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Remon M. Zaki*, Adel M. Kamal El-Dean, Shaban M. Radwan and Ahmed F. Saber

Efficient synthesis, reactions and spectral characterization of pyrazolo[4',3':4,5]thieno[3,2-*d*]pyrimidines and related heterocycles

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Abstract: New pyrazolothienopyrimidines were synthesized. The key intermediate 4-aminothieno[2,3-*c*]pyrazole-5-carbonitrile **1** was converted to the chloroacetyl amino derivative **2** followed by nucleophilic substitution and Dimorth rearrangement upon treatment with nitrogen nucleophiles to give the pyrimidinones **3a-c**. Treatment of **3a** with formaldehyde and with triethyl orthoformate afforded the respective tetracyclic derivatives **4** and **5**. Condensation of the amino group in the *o*-aminocarbonitrile **1** with triethyl orthoformate followed by cycloaddition reaction with hydrazine led to the formation of pyrazolothienopyrimidine **8**. Compound **8** was used as a synthetic precursor to heterocyclic compounds comprised of pyrazole, triazole, triazine, and triazepine derivatives.

Keywords: imidazolyl; pyrazolothienopyrimidine; triazine; triazolo; synthesis.

Introduction

Pyrazoles and their derivatives are an important class of heterocyclic compounds that exhibit a broad spectrum of biological activities [1-22]. Many thienopyrazoles [23-27] and thienopyrimidines [38, 39] also exhibit exceptional bioactivity [23-27]. In continuation of our work on synthesis of new bioactive compounds containing thienopyrazole moiety [40-44], several thienopyrazolopyrimidine derivatives not known previously were synthesized.

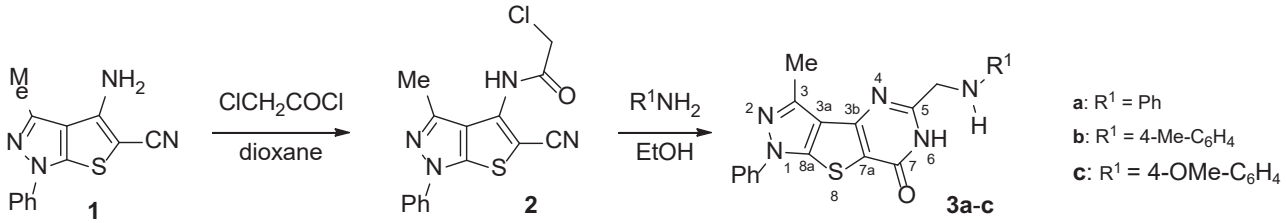
*** Corresponding author: Remon M. Zaki**, Chemistry Department, Faculty of Science, Assiut University, 71516, Egypt, e-mail: remonch2003@yahoo.com or remon.asal2015@gmail.com
Adel M. Kamal El-Dean, Shaban M. Radwan and Ahmed F. Saber, Chemistry Department, Faculty of Science, Assiut University, 71516, Egypt

