Chemical Science Review and Letters ISSN 2278-6783

Research Article

5-(1-Pyrrolyl)-thieno[2,3-*d*]pyrimidine as Building Block in Heterocyclic Synthesis: Synthesis of some new 6-Substituted 5- (1-pyrrolyl)-thieno[2,3-*d*]pyrimidines and 5(4)-Substituted pyrimido-[2,3:4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine Derivatives

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Abstract

Diazotization of 6-carbohydrazide-5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidine **1** with nitrous acid the key intermediate 6-azidocarbonyl-5-(1-pyrrolyl)-thieno[2,3-*d*]- pyrimidine **2** was obtained. A series of novel 6-substituted 5-(1-pyrrolyl)-thieno- [2,3-*d*]pyrimidines **4a-e, 6a, b** and **8a, b** were synthesized by reaction of carboazide **2** with appropriate primary amines, alcohols and secondary amines, respectively. Heating of the carboazide **2** at 200 ℃ in *o*-diclorobenzene leads to Curtius rearrangement to afford the tetracyclic product 4,5-dihydro-4-oxo-8-phenylpyrimido- [2,3:4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **11**, which reacted with different reagents under a variety of conditions afforded the corresponding 5(4)-substituted 4-oxo- pyrimido[2,3:4,5]thino[2,3-*e*]pyrrolo[1,2-*a*]pyrazines **16, 17**, **20a, b**, **22**, **24**, **25**, **27a, b**, **30a-c** and **32**. The structures of the newly synthesized compounds were confirmed by IR, 1H NMR, mass spectra and elemental analysis.

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Keywords: Diazotization, 6-azidocarbonyl-5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidine, Curtius rearrangement, 6-substituted 5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidines, 5(4)-substituted 4-oxo-pyrimido[2,3:4,5]thino[2,3-*e*]pyrrolo[1,2-*a*]pyrazine

Introduction

The considerable biological and medicinal activity caused by fused thienopyrimidines has stimulated much research in this field [1-4]. Among the derivatives of thieno[2,3-*d*]pyrimidines, substances have been observed that have antiviral, fungicidal, insecticidal activity [5], antibacterial and antiplastic properties [6], antihypertensive [7], anticonvulsant activity [8] and antihistaminic action [9]. The broad spectrum of biological activity of condensed thienopyrimidines and the possibility of further modification of their cyclic structure makes these compounds extremely attractive for the synthesis of new biologically active molecules. Likewise, several series of heterocyclic compounds possessing a bridgehead pyrrolic moiety play a vital role in many biological activities [10-14]. The incorporation of two moieties increases biological activity of both and thus it was of value to synthesis some new heterocyclic derivatives having two moieties in the same molecules. In recent years, a great deal of work has been directed to the organic synthesis of pyridazines. These nitrogen heterocyclic compounds are of biological importance and therefore, design and strategy for their synthesis is important. Pyridazines possess antibacterial [15-18], antifungal [18, 19], antinociceptive [20, 21] and insecticidal [22] activities. Furthermore, the pyrrolothienopyrazine derivatives also possess a variety of pharmacological activities [23-26]. El Kashef, et al., [27] has recently described the synthesis of benzothio[2,3-*e*]pyrrolo[1,2-*a*]pyrazines from methyl 2-amino[1]benzo- thiophene-3-carboxylic acid. In the course of our researches devoted to the development of new classes of heterocycle systems which incorporated the pyrrolothienopyrimidine moiety in the hope that they may be biologically active. In continuation of our studies [28, 29], we report here the synthesis of some new 6-substituted 5-(1-pyrrolyl)-thieno[2,3-d]pyrimidines and 5(4)-substituted 4-oxo- pyrimido[2,3:4,5]thino[2,3-*e*]pyrrolo[1,2-*a*]pyrazine derivatives by making use of 6-carbohydrazide-5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidine **1** as the starting materials.

Experimental

General

All melting points were determined in a capillary tube and were uncorrected. The IR spectra were recorded on potassium bromide pellets on a JASCO FTIR-3 spectrometer. The 1H NMR spectra were obtained on a Bruker AM-300WB FT-NMR spectrometer and chemical shifts were expressed in δ ppm using TMS as an internal standard. Electron impact mass spectra were obtained at 70 eV by using a Finnigan Mat TSQ-46C spectrometer. Microanalyses for C, H, and N were performed on a Perkin-Elmer 240 elemental analyzer. Commercially available reagents were purchased from Aldrich and used directly. Reactions were routinely monitored by thin later chromatography (TLC) on silica gel (precoated F245 Merck plates).

Synthesis of 6-azidocarbonyl-5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-d]- pyrimidine (2).

A stirred mixture of carbohydrazide **1** (3.49 g, 0.01 mol) was dissolved in hydrochloride acid (10 mL) and glacial acetic acid (10 ml) and the solution was then cooled to 0 −5oC with stirring. Sodium nitrite (0.7 g, 0.01 mol) in water (5 mL) was gradually added to this solution over 3 min at 0−5oC with stirring. The reaction mixture was then stirred 2 h at 0−5oC. After the addition of ice and water the solid product was collected by filtration, washed with water, to give 3.13 g of pale yellow product (87% yield), mp 257℃(dec); IR: ν 2154 (N3), 1668 (CO) cm-1. MS: 360 (M+). Anal. Calcd. for C18H12N6OS: C, 60.00; H, 3.33; N, 23.33. Found: C, 60.39; H, 3.44; N, 23.47 %.

General procedure for synthesis of N,N'-disubstituted urea derivatives of 4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-d]pyrimidines (4a-d).

A mixture of carboazide **2** (0.36 g, 1 mmol) and appropriate amine compounds (ethylamine **3a**, propylamine **3b**, butylamine **3c** and aniline **3d**) (8 mL) was refluxed for 4 h. A crystalline solid was obtained on cooling. It was recrystallized from an appropriate solvent.

6-Ethylurea-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-d]pyrimidine (4a).

Recrystallized from THF/ethanol to give 0.21 g (56 % yield) of **4a**, mp 250℃; IR: ν 3358 (NH), 1650 (CO) cm-1; 1H NMR (CF3COOD): δ 1.16 (3H, t, J = 2.0 Hz, CH2CH3), 2.71 (3H, s, CH3), 3.48 (2H, q, J = 2.0 Hz, CH2CH3), 6.85 (2H, m, 3,4-H of pyrrolyl), 7.08 (2H, m, 2,5-H of pyrrolyl), 8.39-8.35, 7.78-7.75 (5H, m, phenyl-H), 7.92 (1H, br, NH), 8.46 (1H, br, NH); MS: 377(M+,40), 362(100), 319(40), 290(78), 277(8), 214(4), 185(12), 160(11), 142(8), 104(9), 77(11), 51(4). Anal. Calcd. for C20H19N5OS: C, 63.66; H, 5.04; N, 18.56. Found: C, 63.59; H, 5.12; N, 18.50 %.

4-Methyl-5-(1-pyrrolyl)-6-propylurea-2-phenylthieno[2,3-d]pyrimidine (4b).

