieno[2,3-d][1,3]oxazine]-6′-carbonitrile (4a). This compound was obtained as an off white amorphous solid, 0.233 g (68%), mp 244–246°C; IR: 3168m, 2935s, 2205m, 1669s, 1620m cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.04–2.50 (m, 4H, $2CH_2$), 2.64–2.87 (m, 4H, $2CH_2$), 4.93 (bs, 1H, NH), 6.50 (bs, 1H, NH), 7.48 (d, J = 8.4 Hz, 2H, Ar-H), 7.60 (d, J = 8.4 Hz, 2H, Ar-H); ms: m/z 343 (M^+, 100%), 345 (M+2, 33%). *Anal.* Calcd. for $C_{17}H_{14}ClN_3OS$ (343.05): C, 59.38; H, 4.10; N, 12.22. Found: C, 59.24; H, 4.22; N, 12.35.

5′-(4-Chlorophenyl)-4′-imino-1′,4′-dihydrospiro[cyclohexane-1,2′-thieno[2,3-d][1,3]oxazine]-6′-carbonitrile (4b). This compound was obtained as an off white amorphous solid, 0.250 g (70%), mp 252–253°C; IR: 3180m, 2934s, 2209m, 1663s, 1626m cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80−1.85 (m, 4H, $2CH_2$), 2.34 (m, 2H, CH_2), 2.92 (t, J = 5.4 Hz, 2H, CH_2), 4.04 (t, J = 5.4 Hz, 2H, CH_2), 5.16 (bs, 1H, NH), 6.13 (bs, 1H, NH), 7.47 (d, J = 8.2 Hz, 2H, Ar-H), 7.56 (d, J = 8.2 Hz, 2H, Ar-H); ms: *m/z* 357 (M^+, 100%), 359 (M+2, 33%). *Anal.* Calcd. for $C_{18}H_{16}ClN_3OS$ (357.07): C, 60.41; H, 4.51; N, 11.74. Found: C, 60.59; H, 4.71; N, 11.60.

5-(4-Chlorophenyl)-3,4-dihydro-4-oxothieno[2,3-d]pyrimidine-6-carboxamide (5). Compound **1** (0.259 g, 0.001 mol) in formic acid (5 mL) was refluxed for 12 h (TLC check, chloroform: methanol, 8:1). On cooling to room temperature, the obtained residue was filtered, washed thoroughly with water, dried, and purified by column chromatography (silica gel 5–20 μm) in chloroform: methanol (8:1) as an eluent to afford pale yellow crystals, 0.244 g (80%), mp 265–266°C; IR: 3400m, 3302m, 3263m, 1668s, 1641m cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.40–6.56 (bs, 2H, amide NH_2), 7.27 (d, J = 8.4 Hz, 2H, Ar-H), 7.44 (d, J = 8.4 Hz, 2H, Ar-H), 8.42 (s, 1H, CH), 11.41 (bs, 1H, NH); ms: *m/z* 305 (M^+, 100%), 307 (M+2, 33%). *Anal.* Calcd. for $C_{13}H_8ClN_3O_2S$ (305.00): C, 51.07; H, 2.64; N, 13.74. Found: C, 51.19; H, 2.79; N, 13.59.

***N*-(4-(4-Chlorophenyl)-3,5-dicyanothiophen-2-yl)acetamide (6).** To a mixture of **1** (0.259 g, 0.001 mol) and acetic anhydride (5 mL), a drop of conc. H_2SO_4 was added and then stirred at room temperature for 1 h (TLC check, chloroform: methanol, 8:2). Resulting reaction mixture was poured over crushed ice and stirred overnight. The separated solid was filtered, washed with cold water, dried under vacuum, and crystallized with ethanol: DMF (2:1) afforded pale yellow amorphous solid, 0.287 g (90%), mp 298–300°C; IR: 3267m, 2212m, 2216m, 1703s, 1625m cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.31 (s, 3H, CH_3), 7.64 (d, J = 8.7 Hz, 2H, Ar-H), 7.73 (d, J = 8.7 Hz, 2H, Ar-H), 12.63 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 22.3, 92.7, 96.4, 112.9, 113.7, 129.0, 129.4, 130.3, 135.0, 147.8, 153.1, 170.2; ms: *m/z* 301(M^+, 100%), 303 (M+2, 33%). *Anal.* Calcd. for $C_{14}H_8ClN_3OS$ (301.10): C, 55.72; H, 2.67; N, 13.93. Found: C, 55.66; H, 2.52; N, 13.75.