Results and Discussion

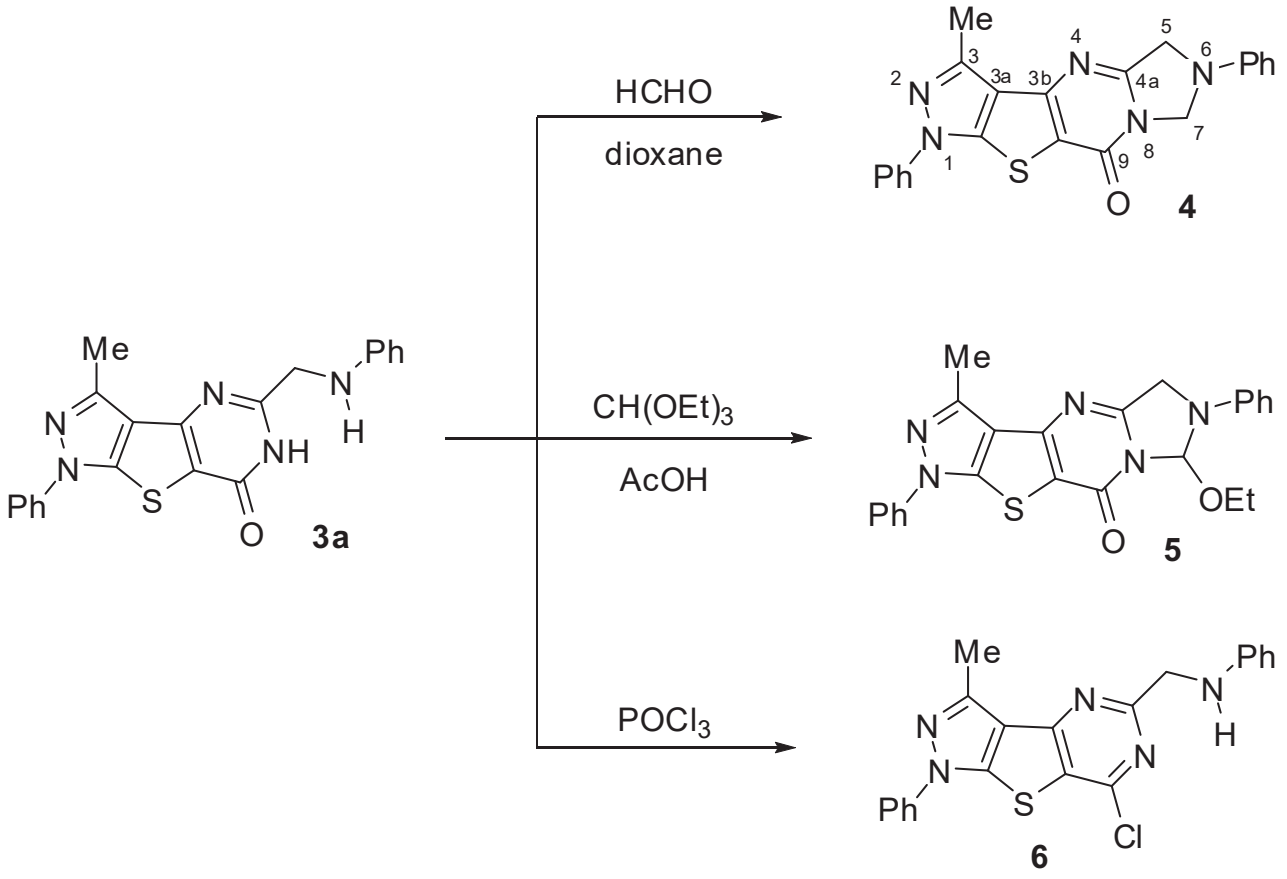
The synthetic work was initiated by chloroacetylation reaction of 4-amino-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazole-5-carbonitrile **(1)**, which afforded the chloroacetamido derivative **2** (Scheme 1). Reaction of **2** with various primary aromatic amines furnished the unexpected pyrimidinones **3a-c** in good yields. This reaction apparently proceeds by nucleophilic substitution of the chloride ion with the primary amino group followed by Dimorth rearrangement in the presence of excess of the amine [45]. IR spectrum of **3a** reveals disappearance of absorption band for the CN group present in compound **2** and appearance of absorption bands at 3440 and 3188 cm^{-1} that are characteristic for NH groups and absorption band at 1660 cm^{-1} for the amidic CONH group of pyrimidine. ^1H NMR spectrum shows singlets at δ 6.10 and 12.68 attributed to exchangeable NHPh and NH pyrimidine groups.

Treatment of the 5-(phenylaminomethyl)pyrimidinone **3a** with formaldehyde in dioxane (Scheme 2) and the reaction with triethyl orthoformate afforded the respective tetracyclic pyrimidinones **4** and **5**. Moreover, chlorination of the pyrimidinone **3a** with phosphorus oxychloride furnished the chloropyrimidine **6**. Both elemental and spectral analyses of compound **4**- **6** fully support the assigned structures.

Condensation of *o*-aminocarbonitrile **1** with triethyl orthoformate in the presence of a catalytic amount of acetic anhydride produced compound **7** (Scheme 3). Stirring of **7** with an equivalent amount of hydrazine hydrate yielded iminopyrimidine derivative **8**. This transformation is characterized by disappearance of absorption band at 2199 cm^{-1} for CN group in compound **7** and appearance of absorption bands at 3439, 3286 and 3131 cm^{-1} due to NH and NH_2 groups in product **8**. ^1H NMR spectra show disappearance of triplet and quartet signals for the ethyl group in compound **7** and appearance of singlet signals at δ 5.80 and 8.19 characteristic of NH_2 and NH groups, respectively. Condensation of the amino-imino compound **8** with triethyl orthoformate produced the corresponding