Recrystallized from THF/ethanol to give 0.19 g (49 % yield) of **4b**, mp 238℃; IR: ν 3362 (NH), 1655 (CO) cm-1; 1H NMR (CF3COOD): δ 0.93 (3H, t, J = 2.0 Hz, CH2CH2CH3), 1.56-1.49 (2H, m, CH2CH2CH3), 2.46 (3H, s, CH3), 3.39 (2H, t, J = 1.4 Hz, CH2CH2CH3), 6.82 (2H, m, 3,4-H of pyrrolyl), 7.06 (2H, m, 2,5-H of pyrrolyl), 8.45-8.43, 7.74-7.68 (5H, m, phenyl-H), 7.88 (1H, br, NH), 8.26 (1H, br, NH); MS: 391(M+,38), 376(100), 319(74), 290(100), 277(14), 223(5), 187(18), 160(19), 143(8), 104(48), 77(37), 51(8). Anal. Calcd. for C21H21N5OS: C, 64.45; H, 5.37; N, 17.90. Found: C, 64.52; H, 5.30; N, 17.95 %.

6-Butylurea-4-methyl-5-(1-pyrrolyl)-2-phenylthieno[2,3-d]pyrimidine (4c).

Recrystallized from THF/ethanol to give 0.20 g (49 % yield) of **4c**, mp 212℃; IR: ν 3409 (NH), 1653 (CO) cm-1; 1H NMR (CDCl3): δ 0.85 (3H, t, J = 2.0 Hz, CH2 (CH2)2CH3), 1.31-1.14 (4H, m, CH2(CH2)2CH3), 3.20 (2H, t, J = 2.0 Hz, CH2(CH2)2CH3), 2.20 (3H, s, CH3), 6.53 (2H, m, 3,4-H of pyrrolyl), 6.85 (2H, m, 2,5-H of pyrrolyl), 8.53-8.51, 7.49-7.47 (5H, m, phenyl-H), 7.87 (1H, br, NH), 8.24 (1H, br, NH); MS: 405(M+,58), 390(100), 376(4), 362(4), 348(8), 333(18), 319(48), 290(52), 277(10), 244(4), 187(8), 185(5), 103(3). Anal. Calcd. for C22H23N5OS: C, 65.18; H, 5.67; N, 17.28. Found: C, 65.22; H, 5.48; N, 17.25 %.

4-Methyl-5-(1-pyrrolyl)-6-phenylurea-2-phenylthieno[2,3-d]pyrimidine (4d).

Recrystallized from THF/benzene to give 0.22 g (52 % yield) of **4d**, mp 242℃; IR: ν 3377 (NH), 1691 (CO) cm-1; 1H NMR (DMSO-d6): δ 2.17 (3H, s, CH3), 6.38 (2H, m, 3,4-H of pyrrolyl), 6.82 (2H, m, 2,5-H of pyrrolyl), 8.46-8.35, 7.39-7.18 (10H, m, phenyl-H), 9.05 (1H, br, NH), 9.22 (1H, br, NH); MS: 425(M+,40), 332(23), 306(100), 291(4), 277(14), 229(2), 202(8), 175(12), 142(5), 120(10), 104(11), 92(14), 77(22), 65(5). Anal. Calcd. for C24H19N5OS: C, 67.76; H, 4.47; N, 16.47. Found: C, 67.77; H, 4.48; N, 16.45 %.

Synthesis of 4-methyl-5-(1-pyrrolyl)- 6-urea-2-phenylthieno[2,3-d]pyrimidine (4e).

A mixture of carboazide **2** (0.36 g, 1 mmol), ammonium hydroxide (20 mL) in chloroform (20 mL) was refluxed for 4 h. After cooling, the resulting solid product was collected by filtration, washed with water, and the crude product recrystallized from THF/ethanol to give 0.14 g (40 % yield), mp 295℃; IR: ν 3410 (NH2), 3359(NH), 1697 (CO) cm-1; 1H NMR (CF3COOD): δ 2.66 (3H, s, CH3), 6.81 (2H, m, 3,4-H of pyrrolyl), 7.06 (2H, m, 2,5-H of pyrrolyl), 8.37-8.35, 7.77-7.74 (5H, m, phenyl-H); MS: 349(M+,45), 334(100), 316(38), 289(80), 278(5), 214(4), 185(16), 167(7), 104(7), 77(9), 51(4). Anal.

Calcd. for C18H15N5OS: C, 61.89; H, 4.29; N, 20.05. Found: C, 61.85; H, 4.32; N, 20.14 %.

General procedure for synthesis of 6-alkyl carbonylamino-5-(1-pyrrolyl)- 4-methyl-2-phenylthieno[2,3-d]pyrimidines (6a, b).

A mixture of carboazide **2** (0.36 g, 1 mmol) and appropriate alcohols (ethanol **5a** and butanol **5b**) (10 mL) was refluxed for 10 h. A crystalline solid was obtained on cooling. It was recrystallized from an appropriate solvent.

6-Ethylcarbonylamino-5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-d]pyrimidine (6a).

Recrystallized from THF/ethanol to give 0.20 g (53 % yield) of **6a**, mp 218℃; IR: ν 3409 (NH), 1731 (CO) cm-1; 1H NMR (CF3COOD): δ 1.86 (3H, t, J = 3.0 Hz, OCH2CH3), 2.68 (3H, s, CH3), 4.01 (2H, q, J = 4.8 Hz, OCH2CH3), 6.77 (2H, m, 3,4-H of pyrrolyl), 7.02 (2H, m, 2,5-H of pyrrolyl), 8.64-8.62, 8.30-8.21 (5H, m, phenyl-H), 9.03 (1H, br, NH); MS: 378(M+,100), 332(8), 305(87), 290(15), 278(19), 264(15), 202(10), 175(12), 142(8), 116(4), 77(7), 51(2). Anal. Calcd. for C20H18N4O2S: C, 63.49; H, 4.76; N, 14.81. Found: C, 63.55; H, 4.78; N, 14.88 %.

6-Butylcarbonylamino-5-(1-pyrrolyl)-4-methyl-2-phenylthieno[2,3-d]pyrimidine (6b).

Recrystallized from THF/ethanol to give 0.18 g (44 % yield) of **6b**, mp 185℃; IR: ν 3387 (NH), 1734 (CO) cm-1; 1H NMR (DMSO-d6): δ 0.90 (3H, t, J = 2.0 Hz, CH2(CH2)2CH3), 1.93-1.89 (4H, m, CH2(CH2)2CH3), 3.09 (3H, s, CH3), 3.90 (2H, t, J = 1.0 Hz, CH2(CH2)2CH3), 6.29 (2H, m, 3,4-H of pyrrolyl), 6.76 (2H, m, 2,5-H of pyrrolyl), 8.38-8.36, 7.38 (5H, m, phenyl-H), 10.02 (1H, br, NH); MS: 406(M+,100), 350(20), 306(68), 290(3), 278(14), 264(7), 202(1), 175(1), 142(1), 51(1). Anal. Calcd. for C22H22N4O2S: C, 65.02; H, 5.41; N, 13.79. Found: C, 65.23; H, 5.41; N, 13.88 %.

General procedure for synthesis of 6-piperidyl(morpholinyl)amido-5-(1-pyrrolyl)- 4-methyl-2-phenylthieno[2,3-d]pyrimidines (8a, b).