(E)-*N*′-(4-(4-chlorophenyl)-3,5-dicyanothiophen-2-yl)-*N*,*N*-dimethylformamidine (7). Compound **1** (0.259 g, 0.001 mol) in dry *p*-xylene (5 mL) and (0.133 mL, 0.001 mol) DMF-DMA was refluxed for 3 h (TLC check, chloroform: methanol 8:2). After evaporating the solvent *in vacuo*, the obtained residue was stirred in hexane for 1 h and filtered, dried, and recrystallized from ethanol: DMF (2:1) gave yellow amorphous solid, 0.283 g (90%), mp 210–211°C; IR: 3312m, 2950s, 2208m, 2210m, 1625m cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.21−3.23 (bs, 6H, $2CH_3$), 7.50 (d, J = 8.4 Hz, 2H, Ar-H), 7.61 (d, J = 8.4 Hz, 2H, Ar-H), 7.84 (s, 1H, CH); ms: *m/z* 315 (M+1, 100%), 317 (M+2, 33%). *Anal.* Calcd. for $C_{15}H_{11}ClN_4S$ (314.04): C, 57.23; H, 3.52; N, 17.80. Found: C, 57.40; H, 3.41; N, 17.78.

3-Amino-5-(4-chlorophenyl)-4-imino-3,4-dihydrothieno[2,3-d]pyrimidine-6-carbonitrile (8). A mixture of **7** (0.314 g, 0.001 mol), hydrazine hydrate (0.05 mL, 0.001 mol) in absolute ethanol (10 mL) was refluxed for 6 h (TLC check, chloroform: methanol 8:2). The solvent was evaporated *in vacuo* to give solid residue, which was filtered, washed with cold ethanol, and dried to afford analytically pure pale yellow amorphous solid, 0.24 g (80%), mp 302–304°C; IR: 3381s, 3306s, 3205m, 2200m, 1637 cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.59 (s, 2H, NH_2), 6.40 (s, 1H, NH), 7.45 (d, J = 8.3 Hz, 2H, Ar-H), 7.51 (d, J = 8.3 Hz, 2H, Ar-H), 8.42 (s, 1H, CH); ms: *m/z* 301 (M^+, 100%), 303 (M+2, 33%). *Anal.* Calcd. for $C_{13}H_8ClN_5S$ (301.02): C, 51.74; H, 2.67; N, 23.21. Found: C, 51.56; H, 2.51; N, 23.11.

General procedure for the synthesis of compounds 9a–c. To a mixture of compound **2** (0.295 g, 0.001 mol) and aromatic aldehyde (0.001 mol) in dry acetonitrile (5 mL), iodine (0.14 g, 0.0011 mol) was added. The mixture was refluxed for 8–10 h (TLC check, chloroform: methanol (8:2) as an eluent. After reaction was completed, the mixture was cooled to room temperature. An aqueous solution of sodium thiosulphate (5%, 5 mL) was added, and the resulted solid was filtered off, dried, and washed with water. The crude product was purified by column chromatography (silica gel 5–20 μm) in chloroform: methanol (8:2) as an eluent.

2,5-Di(4-chlorophenyl)-3,4-dihydro-4-oxothieno[2,3-d]pyrimidine-6-carboxamide (9a). This compound was obtained as colorless amorphous solid, 0.269 g (65%), mp 340–342°C; IR: 3470m, 3330m, 3308m, 1686s, 1639m cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.40–6.50 (bs, 2H, amide NH_2), 7.43 (d, J = 8.1 Hz, 2H, Ar-H), 7.52 (d, J = 8.1 Hz, 2H, Ar-H), 7.53 (d, J = 8.3 Hz, 2H, Ar-H), 8.02 (d, J = 8.3 Hz, 2H, Ar-H), 11.98 (bs, 1H, NH); ms: *m/z* 415 (M^+, 100%), 417 (M+2, 65%), 419 (M+4, 11%). *Anal.* Calcd. for $C_{19}H_{11}Cl_2N_3O_2S$ (417.01): C, 54.82; H, 2.66; N, 10.09. Found: C, 54.64; H, 2.79; N, 9.99.