Scheme 1

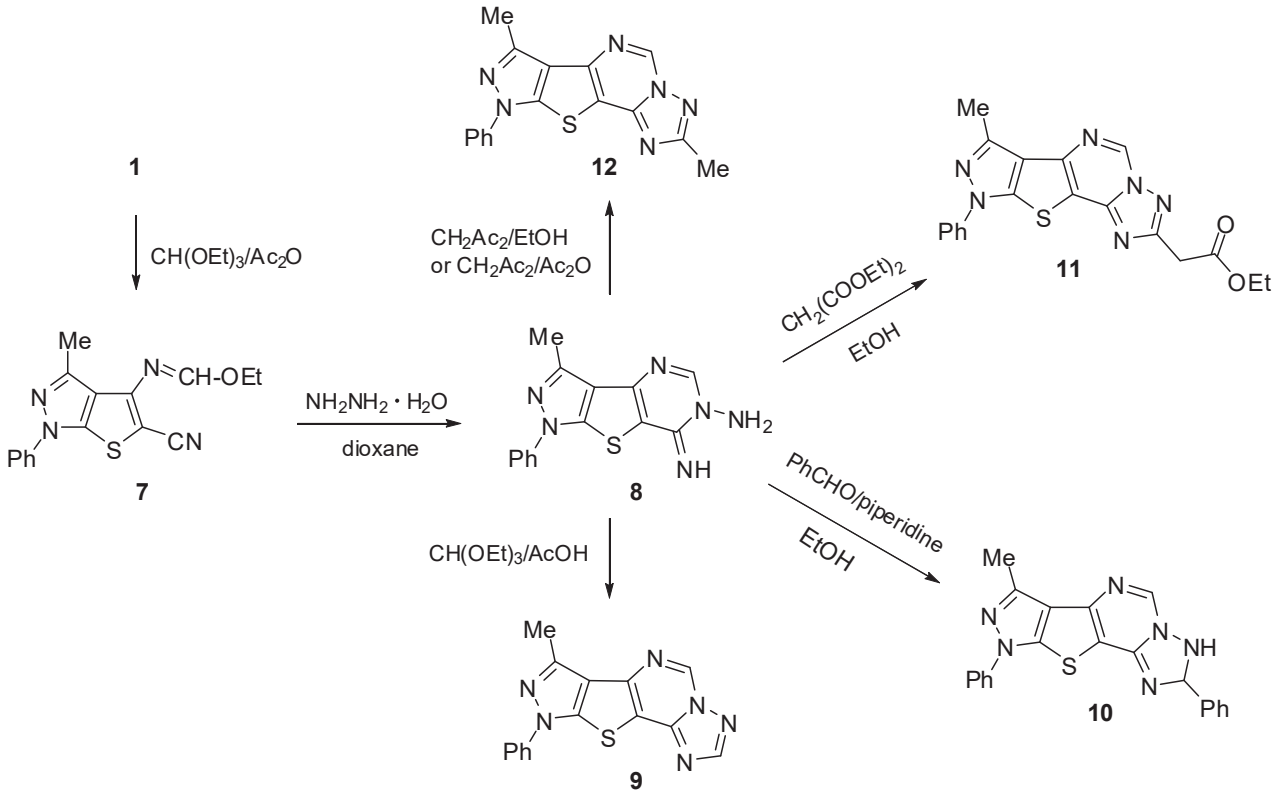


Scheme 2

triazolopyrimidine **9** in an excellent yield, and dihydropyrazolopyrimidine **10** was obtained in low yield upon treatment of **8** with benzaldehyde.

An additional series of novel tetracyclic pyrimidines **11-14** were synthesized by condensation of the amino-imino derivative **8** with different 1,3-dicarbonyl compounds (Schemes 3 and 4). Thus, condensation of compound **8** with diethyl malonate afforded the ethyl triazolopyrimidinyl acetate **11**, while condensation with acetyl acetone produced triazolopyrimidine **12** instead of the expected diazepine product. Assignments of compounds **9-12** were elucidated by analysis of TLC, FT-IR, ^{1}H NMR and ^{13}C NMR data. IR spectrum of **11** lacks absorption bands of NH_2 and NH groups and shows a sharp absorption band at 1740 cm^{-1} due to the ester. ^{1}H NMR spectrum exhibits triplet and quartet signals at δ 1.25 and 4.20 with a J value of 7 Hz attributed to the ethyl ester group. ^{13}C NMR shows signals at δ 14.5 and 61.4 for the ethyl group, in addition to the signal at 168.9 ppm for the ester carbonyl carbon as shown in Scheme 3.

Apparently, the mechanism of condensation of compound **8** with acetylacetone proceeds via cyclization of the imine with a retro-aldol type elimination of acetone. In a similar manner, condensation of **8** with ethyl acetoacetate and ethyl benzoylacetate afforded the corresponding



Scheme 3

triazepinones **13** and **14** (Scheme 4). Surprisingly, the treatment of **8** with phenacyl bromide in refluxing ethanol in the presence of triethylamine yielded the 3,8-diphenyltriazine **15** rather than its 2,8-diphenyl isomer. Formation of **15** can be explained by condensation between NH_2 of the amino-imino **8** and carbonyl group of phenacyl bromide. The structure of compound **15** was confirmed on the basis of IR and ^{1}H NMR spectra.

Fusion of compound **8** with diethyl oxalate in the presence of acetic acid produced the corresponding triazinedione **17** in good yield. Triazolethione **18** was obtained upon heating of **8** with carbon disulfide in pyridine at 100°C. Both elemental and spectral analyses of the newly synthesized compounds **13-18** are in a full agreement with the postulated structures (Scheme 4).