These compounds were synthesized from carboazide **2** (0.36 g, 1 mmol) and piperidine **7a** (morpholine **7b**) (10 mL) in a manner similar to that described for the preparation of **6a, b** followed by recrystallization.

4-Methyl-6-piperidylamido-5-(1-pyrrolyl)-2-phenylthieno[2,3-d]pyrimidine (8a).

Recrystallized from THF/dioxane to give 0.30 g (72 % yield) of **8a**, mp 121℃; IR: ν 3354 (NH), 1636 (CO) cm-1; 1H NMR (DMSO-d6): δ 2.19 (3H, s, CH3), 3.47-2.97, 1.74-1.25 (10H, m, piperidyl-H), 6.26 (2H, m, 3,4-H of pyrrolyl), 6.77 (2H, m, 2,5-H of pyrrolyl), 7.46 (1H, br, NH), 8.43-8.42, 7.41-7.40 (5H, m, phenyl-H); MS: 417(M+,10), 402(62), 333(40), 319(100), 290(97), 277(17), 264(7), 213(9), 187(12), 160(8), 116(2), 84(9). Anal. Calcd. for C23H23N5OS: C, 66.18; H, 5.51; N, 16.78. Found: C, 66.23; H, 5.51; N, 16.88 %.

4-Methyl-6-morpholinylamido-5-(1-pyrrolyl)-2-phenylthieno[2,3-d]pyrimidine (8b).

Recrystallized from THF/dioxane to give 0.22 g (53 % yield) of **8b**, mp 180℃; IR: ν 3298 (NH), 1637 (CO) cm-1; 1H NMR (DMSO-d6): δ 2.22 (3H, s, CH3), 3.82-3.12 (8H, m, morpholinyl-H), 6.30 (2H, m, 3,4-H of pyrrolyl), 6.78 (2H, m, 2,5-H of pyrrolyl), 7.45 (1H, br, NH), 8.44-8.41, 7.41-7.40 (5H, m, phenyl-H); MS: 419(M+,38), 404(62), 333(29), 319 (100), 290(58), 277(17), 264(2), 214(9), 187(11), 160 (4), 103(2). Anal. Calcd. for C22H21N5O2S: C, 63.00; H, 5.01; N, 16.70. Found: C, 63.02; H, 5.11; N, 16.78 %.

Synthesis of 4,5-dihydro-10-methyl-4-oxo-8-phenylpyrimido[2,3:4,5]thieno[2,3-e]- pyrrolo[1,2-a]pyrazine (11).

Method A

A solution of carboazide **2** (0.36 g, 1 mmol) in *o*-dichlorobenzene (6 ml) is heated at reflux temperature (200 ℃) for 2 h and then allowed to cool. The precipitated product is isolated by suction, washed with ethanol and water, and the crude product recrystallized from DMF to give 0.31 g of needles (93 % yield), mp >330℃; IR: ν 3345 (NH), 1645 (C=O) cm-1; 1H NMR (CF3COOD): δ 3.55 (3H, s, CH3), 4.63 (1H, br, NH), 7.64 (1H, m, 2-H), 7.82-7.78 (2H, m, 1-H, 3-H), 8.92-8.79 (5H, m, phenyl-H); MS: 332(M+,100), 318(18), 289(30), 278(17), 263(4), 229(14), 212(9), 185(11), 175(18), 143(10), 104(49), 77(34), 69(14). Anal. Calcd. for C18H12N4OS: C, 65.06; H, 3.61; N, 16.86. Found: C, 65.12; H, 3.06; N, 16.86 %.

Method B

A mixture of carboazide **2** (0.36 g, 1 mmol) and glacial acetic acid (10 ml) was refluxed for 4 h and then allowed to cool. The precipitated product is isolated by suction, washed with ethanol and water, and the crude product recrystallized to give 0.30 g (90 % yield).

Synthesis of 5,10-dimethyl-4-oxo-8-phenylpyrimido[2,3:4,5]thieno[2,3-e]pyrrolo- [1,2-a]pyrazine (16).

A mixture of oxopyrazine **11** (0.33 g, 1 mmol), methyl iodide (0.5 g, 3.5 mmol), anhydrous potassium hydroxide (0.56 g, 1 mmol) and dry DMF (10 mL) was stirred at room temperature for 24 h. The precipitated product was collected and recrystallized from DMF/acetic acid to give 0.25 g of needles (72 % yield),

mp 232 ℃ ; IR: ν 1689 (C=O) cm-1; 1H NMR (CF3COOD): δ 3.60 (3H, s, CH3), 4.03 (3H, s, N-CH3), 7.05 (1H, m, 2-H), 8.39-8.37, 7.79-7.74 (6H, m, 3-H and phenyl-H), 8.28 (1H, d, J = 1.5 Hz, 1-H); MS: 346(M+,54), 331(2), 289(30), 243(40), 229(12), 200(13), 173(24), 142(8), 104(100), 94(37), 77(36), 51(20). Anal. Calcd. for C19H14N4OS: C, 65.89; H, 4.04; N, 16.18. Found: C, 65.91; H, 4.00; N, 16.28 %.

Synthesis of 5-acetyl-10-methyl-4-oxo-8-phenyl-pyrimido[2,3:4,5]thieno[2,3-e]- pyrrolo[1,2-a]pyrazine (17).

A mixture of oxopyrazine **11** (0.33 g, 1 mmol) and acetic anhydride (8 mL) was refluxed in pyridine (8 mL) for 24 h. After cooling, the resulting solid product was collected by filtration, washed with water, and the crude product recrystallized from ethanol/acetic acid to give 0.29 g of needles (77 % yield), mp 280℃; IR: ν 1684 (C=O) cm-1; 1H NMR (CF3COOD): δ 2.78 (3H, s, COCH3), 3.65 (3H, s, CH3), 8.43 (1H, dd, J = 1.0, 1.0 Hz, 2-H), 9.71-9.70, 9.27-9.05 (6H, m, 3-H and phenyl-H), 9.51 (1H, d, J = 1.5 Hz, 1-H); MS: 374(M+,8), 331(100), 303(6), 244(4), 229(17), 200(10), 175(8), 142(7), 104(9), 92(8), 77(5), 51(2). Anal. Calcd. for C20H14N4O2S: C, 64.17; H, 3.74; N, 14.97. Found: C, 64.12; H, 3.55; N, 14.89 %.

Synthesis of 5-piperidino(morpholino)methylene-10-methyl-4-oxo-8-phenyl- pyrimido[2,3:4,5]thieno[2,3-e]pyrrolo[1,2-a]pyrazine (20a,b) General procedure.

A mixture of oxopyrazine **11** (0.33 g, 1 mmol), piperidine **19a** (morpholine **19b**) (8 mmol), formaldehyde (10 mL of a 40 % aqueous solution), and DMF (10 mL) was stirred. The reaction mixture was left at room temperature for 24 h and the resulting precipitate filtered, washed with petroleum ether, and the crude product recrystallized from an appropriate solvent.

5-Piperidinomethylene-10-methyl-4-oxo-8-phenyl-pyrimido[2,3:4,5]thieno[2,3-e]- pyrrolo[1,2-a]pyrazine (20a).