5-(4-Chlorophenyl)-3,4-dihydro-2-(2,4-dimethoxyphenyl)-4-oxothieno[2,3-d]pyrimidine-6-carboxamide (9b). This compound was obtained as off white amorphous solid, 0.299 g (68%), mp 336–337°C; IR: 3470m, 3332m, 3313m, 1688s, 1638m, 1240m cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.53–7.62 (bs, 2H, amide NH_2), 6.67–6.70 (m, 2H, Ar-H), 7.39 (d, J = 8.5 Hz, 2H, Ar-H), 7.46 (d, J = 8.5 Hz, 2H, Ar-H), 7.79 (d, 1H, Ar-H), 11.87 (s, 1H, NH); ms: *m/z* 441(M^+, 100%), 443 (M+2, 33%). *Anal.* Calcd. for $C_{21}H_{16}ClN_3O_4S$ (441.06): C, 57.08; H, 3.65; N, 9.51. Found: C, 57.18; H, 3.59; N, 9.62.

5-(4-Chlorophenyl)-3,4-dihydro-2-(4-nitrophenyl)-4-oxothieno[2,3-d]pyrimidine-6-carboxamide (9c). This compound was obtained as yellow amorphous solid, 0.282 g (66%), mp 345–346°C; IR: 3474m, 3341m, 3318m, 1684s, 1638m, 1530m, 1320s cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.67–7.70 (bs, 2H, amide NH_2), 7.41 (d, J = 8.5 Hz, 2H, Ar-H), 7.48 (d, J = 8.5 Hz, 2H, Ar-H), 8.36 (d, J = 9.0 Hz, 2H, Ar-H), 8.38 (d, J = 9.0 Hz, 2H, Ar-H), 12.99 (bs, 1H, NH); ms: *m/z* 428 (M^+, 100%), 430 (M+2, 33%). *Anal.* Calcd. for $C_{19}H_{11}ClN_4O_4S$ (428.03): C, 53.46; H, 2.60; N, 13.13. Found: C, 53.58; H, 2.49; N, 13.09.

General procedure for the synthesis of 10a–b. Stoichiometric amounts of **2** (0.295 g, 0.001 mol) and cyclohexanone/cyclopentanone (0.001 mol) in a round-bottomed flask (10 mL) sealed with a teflon cap were vigorously stirred for 2–3 h (TLC check, chloroform: methanol, 8:2). After standing overnight at room temperature, the solid separated was then stirred in diethyl ether (5 mL) for 1 h. It was then filtered, dried, and without any further purification directly analyzed by spectroscopic methods.

5′-(4-Chlorophenyl)-3′,4′-dihydro-4′-oxo-1′H-spiro[cyclopentane-1,2′-thieno[2,3-d]pyrimidine]-6′-carboxamide (10a). This compound was obtained as white amorphous solid, 0.353 g (98%), mp 264–265°C; IR: 3490m, 3469m, 3380m, 3290m, 3312m, 2935s, 1660s, 1630m cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.90–1.92 (m, 4H, $2CH_2$), 2.18–2.24 (m, 4H, $2CH_2$), 6.47 (bs, 2H, amide NH_2), 7.32 (d, J = 8.3 Hz, 2H, Ar-H), 7.50 (d, J = 8.3 Hz, 2H, Ar-H), 7.52 (bs, 1H, NH), 8.26 (bs, 1H, NH); ms: *m/z* 361 (M^+, 100%), 363 (M+2, 33%). *Anal*. Calcd. for $C_{17}H_{16}ClN_3O_2S$ (361.07): C, 56.43; H, 4.46; N, 11.61. Found: C, 56.34; H, 4.59; N, 11.51.

5′-(4-Chlorophenyl)-3′,4′-dihydro-4′-oxo-1′H-spiro[cyclohexane-1,2′-thieno[2,3-d]-pyrimidine]-6′-carboxamide (10b). This compound was obtained as white amorphous solid, 0.371 g (99%), mp 240–242°C; IR: 3498m, 3473m, 3381m, 3288m, 3213m, 2937s, 1654s, 1629m cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.19–1.48 (m, 4H, 2 CH_2), 1.76–1.87 (m, 4H, 2 CH_2), 2.25 (m, 2H, CH_2), 5.37 (bs, 1H, NH), 7.18–7.38 (bs, 2H, amide NH_2), 7.27 (d, J = 8.3 Hz, 2H, Ar-H), 7.44 (d, J = 8.3 Hz, 2H, Ar-H), 8.30 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 20.9, 24.4, 26.3, 36.3, 41.2, 70.3, 110.1, 117.7, 127.8, 131.0, 132.3, 134.1, 139.6, 159.1, 160.3, 163.0; ms: *m/z* 375 (M^+, 100%), 377 (M+2, 33%). *Anal*. Calcd. for $C_{18}H_{18}ClN_3O_2S$ (375.08): C, 57.52; H, 4.83; N, 11.18. Found: C, 57.46; H, 4.68; N, 11.30.