Conclusions

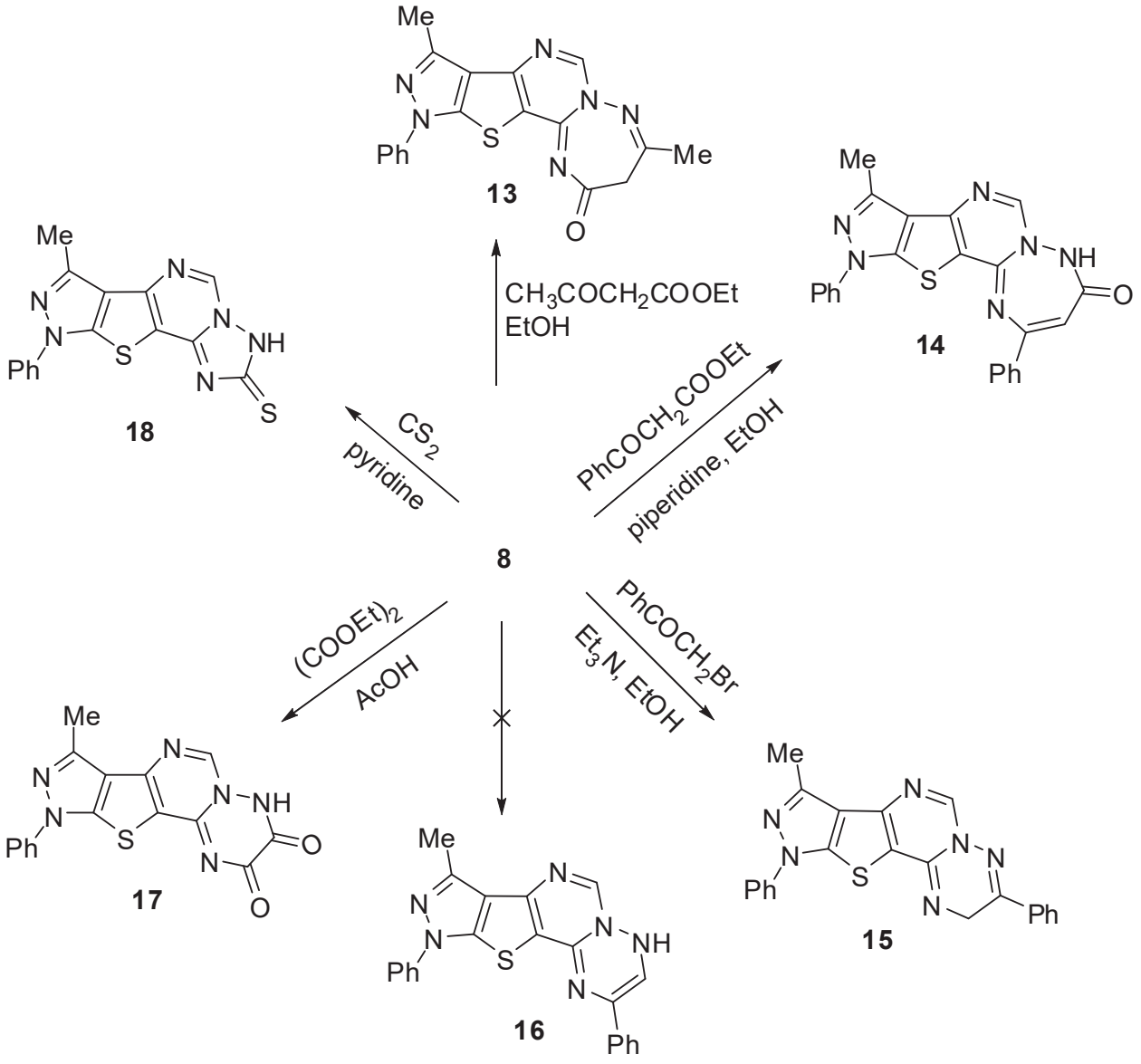
Convenient and efficient methods for synthesis of novel pyrazolothienopyrimidines **3, 6** and **8** were described. These products were used as versatile starting materials for synthesis of new heterocyclic ring systems with imidazole, triazole, triazine and triazepine rings fused to a pyrazolothienopyrimidine moiety.

Experimental

All melting points are uncorrected. Elemental analyses were carried out at the Micro Analytical Center of Chemistry Department, Assiut University. The analysis for chlorine in compounds **2** and **6** was carried out by titration of chloride ion with mercuric nitrate solutions using a diphenylcarbazide indicator as reported [46, 47]. The FT-IR spectra were recorded using potassium bromide disks on a FT-IR 8201 PC Shimadzu instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75MHz) spectra were obtained on a Bruker spectrometer in $CDCl_3$ and DMSO-d_6 using Me_4Si as internal standard. All reactions were monitored by thin layer chromatography (TLC) on silica gel coated aluminum sheets. Compound **1** was synthesized according to the literature procedure [**40, 41**], mp 198-200°C.