Recrystallized from THF/dioxane to give 0.33g (78 % yield) of **20a**, mp >330 ℃; IR: ν 1654 (C=O) cm-1; 1H NMR (CF3COOD): δ 4.44-3.50, 2.37-2.20 (10H, m, piperidyl-H), 3.80 (3H, s, CH3), 4.47 (2H, s, N-CH2), 7.29 (1H, dd, J = 1.0, 1.0 Hz, 2-H), 8.67-8.45, 8.07-7.92 (7H, m, 1-H, 3-H and phenyl-H); MS: 429(M+,100). Anal. Calcd. for C24H23N5OS: C, 67.13; H, 5.36; N, 16.31. Found: C, 67.02; H, 5.33; N, 16.25 %.

5-Morpholinomethylene-10-methyl-4-oxo-8-phenyl-pyrimido[2,3:4,5]thieno[2,3-e]- pyrrolo[1,2-a]pyrazine (20b).

Recrystallized from THF/dioxane to give 0.30 g (79 % yield) of **20a**, mp >330 ℃; IR: ν 1656 (C=O) cm-1; 1H NMR (CF3COOD): δ 2.69 (3H, s, CH3), 3.63-3.52 (8H, m, morpholyl-H), 3.82 (2H, s, N-CH2), 7.30 (1H, dd, J = 1.2, 1.0 Hz, 2-H), 8.69-8.56, 8.40-7.97 (7H, m, 1-H, 3-H and phenyl-H); MS: 431(M+,100). Anal. Calcd. for C23H21N5O2S: C, 64.03; H,4.87; N, 16.24. Found: C, 64.02; H, 4.87; N, 16.25 %.

Synthesis of 5-benzyl-10-methyl-4-oxo-8-phenyl-pyrimido[2,3:4,5]thieno[2,3-e]- pyrrolo[1,2-a]pyrazine (22).

To a solution containing oxopyrazine **11** (0.33 g, 1 mmol), was added benzyl chloride **21** (0.13 g, 1 mmol) and potassium hydroxide (0.196 g, 3.5 mmol) in dry DMF (10 mL). The mixture was refluxed for 4 h and poured into ice-water. The precipitated product was collected and recrystallized from DMF/H2O to give 0.35 g (83 % yield), mp 169℃; IR: ν 1654 (C=O) cm-1; 1H NMR (CF3COOD): δ 3.05 (3H, s, CH3), 5.42 (2H, s, NCH2), 7.32 (1H, dd, J = 1.3, 1.6 Hz, 2-H), 7.49-7.30 (11H, m, 3-H and phenyl-H), 8.46 (1H, d, J = 1.9 Hz, 1-H); MS : 422(M+,10), 408(2), 343(11), 332(19), 305(3), 229(5), 200(3), 171(8), 115(3), 104(16), 91(100), 77(12). Anal. Calcd. for C25H18N4OS: C, 71.09; H, 4.26; N, 13.27. Found: C, 71.02; H, 4.33; N, 13.25 %.

Synthesis of 4-chloro-10-methyl-8-phenylpyrimido[2,3:4,5]thieno[2,3-e]pyrrolo- [1,2-a]pyrazine (24).

A mixture of oxopyrazine **11** (0.33 g, 1 mmol) and phosphorus pentachloride (0.31 g, 1.5 mmol) was refluxed in phosphoryl chloride (10 mL) for 10 h. After removing the excess phosphoryl chloride in vacuo, the residual product was worked up in ice-water, the resulting solid product was collected by filtration, washed with water, and the crude product recrystallized from ethanol/THF to give 0.32 g (91 % yield), mp 180℃ ; 1H NMR (DMSO-d6): δ 3.17 (3H, s, CH3), 7.15 (1H, dd, J = 1.0, 1.0 Hz, 2-H), 7.30 (1H, d, J = 1.0 Hz, 3-H), 8.40-8.38, 7.52-7.48 (5H, m, phenyl-H), 8.62 (1H, d, J = 1.0 Hz, 1-H); MS : 350.5(M+,100), 313(18), 273(25), 246(37), 237(15), 210(14), 183(9), 152(8), 137(4), 94(37), 77(2). Anal. Calcd. for C18H11N4ClS: C, 61.62; H, 3.13; N, 15.97. Found: C, 61.66; H, 3.00; N, 16.01 %.

Synthesis of 4-azido-10-methyl-8-phenylpyrimido[2,3:4,5]thieno[2,3-e]pyrrolo- [1,2-a]pyrazine (25).

To a solution of compound **24** (0.1 g, 0.29 mmol) in DMF (5 mLl), sodium azide solution (0.02 g of sodium azide in 2 mL water) was added. The reaction mixture was stirred at room temperature for 3 h. The resulting solid product was collected by filtration and recrystallized from THF, to give 0.09 g (91% yield), mp 206℃; IR: ν 2125 (N3) cm-1; MS : 357(M+,100), 330(7), 314(5), 246(30), 212(7), 170(5), 103(18), 77(12). Anal. Calcd. for C18H11N7S: C, 60.50; H, 3.08; N, 27.45. Found: C, 60.51; H, 3.10; N, 27.41 %.

Synthesis of 4-methoxy-10-methyl-8-phenylpyrimido[2,3:4,5]thieno[2,3-e]pyrrolo- [1,2-a]pyrazine (27a).

A mixture of compound **24** (0.35 g, 1 mmol) and sodium methoxide **26a** (0.07 g, 1.3 mmol) was refluxed in methanol (10 mL) for 6-7 h. After cooling, the mixture poured into water, acidified with hydrochloric acid and the precipitated product was collected by filtration, washed with water, and the crude product recrystallized from ethanol/THF to give 0.26 g (75% yield), mp 196℃; 1H NMR (CDCl3): δ 3.29 (3H, s, CH3), 4.19 (3H, s, OCH3), 6.86 (1H, dd, J = 1.0, 1.0 Hz, 2-H), 7.12 (1H, d, J = 1.1 Hz, 3-H), 8.20 (1H, d, J = 1.0 Hz, 1-H), 8.58-8.54, 7.52-7.50 (5H, m, phenyl-H); MS : 346(M+,100), 332(18), 304(14), 288(9), 244(12), 229(9), 200(5), 173(9), 142(3), 103(24), 94(8), 77(12). Anal. Calcd. for C19H14N4OS: C, 65.89; H, 4.04; N, 16.18. Found: C, 65.94; H, 4.10; N, 16.18 %.

Synthesis of 4-ethoxy-10-methyl-8-phenylpyrimido[2,3:4,5]thieno[2,3-e]pyrrolo- [1,2-a]pyrazine (27b).

This compound was synthesized from compound **24** (0.35 g, 1 mmol) and sodium ethoxide **26b** (0.09 g, 1.3 mmol) and absolute ethanol (10 mL) in a manner similar to that described for the preparation of **27a**. It was recrystallized from ethanol/THF to give 0.23 g (64 % yield), mp 251℃; 1H NMR (CDCl3): δ 1.25 (3H, t, J = 1.4 Hz, OCH2CH3), 2.87 (3H, s, CH3), 4.66 (2H, q, J = 1.4 Hz, OCH2CH3), 6.80 (1H, dd, J = 1.0, 1.0 Hz, 2-H), 7.01 (1H, d, J = 1.0 Hz, 3-H), 8.41 (1H, d, J = 1.0 Hz, 1-H), 8.57-8.55, 7.53-7.51 (5H, m, phenyl-H); MS: 360(M+,100), 345(30), 322(15), 315(14), 303(5), 288(2), 246(33), 210(5), 173(6), 142(2), 103(36), 94(9), 77(20), 51(5). Anal. Calcd. for C20H16N4OS: C, 66.66; H, 4.44; N, 15.55. Found: C, 66.74; H, 4.34; N, 15.59 %.