General procedure for the synthesis of compounds 11a–d. A mixture of **2** (0.295 g, 0.001 mol) and various acid chlorides (0.001 mol) were stirred at 115°C in glacial acetic acid (4 mL) for 10–12 h (TLC check, chloroform: methanol, 8:2). Excess acetic acid was distilled off under vacuum, and residue obtained was poured over crushed ice (15 mL), filtered and dried. The solid was then purified by column chromatography (silica gel 5–20 μm) in chloroform: methanol (8:2) as an eluent.

5-(4-Chlorophenyl)-3,4-dihydro-2-methyl-4-oxothieno[2,3-d]-pyrimidine-6-carboxamide (11a). This compound was obtained as an off white amorphous solid, 0.207 g (65%), mp 277–280°C; IR: 3490m, 3470m, 1668s, 1629m cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.14 (s, 3H, CH_3), 6.32–6.54 (bs, 2H, amide NH_2), 7.34 (d, J = 8.4 Hz, 2H, Ar-H), 7.49 (d, J = 8.4 Hz, 2H, Ar-H), 11.29 (bs, 1H, NH); ms: *m/z* 319 (M^+, 100%), 321 (M+2, 33%). *Anal*. Calcd. for $C_{14}H_{10}ClN_3O_2S$ (319.02): C, 52.59; H, 3.15; N, 13.14. Found: C, 52.48; H, 3.21; N, 13.21.

5-(4-Chlorophenyl)-3,4-dihydro-2-phenyl-4-oxothieno[2,3-d]-pyrimidine-6-carboxamide (11b). This compound was obtained as white amorphous solid, 0.236 g (62%), mp 268–270°C; IR: 3488m, 3468m, 2931s, 1665s, 1624m cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.31–6.56 (bs, 2H, amide NH_2), 7.10–7.40 (m, 5H, Ar-H), 7.45 (d, J = 8.4 Hz, 2H, Ar-H), 7.52 (d, J = 8.4 Hz, 2H, Ar-H), 11.25 (bs, 1H, NH); ms: *m/z* 381 (M^+, 100%), 383 (M+2, 33%). *Anal*. Calcd. for $C_{19}H_{12}ClN_3O_2S$ (381.03): C, 59.76; H, 3.17; N, 11.00. Found: C, 59.68; H, 3.28; N, 11.16.

5-(4-Chlorophenyl)-3,4-dihydro-2-(chloromethyl)-4-oxothieno-[2,3-d]pyrimidine6-carboxamide (11c). This compound was obtained as white amorphous solid, 0.246 g (70%), mp 267–269°C; IR: 3489m, 3468m, 1665s, 1630m cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.56 (s, 2H, CH_2), 6.35–6.58 (bs, 2H, amide NH_2), 7.36 (d, J = 8.3 Hz, 2H, Ar-H), 7.52 (d, J = 8.3 Hz, 2H, Ar-H), 12.04 (bs, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 166.0, 164.9, 163.4, 143.2, 136.8, 133.7, 133.1, 131.6, 128.9, 125.6, 120.2, 42.4; ms: *m/z* 353 (M^+, 100%), 355 (M+2, 65%), 357 (M+4, 11%). *Anal*. Calcd. for $C_{14}H_9Cl_2N_3O_2S$ (352.98): C, 47.47; H, 2.56; N, 11.86. Found: C, 47.31; H, 2.42; N, 11.76.

5-(4-Chlorophenyl)-3,4-dihydro-2-(3-chloropropyl)-4-oxothieno-[2,3-d]pyrimidine-6-carboxamide (11d). This compound was obtained as colorless amorphous solid, 0.247 g (65%), mp 274–275°C; IR: 3456m, 3356m, 3311m, 3169m, 1672s, 1649m cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.15–2.17 (m, 4H, $2CH_2$), 3.31 (m, 2H, CH_2), 6.51–7.39 (bs, 2H, amide NH_2), 7.36 (d, J = 8.3 Hz, 2H, Ar-H), 7.52 (d, J = 8.3 Hz, 2H, Ar-H), 11.30 (bs, 1H, NH); ms: *m/z* 381 (M^+, 100%), 383 (M+2, 65%), 385 (M+4, 11%). *Anal*. Calcd. for $C_{16}H_{13}Cl_2N_3O_2S$ (381.01): C, 50.27; H, 3.43; N, 10.99. Found: C, 50.19; H, 3.19; N, 10.85.