2-Chloro-*N*-(5-cyano-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*]pyrazol-4-yl)acetamide (2)

To a solution of *o*-amino-carbonitrile **1** (1.60 g, 6.29 mmol) in dioxane (25 mL), chloroacetyl chloride (0.80 mL, 10.0 mmol) was added, and the mixture was heated at 60-70°C for 2 h. After cooling and addition of diluted sodium



Scheme 4

carbonate solution, the resultant precipitate was filtered, dried and crystallized from ethanol: pale yellow crystals; yield 1.50 g (72%); mp > 360 °C; IR: ν 3360, 2185, 1655 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.61 (s, 3H, CH_3), 4.64 (s, 2H), 7.58-7.76 (m, 5H) and 8.96 (s, 1H). Anal. Calcd for $C_{15}H_{11}ClN_4OS$ (330.79): C, 54.46; H, 3.35; Cl, 10.72; N, 16.94; S, 9.69. Found: C, 54.56; H, 3.41; Cl, 10.77; N, 16.86; S, 9.63.

3-Methyl-1-phenyl-5((alkylarylamino)methyl)-1*H*-pyrazolo[4',3':4,5]thieno[3,2-*d*] pyrimidin-7(6*H*)-ones 3a-c

A mixture of chloroacetamide **2** (0.50 g, 1.5 mmol) and the corresponding amine (2 mmol) was gently heated without solvent for 10 min and then treated with ethanol (10 mL). The mixture was heated under reflux for 3 h. The resultant precipitate was filtered off, dried and crystallized from the proper solvent.

4.2.1. 3-Methyl-1-phenyl-5((phenylamino)methyl)-1*H*-pyrazolo[4',3':4,5]thieno[3,2-*d*]pyrimidin-7(6*H*)-one (3a)

Obtained by the reaction with aniline; crystallized from dioxane as yellow needles; yield 0.47 g (80%); mp 250-252°C; IR: ν 3440, 3188 (NH), 1660 (CO) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 3H), 4.34 (s, 2H), 6.10 (s, 1H), 6.58-7.77 (m, 10H) and 12.68 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.2, 53.5, 107.3, 113.2, 117.3, 117.6, 118.0, 125.6, 126.7, 129.4, 130.5, 138.9, 143.0, 144.8, 148.3, 158.6, 160.0. Anal. Calcd for $C_{21}H_{17}N_5OS$

(387.46): C, 65.10; H, 4.42; N, 18.08; S, 8.27. Found: C, 65.22; H, 4.53; N, 17.96; S, 8.42.

3-Methyl-1-phenyl-5-[(*p*-tolylamino)methyl]-1*H*-pyrazolo[4',3':4,5]thieno[3,2-*d*] pyrimidin-7(6*H*)-one (3b)

Obtained by the reaction with *p*-toluidine; crystallized from dioxane as brown crystals; yield 0.30 g (50%); mp 220-222°C; IR: ν 3423, 3370, 1664 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.18 (s, 3H), 2.22 (s, 3H), 3.50 (s, 2H), 6.32 (s, 1H), 6.58-7.72 (m, 9H), 12.74 (s, 1H). Anal. Calcd for $C_{22}H_{19}N_5OS$ (401.13): C, 65.82; H, 4.77; N, 17.44; S, 7.99. Found: C, 65.73; H, 4.83; N, 17.43; S, 7.88.

5-{[(4-Methoxyphenyl)amino]methyl}-3-methyl-1-phenyl-1*H*-pyrazolo[4',3':4,5] thieno[3,2-*d*]pyrimidin-7(6*H*)-one (3c)

Obtained by the reaction with *p*- anisidine; crystallized from ethanol as brown crystals; yield 0.40 g (64%); mp 230-232°C; IR: ν 3425, 3210, 1676 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.60 (s, 3H), 3.61 (s, 3H, CH_3), 4.27 (s, 2H), 5.70 (s, 1H), 6.63-7.75 (m, 9H) and 12.69 (s, 1H). Anal. Calcd for $C_{22}H_{19}N_5O_2S$ (417.49): C, 63.29; H, 4.59; N, 16.78; S, 7.68. Found: C, 63.33; H, 4.43; N, 16.73; S, 7.58.

3-Methyl-1,6-diphenyl-6,7-dihydro-1*H*-imidazo[1,5-*a*] pyrazolo[4',3';4,5]thieno[3,2-*d*]pyrimidin-9(5*H*)-one (4)

Formaldehyde was added to a stirred solution of pyrimidinone **3a** (3.00 g, 7.74 mmol) in dioxane (30 mL). Stirring of the mixture was continued for 2 h. The resultant solid product was filtered off, dried and crystallized from dioxane to afford white crystals; yield 2.23 g, (72%); mp >300°C; IR: ν 1675 cm^{-1}; ^1H NMR: ($CDCl_3$): δ 2.54 (s, 3H), 5.35 (s, 2H), 7.00 (s, 2H) and 7.33-7.70 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 13.6, 66.5, 78.1, 105.3, 111.4, 117.2, 121.1, 124.6, 126.1, 128.4, 129.6, 135.3, 141.4, 145.5, 148.3, 152.6, 158.7, 168.5. Anal. Calcd for $C_{22}H_{17}N_5OS$ (399.47): C, 66.15; H, 4.29; N, 17.53; S, 8.03. Found: C, 66.18; H, 4.24; N, 17.42; S, 8.13.