Synthesis of 4-ethylamino-10-methyl-8-phenylpyrimido[2,3:4,5]thieno[2,3-e]- pyrrolo[1,2-a]pyrazine (30a).

A mixture of compound **24** (0.35 g, 1 mmol) and ethylamine **29a** (10 mL) was refluxed in absolute ethanol (5 mL) for 11 h. After cooling, the mixture poured into water, acidified with hydrochloric acid and the precipitated product was collected by filtration, washed with water, and the crude product recrystallized from ethanol/THF, to give 0.31 g (85 % yield), mp 210 ℃; IR: ν 3425 (NH) cm-1; 1H NMR (DMSO-d6): δ 1.25 (3H, t, J = 1.4 Hz, CH2CH3), 3.08 (3H, s, CH3), 4.10 (2H, q, J = 1.4 Hz, CH2CH3), 7.15 (1H, m, 2-H), 8.42-8.40, 7.51-7.49 (7H, m, 1-H, 3-H and phenyl-H); MS: 359(M+,100), 344(28), 331(60), 317(17), 304(18), 288(3), 241(4), 227(10), 200(12), 179(16), 165(7), 141(3), 104(10), 94(4), 77(9), 51(4). Anal. Calcd. for C20H17N5S: C, 66.85; H, 4.73; N, 19.50. Found: C, 66.94; H, 4.70; N, 19.61 %.

Synthesis of 10-methyl-4-propylamino-8-phenylpyrimido[2,3:4,5]thieno[2,3-e]- pyrrolo[1,2-a]pyrazine (30b).

This compound was synthesized from compound **24** (0.35 g, 1 mmol) and propylamine **29b** (10 mL) and absolute ethanol (5 mL) in a manner similar to that described for the preparation of **30a**. It was recrystallized from ethanol/THF, to give 0.26 g (70 % yield), mp 159 ℃; IR: ν 3440 (NH) cm-1 ; 1H NMR (CF3COOD): δ 1.17 (3H, t, J = 1.5 Hz, CH2CH2CH3), 2.54 (3H, s, CH3), 2.02-1.96 (2H, m, CH2CH2CH3), 3.78 (2H, t, J = 1.5 Hz, CH2CH2CH3), 7.17 (1H, m, 2-H), 8.44-8.34, 7.86-7.69 (7H, m, 1-H, 3-H and phenyl-H); MS: 373(M+,44), 344(20), 331(40), 303(5), 289(2), 252(5), 241(18), 200(19), 173(6), 141(16), 103(100), 94(9), 77(80), 51(18). Anal. Calcd. for C21H19N5S: C, 67.56; H, 5.09; N, 18.76. Found: C, 67.54; H, 5.12; N, 18.56 %.

Synthesis of 4-butylamino-10-methyl-8-phenylpyrimido[2,3:4,5]thieno[2,3-e]- pyrrolo[1,2-a]pyrazine (30c).

This compound was synthesized from compound **24** (0.35 g, 1 mmol) and butylamine **29c** (10 mL) and absolute ethanol (5 mL) in a manner similar to that described for the preparation of **30a**. It was recrystallized from ethanol/THF, to give 0.29 g (74 % yield), mp 148 ℃; IR: ν 3446 (NH) cm-1 ; 1H NMR (CDCl3): δ 1.51 (3H, t, J = 2.3, Hz, CH2(CH2)2CH3), 3.32-1.91 (4H, m, CH2(CH2)2CH3), 3.62 (3H, s, CH3), 4.16 (2H, t, J = 2.0 Hz, CH2(CH2)2CH3), 5.87 (1H, br, NH), 7.27 (1H, m, 2-H), 9.14-8.97, 7.97-7.75 (7H, m, 1-H, 3-H and phenyl-H); MS: 387(M+,100), 372(22), 331(81), 317(19), 304(18), 251(2), 241(8), 227(19), 172(11), 141(8), 104(19), 77(11), 51(2). Anal. Calcd. for C22H21N5S: C, 68.21; H, 5.42; N, 18.08. Found: C, 68.31; H, 5.32; N, 18.16 %.

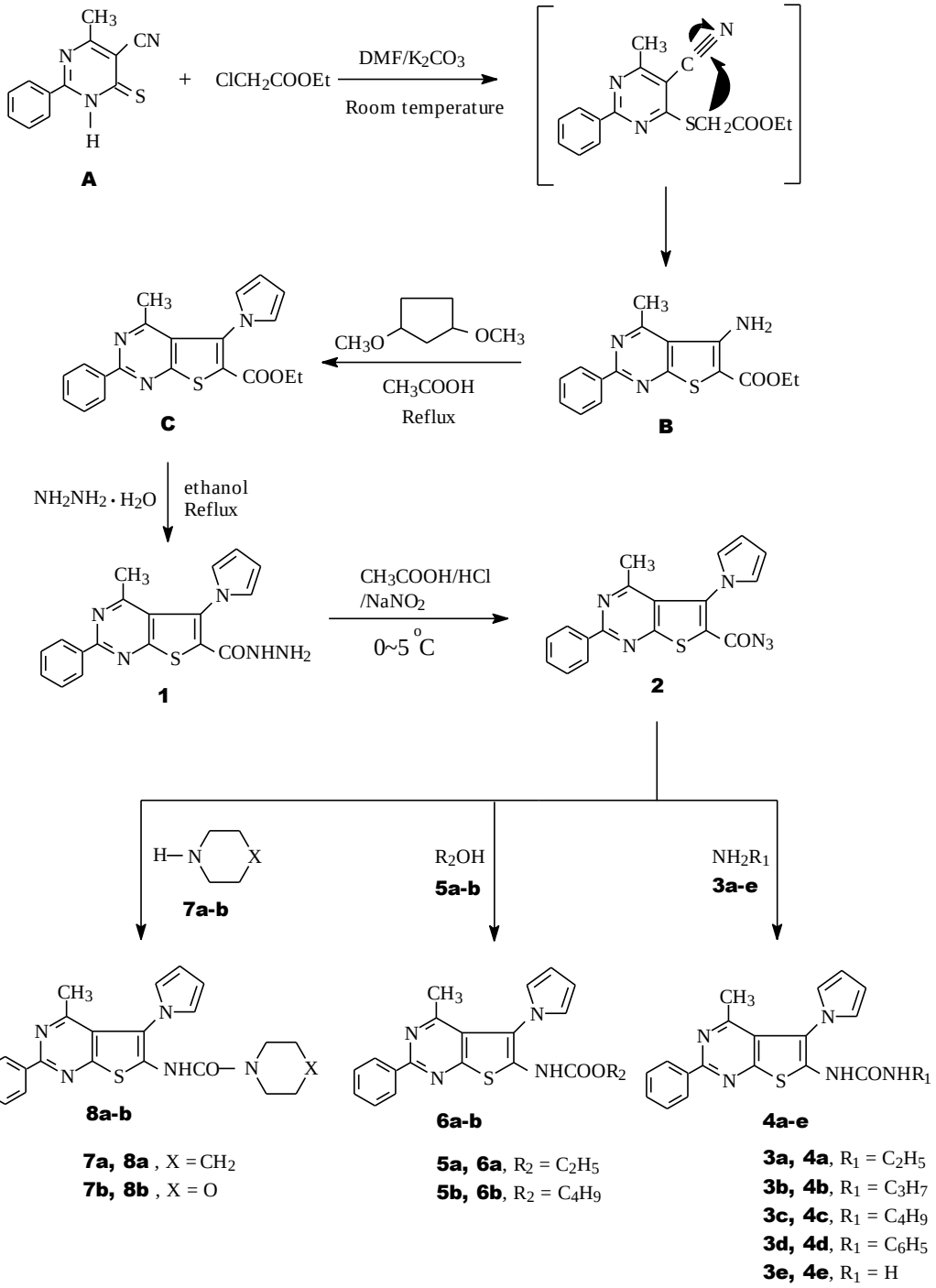
Synthesis of 4-cyano-10-methyl-8-phenylpyrimido[2,3:4,5]thieno[2,3-e]pyrrolo- [1,2-a]pyrazine (32).