General procedure for the synthesis of compounds 12a–c. A mixture of compound **2** (0.295 g, 0.001 mol) and aromatic aldehyde (0.001 mol) in ethanol (10 mL) with catalytic amount of piperidine was refluxed in oil bath with stirring for 10–12 h (TLC check, chloroform: methanol, 8:2). The reaction mixture was cooled and stirred in crushed ice (25 mL). The residue obtained was filtered and purified by column chromatography (silica gel 5–20 μm) in chloroform: methanol (8:2) as an eluent.

2,5-Di-(4-chlorophenyl)-1,2,3,4-tetrahydro-4-oxothieno[2,3-d]-pyrimidine-6-carboxamide (12a). This compound was obtained as colorless amorphous solid, 0.242 g (52%), mp 310–312°C; IR: 3475m, 3327m, 3308m, 1689s, 1641s cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.82 (s, 1H, CH), 6.31–6.48 (bs, 2H, amide NH_2), 7.42 (d, J = 8.1 Hz, 2H, Ar-H), 7.49 (d, J = 8.1 Hz, 2H, Ar-H), 7.62 (d, J = 8.4 Hz, 2H, Ar-H), 8.4 (bs, 1H, NH), 8.16 (d, J = 8.4 Hz, 2H, Ar-H), 12.76 (bs, 1H, NH); ms: *m/z* 417 (M^+, 100%), 419 (M+2, 65%), 421 (M+4, 11%). *Anal*. Calcd. for $C_{19}H_{13}Cl_2N_3O_2S$ (417.01): C, 54.56; H, 3.13; N, 10.05. Found: C, 54.64; H, 3.24; N, 9.89.

5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2-(2,4-dimethoxyphenyl)-4-oxothieno[2,3-d]-pyrimidine-6-carboxamide (12b). This compound was obtained as pale green amorphous solid, 0.243 g (55%), mp 330–332°C; IR: 3472m, 3330m, 3310m, 1687s, 1641m, 1242m cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.86 (s, 1H, CH), 6.52–7.11 (bs, 2H, amide NH_2), 6.65–6.80 (m, 2H, Ar-H), 7.72 (d, 1H, Ar-H), 8.21 (d, J = 8.3 Hz, 2H, Ar-H), 8.32 (d, J = 8.3 Hz, 2H, Ar-H), 8.50 (bs, 1H, NH), 9.78 (bs, 1H, NH); ms: *m/z* 441 (M^+, 100%), 443 (M+2, 33%). *Anal*. Calcd. for $C_{21}H_{18}ClN_3O_4S$ (441.06): C, 56.82; H, 4.09; N, 9.47. Found: C, 56.95; H, 4.21; N, 9.35.

5-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2-(4-nitrophenyl)-4-oxothieno[2,3-d]pyrimidine-6-carboxamide (12c). This compound was obtained as yellow amorphous solid, 0.236 g (55%), mp 329–330°C; IR: 3476m, 3339m, 3315m, 1687s, 1640m, 1531m, 1323s cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.60–7.20 (bs, 2H, amide NH_2), 6.65 (s, 1H, CH), 7.25 (d, J = 8.4 Hz, 2H, Ar-H), 7.32 (d, J = 8.4 Hz, 2H, Ar-H), 7.82 (d, J = 8.9 Hz, 2H, Ar-H), 8.16 (d, J = 8.9 Hz, 2H, Ar-H), 8.52 (bs, 1H, NH), 11.08 (bs, 1H, NH); ms: *m/z* 429 (M^+, 100%), 431 (M+2, 33%). *Anal*. Calcd. for $C_{19}H_{13}ClN_4O_4S$ (429.04): C, 53.21; H, 3.06; N, 13.06. Found: C, 53.37; H, 3.24; N, 12.90.

Acknowledgments. The authors gratefully acknowledge the support for this research by UGC and CSIR New Delhi and University of Pune for spectroscopic analysis and Principal KTHM College, Nashik-02 for facilities.

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