7-Ethoxy-3-methyl-1,6-diphenyl-6,7-dihydro-1*H*-imidazo[1,5-*a*]pyrazolo[4',3';4,5] thieno[3,2-*d*]pyrimidine-9(5*H*)-one (5)

A mixture of pyrimidinone **3a** (3.00 g, 7.74 mmol), triethyl orthoformate (1.30 mL, 7.82 mmol) and a catalytic amount of acetic acid (0.25 mL) was heated under reflux for 1 h. The resultant solid product was filtered off, dried and crystallized from ethanol as brown crystals; yield 2.23 g (65%); mp 298-300°C; IR: ν 1670 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48 (t, J = 7 Hz, 3H), 2.54 (s, 3H), 4.50 (q, J = 7 Hz, 2H), 5.00 (s, 2H), 6.71 (s, 1H), 7.33-8.10 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 13.0, 57.4, 60.6, 109.5, 109.7, 113.6, 117.4, 118.0, 123.9, 126.7, 129.7, 130.4, 141.8, 157.4, 158.1, 158.6, 159.1, 159.6, 169.5. Anal. Calcd for $C_{24}H_{21}N_5O_2S$ (443.53): C, 64.99; H, 4.77; N, 15.79; S, 7.23. Found: C, 64.88; H, 4.74; N, 15.72; S, 7.13.

***N*-[(7-Chloro-3-methyl-1-phenyl-1*H*-pyrazolo[4',3';4,5] thieno[3,2-*d*]pyrimidine-5-yl) methyl]aniline (6)**

A solution of pyrimidinone **3a** (3.00 g, 7.74 mmol) in phosphorus oxychloride (30 mL) was heated under reflux for 2 h, then cooled and poured into an ice-water. The precipitate was filtered off, dried and crystallized from ethanol to give pale yellow crystals; yield 2.20 g (70%); mp 288-290°C; IR: ν 3380 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.81 (s, 3H), 4.73 (s, 2H), 6.90-7.80 (m, 10H) and 8.58 (s, 1H). Anal. Calcd for $C_{21}H_{16}ClN_5S$ (405.90): C, 62.14; H, 3.97; Cl, 8.73; N, 17.25; S, 7.90. Found: C, 62.18; H, 3.84; Cl, 8.70; N, 17.32; S, 7.83.

Ethyl *N*-(5-cyano-3-methyl-1-phenyl-1*H*-thieno[2,3-*c*] pyrazol-4-yl)formimidate (7)

A mixture of *o*-amino-carbonitrile **1** (3.00 g, 11.8 mmol), and triethyl orthoformate (6.00 mL, 36.1 mmol) in acetic acid (30 mL) was heated under reflux for 2 h. The resultant solid product was collected, dried and crystallized from ethanol as brown crystals; yield 2.89 g (79%); mp 80-82°C; IR: ν 2199 (CN) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50 (t, J = 7 Hz, 3H), 2.54 (s, 3H), 4.46 (q, J = 7 Hz, 2H), 7.33-7.70 (m, 5H) and 8.10 (s, 1H). Anal. Calcd for $C_{16}H_{14}N_4OS$ (310.38): C, 61.92; H, 4.55; N, 18.05; S, 10.33. Found: C, 61.88; H, 4.64; N, 18.12; S, 10.28.

6-Amino-7-imino-3-methyl-1-phenyl-1,7-dihydro-6*H*-pyrazolo[4',3':4,5]thieno[3,2-*d*] pyrimidine (8)

To a stirred solution of the formimidate **7** (2.96 g, 9.54 mmol) in warm dioxane (30 mL), hydrazine hydrate (0.80 mL, 16 mmol) was added dropwise during 5 min. Stirring of the mixture was continued for an additional 1h. The solid precipitate was filtered off, dried and crystallized from ethanol as white crystals; yield 2.40 g (85%); mp 220-222°C; IR: ν 3439, 3286, 3131 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.57 (s, 3H), 5.80 (s, 2H), 7.00 (s, 1H), 7.33-7.76 (m, 5H) and 8.19 (s, 1H). Anal. Calcd for $C_{14}H_{12}N_6S$ (296.35): C, 56.74; H, 4.08; N, 28.36; S, 10.82. Found: C, 56.70; H, 4.22; N, 28.42; S, 10.76.