To a solution of compound **24** (0.1 g, 0.29 mmol) in DMF (5 mL), sodium cyanide solution (0.20 g of sodium cyanide in 2 mL water) was added. The reaction mixture was stirred at room temperature for 24 h and poured into ice-water. The resulting solid product was collected by filtration and recrystallized from THF, to give 0.07 g (71% yield), mp 218℃; IR: ν 2203 (C≡N) cm-1; MS: 341(M+,45), 315(10), 274(11), 246(28), 237(41), 170(28), 153(17), 103(96), 77(100), 51(22). Anal. Calcd. for C19H11N5S: C, 66.86; H, 3.22; N, 20.52. Found: C, 66.51; H, 3.10; N, 20.41 %.

Results and discussion

The required intermediate 6-carbohydrazide-5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidine **1** was prepared from our previous work [28, 29] (**Scheme** 1). Diazotization of

Scheme 1



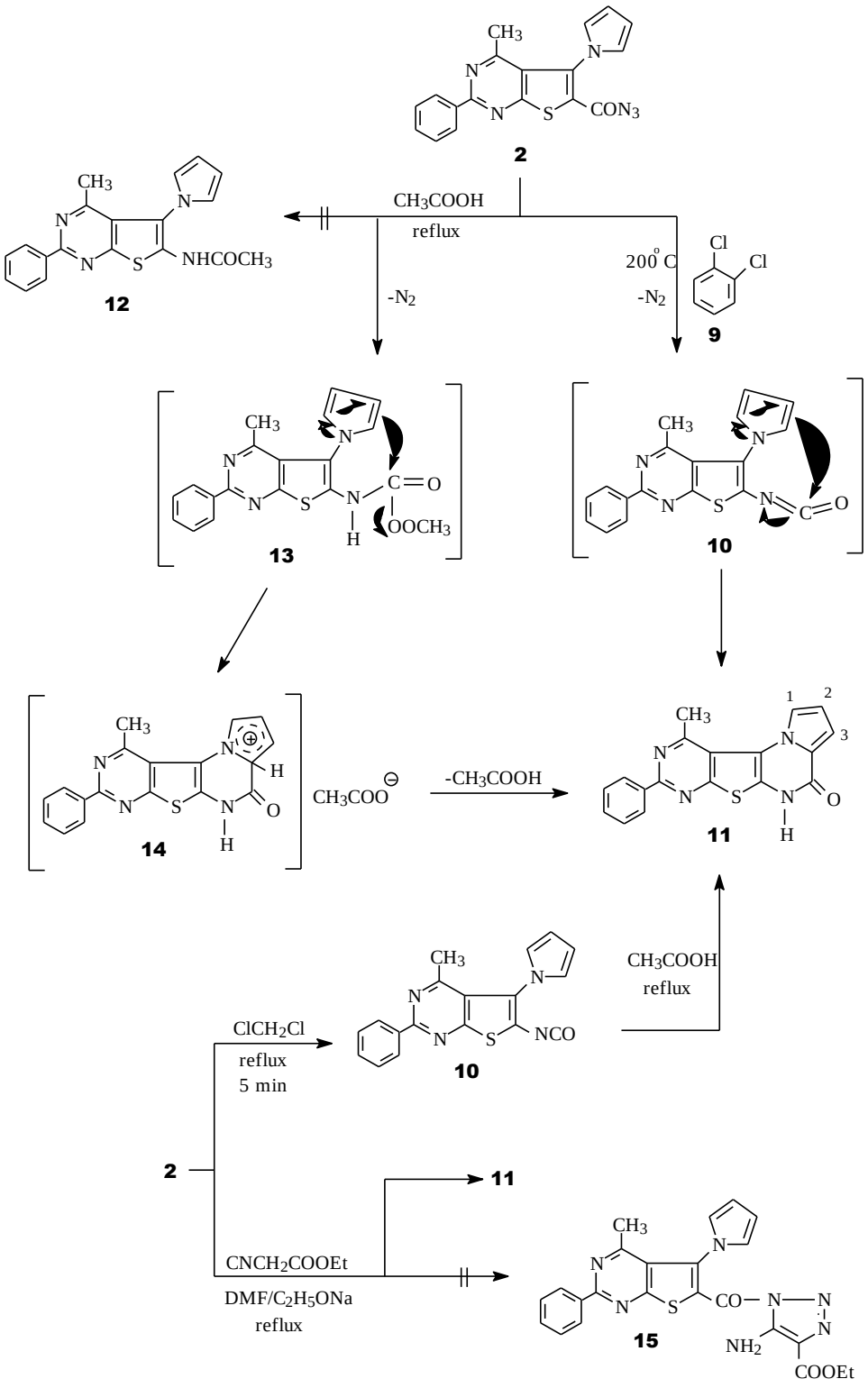
7a, 8a , X = CH_2
7b, 8b , X = O

5a, 6a, $R_2 = C_2H_5$
5b, 6b, $R_2 = C_4H_9$

3a, 4a, $R_1 = C_2H_5$
3b, 4b, $R_1 = C_3H_7$
3c, 4c, $R_1 = C_4H_9$
3d, 4d, $R_1 = C_6H_5$
3e, 4e, R_1 = H

Scheme 1. Synthetic routes of compounds **2, 4a-c, 6a,b** and **8a,b**

Scheme 2



Scheme 2. Synthetic routes of compound **11**

carbohydrazide **1** with nitrous acid in glacial acetic acid the key intermediate 6-azidocarbonyl-5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidine **2** was obtained. The IR spectra of carboazide **2** indicated the absence of the NH2 and NH group and showed the characteristic absorption band at 2154 cm-1 due to the azido group (N3) and at 1668 cm-1 for the C=O group, was also confirmed by the mass spectrum m/z (360 M+). Next, several pyrrolothienopyrimidines substituted at position-6 with different residues were obtained *via* treatment of carboazide **2** with different reagents. Thus, carboazide **2** transformed by a Curtius rearrangement [30] of acid azide to isocyanate reacted further with appropriate primary amines **3a-d** to give N,N'-disubstituted urea derivatives of 5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidines **4a-d** (**Scheme** 1). Similarly, carboazide **2** was converted into the mono-substituted urea **4e** by heating its solution in chloroform under reflux with ammonium hydroxide. The structures of compounds **4a-e** were established on the basis of their elemental analysis and spectral data. The IR spectra of compounds **4a-e** indicated the characteristic absorption band at 3410-3358 cm-1 due to the NH group and at 1697-1650 cm-1 for the CO group.

Moreover, the Curtius rearrangement of the carboazide **2** was carried out in boiling appropriate alcohols (ethanol and butanol) **5a, b** gave the corresponding 6-alkyl carbonylamino-5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidines **6a, b**. A similar spectral pattern was observed for the carbamates **6a, b**. Also, reaction of carboazide **2** with secondary amines (piperidine and morpholine) **7a, b** yielded the 6-piperidyl- (morpholinyl)amido-5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidines **8a, b** (**Scheme** 1). The IR spectra of compounds **8a, b** showed the characteristic absorption bands at 3354-3298 cm-1 for the NH group, and 1637-1636 cm-1 for the CO group, respectively. The 1H NMR spectra (DMSO-d6) of compounds **8a, b** revealed a broad singlet at δ 7.46, 7.45 assigned for the NH group, respectively, a multiplet at δ 3.47-2.97, 1.74-1.25 (10H, m) assigned to the piperidyl protons of compound **8a**, and a multiplet at δ 3.82-3.12 (8H, m) assigned to the morpholyl protons of compound **8b**.

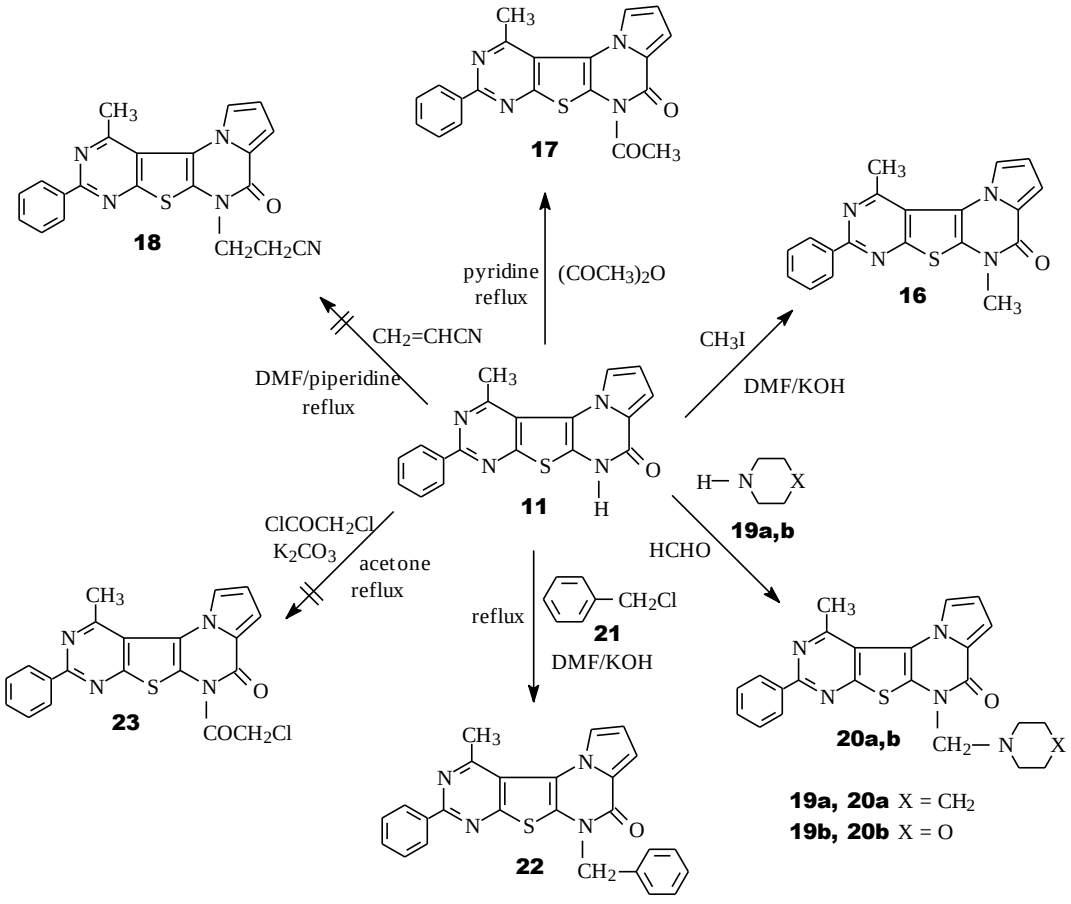
On the other hand, heating of the carboazide **2** at 200 ℃ in *o*-diclorobenzene leads to Curtius rearrangement of acid azide to isocyanate **10** with subsequent ring closure to afford the tetracyclic product namely 4,5-dihydro-10-methyl-4-oxo-8- phenylpyrimido[2,3:4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **11** (**Scheme** 2). The IR spectra of oxopyrazine **11** indicated the absence of the azido group (N3) and showed the characteristic absorption band at 3345 cm-1 for the NH group, and at 1654 cm-1 for the CO group. In addition, the structure was supported by the 1H NMR spectrum (CF3COOD), which revealed two multiplets at δ 7.64 (1H, m) and 7.82-7.78 (2H, m), which were readily assigned to the hydrogen attached at C2 and C1, C3 of pyrimido[2,3:4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine moiety, respectively, a broad singlet at δ 4.68-4.58 (1H, br) assigned to the NH proton, and a multiplet at δ 8.92-8.79 (5H, m) assigned to the phenyl protons, was also confirmed by the mass spectrum m/z 332 (M+). Moreover, treatment of carboazide **2** at reflux in glacial acetic acid yielded a high melting point product of molecular formula C18H12N4OS (90% yield, mp >330 ℃). Spectroscopic analyses revealed that oxopyrazine **11** had been obtained instead of the acetamide derivative **12** (**Scheme** 2). The formation of oxopyrazine **11** would involves the acetylating isocyanate with carboxylic acid to form the carboxylic carbamic acid anhydride **13**, which then undergoes cyclization via elimination of an acetate anion and formation of the adduct **14**, followed by loss of acetic acid affording the final product **11**. Also, the structure of oxopyrazine **11** was further confirmed from an independent synthesis of oxopyrazine **11** by the reacting of carboazide **2** in dichloromethane under reflux 5 min to afford isocyanate **10**, which reaction with glacial acetic acid afford a product identical in all respects (mp., mixed mp., TLC and spectra). Furthermore, attempted preparation of compound **15** via condensation of carboazide **2** with ethyl cyanoacetate failed. Only oxopyrazine **11** was obtained (**Scheme** 2).