7-Methyl-9-phenyl-9*H*-pyrazolo[4',3':4,5]thieno[2,3-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidine (9)

A mixture of the aminoiminopyrimidine **8** (0.70 g, 2.4 mmol) and triethyl orthoformate (5.00 mL, 30.1 mmol) and a catalytic amount of acetic acid (0.30 mL) was heated under reflux for 3 h at 120°C. The separated solid product was filtered off, dried and crystallized from dioxane as white crystals; yield 0.67 g (92%); mp 266-268°C; IR: ν 1595 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.74 (s, 3H), 7.40-7.85 (m, 5H), 8.75 (s, 1H) and 9.91 (s, 1H). Anal. Calcd for $C_{15}H_{10}N_6S$ (306.35): C, 58.81; H, 3.29; N, 27.43; S, 10.47. Found: C, 58.70; H, 3.32; N, 27.52; S, 10.55.

7-Methyl-2,9-diphenyl-2,9-dihydro-9*H*-pyrazolo[4',3':4,5] thieno[2,3-*e*][1,2,4]triazolo [1,5-*c*]pyrimidine (10)

A solution of pyrimidine **8** (0.70 g, 2.4 mmol), benzaldehyde (2.10 mL, 20.6 mmol) and a catalytic amount of piperidine (0.25 mL) was heated at 180°C for 10 min, then cooled, treated with absolute ethanol (20 mL) and heated under reflux for an additional 2h. The solid precipitate was filtered off and crystallized from acetic acid as white crystals; yield 0.29 g (38%); mp 300-302°C; IR: ν 3302 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.67 (s, 3H), 4.13 (s, 1H), 5.24 (s, 1H), 7.38-7.86 (m, 10H) and 8.63 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.3, 85.9, 108.8, 119.7, 124.1, 125.7, 127.1, 128.9, 130.7, 131.4, 134.2, 138.1, 140.3, 141.3, 143.4, 146.9, 160.3. Anal. Calcd for $C_{21}H_{16}N_6S$ (384.12): C, 65.61; H, 4.19; N, 21.86; S, 8.34. Found: C, 65.76; H, 4.25; N, 21.92; S, 8.33.

Ethyl (7-methyl-9-phenyl-9*H*-pyrazolo[4',3':4,5] thieno[2,3-*e*] [1,2,4]triazolo[1,5-*c*] pyrimidine)-2-yl-acetate (11)

A mixture of pyrimidine **8** (0.70 g, 2.4 mmol) and diethyl malonate (5.00 mL, 32.8 mmol) was heated for 10 min, then treated with ethanol (20 mL) and heated under reflux for an additional 2h. The solid product that formed on cooling was collected, dried and crystallized from ethanol as pale brown crystals; yield 0.45 g (49%); mp 100-102°C; IR: ν 1740 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.25 (t, J = 7 Hz, 3H), 2.69 (s, 3H), 4.10 (s, 2H), 4.20 (q, J = 7 Hz, 2H), 7.40-7.78 (m, 5H) and 9.80 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.2, 14.5, 35.1, 61.4, 116.8, 117.0, 124.9, 126.7, 130.4, 138.5, 140.9, 141.5, 144.0, 148.7, 165.8, 168.9; Anal. Calcd for $C_{19}H_{16}N_6O_2S$ (392.44): C, 58.15; H, 4.11; N, 21.42; S, 8.17. Found: C, 58.20; H, 4.07; N, 21.36; S, 8.27.

2,7-Dimethyl-9-phenyl-9*H*-pyrazolo[4',3':4,5]thieno[2,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine (12)

A mixture of pyrimidine **8** (0.70 g, 2.4 mmol) and acetylacetone (3.00 mL, 29.4 mmol) was gently heated for 15 min, then treated with ethanol (20 mL) and heated under reflux for an additional 3h. The solid product formed after cooling was filtered off and crystallized from dioxane as brown crystals; yield 0.38 g (50%); mp 180-182°C; IR: ν 1598 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.57 (s, 3H), 2.99 (s, 3H), 7.40-7.85 (m, 5H) and 9.92 (s, 1H); MS (EI, 70 eV): *m/z* 320 (M^+, 100%). Anal. Calcd for $C_{16}H_{12}N_6S$ (320.37): C, 59.98; H, 3.78; N, 26.23; S, 10.01. Found: C, 59.95; H, 3.74; N, 26.11; S, 10.11.

4,9-Dimethyl-11-phenyl-11*H*-pyrazolo[4'',3'';4',5'] thieno [3',2';4,5]pyrimido[1,6-*b*] [1,2,4]triazepin-2(3*H*)-one (13)

A mixture of pyrimidine **8** (0.70 g, 2.4 mmol) and ethyl acetoacetate (2.00 mL, 15.7 mmol) was gently heated for 15 min, then treated with ethanol (20 mL) and heated under reflux for an additional 2h. The solid product which separated out during reflux was collected, dried and crystallized from ethanol as brown crystals; yield 0.63 g (86 %); mp 200-202°C; IR: ν 1715 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.28 (s, 3H), 2.70 (s, 3H), 4.16 (s, 2H), 7.39-7.85 (m, 5H), 9.80 (s, 1H). Anal. Calcd for $C_{18}H_{14}N_6OS$ (362.41): C, 59.66; H, 3.89; N, 23.19; S, 8.85. Found: C, 59.55; H, 3.75; N, 23.22; S, 8.77.

9-Methyl-2,11-diphenyl-11*H*-pyrazolo[4",3";4',5']thieno [3',2';4,5]pyrimido[1,6-*b*][1,2,4]triazepin-4(5*H*)-one (14)

A solution of pyrimidine **8** (0.74 g, 2.5 mmol), ethyl benzoylacetate (2.00 mL, 11.5 mmol) and a catalytic amount of piperidine (0.25 mL) was gently heated for 15 min, then treated with ethanol (20 mL) and heated under reflux for an additional 2h. The solid product that formed during reflux was filtered off and crystallized from ethanol as brown crystals; yield 0.36 g (42%); mp 188-190°C; IR: ν 3462 (NH), 1685 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.71 (s, 3H), 4.80 (s, 1H), 7.41 (s, 1H), 7.56-8.13 (m, 10H) and 9.82 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.3, 98.3, 103.7, 110.2, 117.9, 126.8, 129.1, 129.3, 130.5, 134.1, 136.4, 137.2, 141.0, 145.0, 152.5, 160.1, 162.3, 167.5, 170.7; MS (EI, 70eV) *m/z* 424 (M^+, 100%). Anal. Calcd for $C_{23}H_{16}N_6OS$ (424.48): C, 65.08; H, 3.80; N, 19.80; S, 7.55. Found: C, 65.20; H, 4.00; N, 19.62; S, 7.37.

8-Methyl-3,10-diphenyl-2,10-dihydropyrazolo[4'',3'':4',5'] thieno[3',2':4,5]pyrimido [1,6-*b*][1,2,4] triazine (15)

A mixture of compound **8** (0.74 g, 2.5 mmol), phenacyl bromide (0.50 g, 2.5 mmol) and triethylamine (0.30 mL) in ethanol (20 mL) was heated under reflux for 3h. The solid product that formed on cooling was filtered off, dried and crystallized from ethanol as white crystals; yield 0.59 g (74 %); mp 280-282°C; IR: ν 1597 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.60 (s, 2H), 2.79 (s, 3H), 7.53-8.21 (m, 10H) and 8.64 (s, 1H). Anal. Calcd for $C_{22}H_{16}N_6S$ (396.47): C, 66.65; H, 4.07; N, 21.20; S, 8.09. Found: C, 66.58; H, 4.17; N, 21.22; S, 8.18.

8-Methyl-10-phenylpyrazolo[4'',3'';4',5']thieno [3',2':4,5]pyrimido[1,6-*b*][1,2,4] triazine-2,3(4*H*,10*H*)-dione (17)

A mixture of compound **8** (0.74 g, 2.5 mmol) and diethyl oxalate (0.40 mL, 2.9 mmol) in acetic acid (20 mL) was heated under reflux for 6 h. The solid product that formed on cooling was filtered off, dried and crystallized from ethanol as pale yellow crystals; yield 0.68 g (73%); mp 175-177°C; IR: ν 3375 (NH), 1700, 1661 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.61 (s, 3H), 7.35-7.76 (m, 5H), 8.31 (s, 1H) and 12.83 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.3, 107.5, 117.9, 121.2, 125.6, 126.7, 130.5, 138.9, 142.8, 144.7, 148.7, 157.9, 160.1, 170.2. Anal. Calcd for $C_{16}H_{10}N_6O_2S$ (350.36): C, 54.85; H, 2.88; N, 23.99; S, 9.15. Found: C, 54.98; H, 2.95; N, 24.20; S, 9.05.

7-Methyl-9-phenyl-9*H*-pyrazolo[4',3':4,5]thieno [2,3-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine-2(3*H*)-thione (18)

A solution of compound **8** (0.74 g, 2.5 mmol) and carbon disulfide (2.00 mL, 33.1 mmol) in pyridine (10 mL) was heated under reflux for 8h. The solid product that separated out during reflux was filtered off, dried and crystallized from ethanol as yellow crystals; yield 0.28 g, (35%); mp 286-288°C; IR: ν 3447, 1239 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.73 (s, 3H), 7.44-7.84 (m, 5H), 8.44 (s, 1H) and 9.88 (s, 1H). Anal. Calcd for $C_{15}H_{10}N_6S_2$ (338.41): C, 53.24; H, 2.98; N, 24.83; S, 18.95. Found: C, 53.27; H, 2.94; N, 24.75; S, 18.83.

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