On the other hand, the oxopyrazine **11** could be reacted under different conditions to form different N-substituted oxopyrazines (**Scheme** 3). Thus, oxopyrazine **11** was readily methylated in alkaline medium giving the N-methyl oxopyrazine **16**, while with benzylchloride **21** it gave the N-benzyl oxopyrazine **22**. The N-acetyl oxopyrazine **17** was obtained when oxopyrazine **11** was reacting with acetic anhydride at refluxing in pyridine. Nevertheless, when reaction of oxopyrazine **11** with acrylonitrile in refluxing DMF in the presence of catalytic amounts of piperidine did not produce the desired compound **18**, but led only to the recovery of starting material. Moreover, when oxopyrazine **11** was treated with formaldehyde and secondary amines (piperidine and morpholine) **19a,b** yielded the corresponding Mannich-type base 5-piperidino(morpholino)methylene-4-oxo-pyrimido[2,3:4,5]- thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazines **20a,b**. The 1H NMR spectra (CF3COOD) of compounds **20a,b** revealed a sharp two protons singlet at δ 4.47 (2H, s) and 3.82 (2H, s), which were readily assigned to the N-CH2-N group of the pyrrolo[1,2-*a*]pyrazine ring, respectively, a multiplet at δ 4.44-3.50, 2.37-2.20 (10H, m) assigned to the piperidyl protons of compound **20a**, and a multiplet at δ 3.63-3.52 (8H, m) assigned to the morpholyl protons of compound **20b**. Our attempts to treated oxopyrazine **11** with chloroacetyl chloride into compound **23** failed (**Scheme** 3).

Next, heating oxopyrazine **11** with phosphorus pentachloride at refluxing in phosphoryl chloride afforded the 4-chloro-pyrimido[2,3:4,5]thieno[2,3-*e*]pyrrolo- [1,2-*a*]pyrazine **24** which has served as a

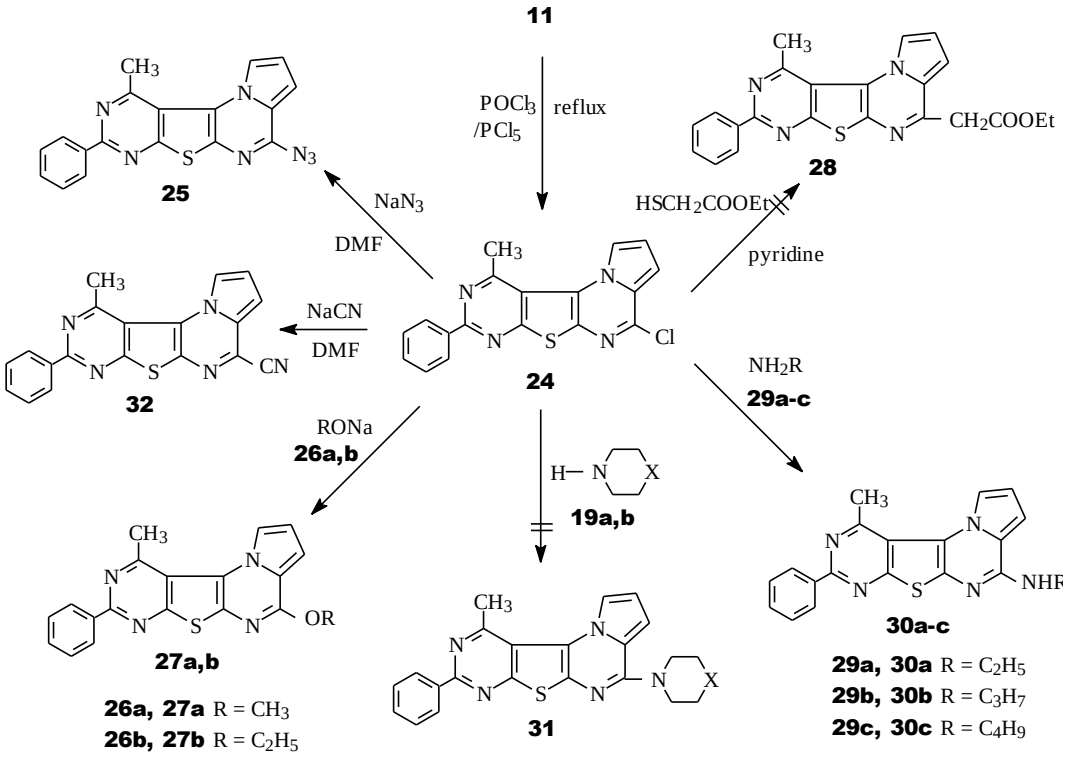
facile point of departure into the desired molecules. The chlorine atom of 4-chloropyrazine **24** showed the expected reactivity towards nucleophilic reagents such as sodium azide, alcoholates and sodium cyanide yielded the 4-substituted pyrimido[2,3:4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazines **25, 27a, b** and **32**, respectively (**Scheme** 4). The IR spectra of compounds **25** and **32** showed the characteristic absorption band at 2125 cm-1 due to the azido group (N3) and at 2203 cm-1 for the C≡N group, respectively. The 1H NMR spectra (CDCl3) of compound **27a** revealed a sharp three protons singlet at δ 4.19 (3H, s) assigned for the methoxy group (OCH3) and compound **27 b** revealed a triplet at δ 1.25 (3H, t,) and a quartet at δ 4.66 (2H, q) assigned to the ethoxy group (OCH2CH3). Nevertheless, attempted preparation of compound **28** via condensation of 4-chloropyrazine **24** with thioglycolic acid ethyl ester failed. On the other hand, treatment of 4-chloropyrazine **24** with the appropriate primary aliphatic amines **29a-c**, such as ethylamine, propylamine and butylamine gave the corresponding 4-alkylamino-pyrimido-[2,3:4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazines **30a-c**. The structure of compounds **30a-c** were assigned by its IR spectrum [ν 3446-3425 cm-1 (NH)] and confirmed by the satisfactory elemental analysis. The 1H NMR spectra (DMSO-d6) of compound **30a** revealed a triplet at δ 1.25 (3H, t,) and a quartet at δ 4.10 (2H, q) assigned to the ethyl group (CH2CH3). Finally, attempts to reacted 4-chloropyrazine **24** with secondary amines (piperidine and morpholine) **19a, b** to give compound **31** was unsuccessful and the starting material was recovered.

Scheme 3



Scheme 3. Synthetic routes of compounds **16, 17, 20a,b** and **22**

Scheme 4



Scheme 4. Synthetic routes of compounds **24, 25, 27a,b, 30a-c** and **32**

Conclusion

In conclusion, the 6-azidocarbonyl-5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidine **2** and 4,5-dihydro-4-oxopyrimido[2,3:4,5]thieno[2,3-e]pyrrolo[1,2-a]pyrazine **11** have been shown to be a useful building block for the synthesis of some new 6-substituted -5-(1-pyrrolyl)-thieno[2,3-*d*]pyrimidines and 5(4)-substituted pyrimido[2,3:4,5]- thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine derivatives, respectively. The structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR, mass spectra and elemental analysis.

Acknowedgement

We are grateful to the high valued instrument Cent of National Taiwan Normal University for measuring the data of spectroscopy. We also want to thank National Science Council of Taiwan for their financial support.

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Received : 23rd May, 2013
Revised : 9th June, 2013
Online : 24th June, 2013