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A new strategy for the synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidines and pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines

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ABSTRACT

A series of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines were prepared via oxidative cyclization of aldehyde *N*-(1,3-diphenylpyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazones. Dimroth rearrangement of such a series yielded pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines.

1. Introduction

Reports from our laboratory[1] and from others[2] revealed that the only possible route for the synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives involves reaction of 5-amino-4-imino-pyrazolo[3,4-*d*]pyrimidine with one-carbon cyclizing agents. Furthermore, attempts to prepare the isomeric pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines via dehydrative cyclization of the 4-acylhydrazino-pyrazolo[3,4-*d*]pyrimidines was reported to give the corresponding pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidines.[3] In view of these findings and in continuation of our long standing interest for the utility of nitrilimines derived from either hydrazonoyl halides or hydrazones in the synthesis of heterocycles,[4–13] we wish to report herein a simple and convenient route for the synthesis of the title compounds. This route involves 1,5-electrocyclization of nitrilimines generated in situ from the hitherto unreported aldehyde *N*-(pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazones to give the respective pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines and Dimroth rearrangement of the latter to give their isomeric pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives.

Our interest in developing a new synthesis of these two ring systems results from the fact that some derivatives of both pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine and pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine exhibit interesting pharmacological activities.[14] For example, several 3- and/or 5-substituted 7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines were reported to be potent xanthine oxidase (XO) inhibitors.[14] Also efforts made in medicinal chemistry in the past 25 years have revealed that the isomeric ring system pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine is one of the structural requirements for compounds that behave as selective antagonists for human A_{2A} and A_3 adenosine receptor subtypes.[2] In addition, various derivatives have been used as a new pharmacological tool for characterization of human A_3 adenosine receptors.[15]

2. Results and discussion

The starting 5-amino-1,3-diphenyl-4-imino-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine **1** was prepared as previously reported from our laboratory.[1] When compound **1** was stirred in ethanol in the presence of excess hydrazine hydrate at room temperature, it underwent Dimroth type rearrangement to give 1,3-diphenyl-4-hydrazino-pyrazolo[3,4-*d*]-pyrimidine **2**, which has not been reported hitherto (Scheme 1). The isomerization of **1** into **2** seems to occur through base-catalyzed tandem ring opening and ring closure as shown in Scheme 2. This is consistent with a similar rearrangement that was reported recently.[16] The structure of **2** was evidenced by its spectra and elemental analysis (see Section 3).

The required aldehyde *N*-(1,3-diphenylpyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazones **4** were prepared by condensation of the hydrazine derivative **2** with the appropriate aldehydes **3** (Scheme 1).

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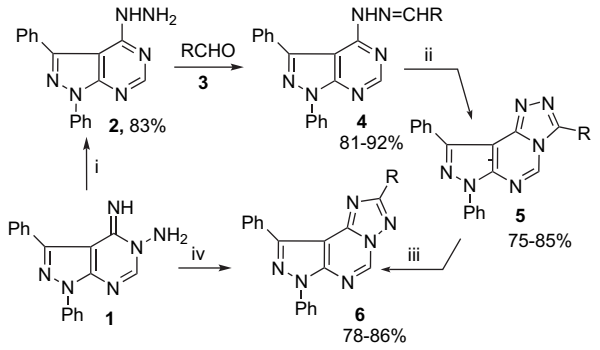
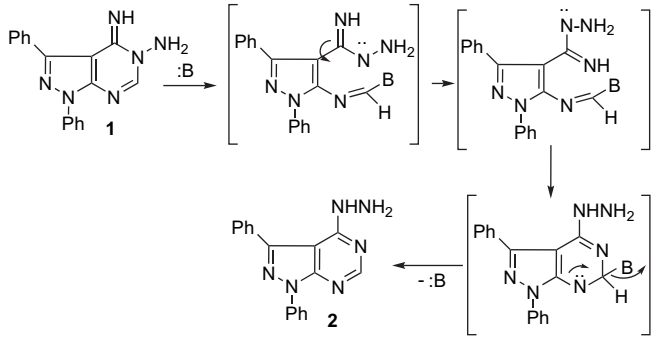


Scheme 1. Reagents: (i) $H_2NNH_2 \cdot H_2O$/rt; (ii) $FeCl_3$/EtOH/rt; (iii) MeCOONa/heat; (iv) RCOCl, $(RCO)_2O$ or RCOOH. R= (a) C_6H_5; (b) 4-MeC_6H_4; (c) R = 4-ClC_6H_4; (d) 4-$MeOC_6H_4$; (e) 4-$O_2NC_6H_4$; (f) 4-$Me_2NC_6H_4$; (g) PhCH=CH–; (h) 1-naphthyl; (i) 2-furyl; (j) 2-thienyl; (k) CH_3; (l) H.

All such hydrazones have not been reported hitherto. Their structures were confirmed by their elemental analyses and spectral (MS, IR and ^{1}H NMR) data (see Section 3). For example, their ^{1}H NMR spectra in $CDCl_3$ revealed, in each case, a characteristic signal in the region δ 8.0–8.2 assignable to the –N=CH– proton. Their IR spectra showed the characteristic band for the N–H stretch of the hydrazone group in the region 3393–3248 cm^{-1}.

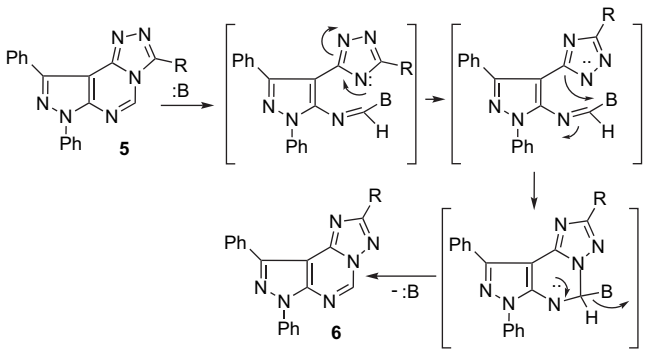


Scheme 2.

Treatment of each of the hydrazones **4** with 4 equiv of iron(III) chloride in ethanol for 12 h gave, in each case, a single product as evidenced by TLC analysis. Elemental analyses and mass spectra revealed that each of such isolated products has two hydrogens less than the respective hydrazone. This finding was confirmed by the ^{1}H NMR spectra, which indicated the absence of the –N=CH– and hydrazone –NH-N=C protons. On the basis of this finding, the isolated products were assigned the structure of 3-substituted-7,9-diphenylpyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **5a**–**l** (Scheme 1). The conversion of **4** into **5** is reminiscent of other related oxidative cyclization of aldehyde *N*-heteroarylhydrazones with iron(III) chloride, which have been reported to proceed via generation of the respective nitrilimines, which undergo in situ 1,5-electrocyclization to give the respective fused heterocycles.[17,18]

When each of the pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine derivatives **5** was heated in ethanol in the presence of sodium acetate, they isomerized to the thermodynamically more stable pyrazolo[4,3-*e*][1,2,4] [1,5-*c*]pyrimidine derivative **6** through tandem ring opening and ring closure reactions (Scheme 3). This rearrangement is consistent with those reported in some earlier reports.[16, 19] The structures of 6 were determined by elemental analyses and spectral (MS, IR, ^{1}H NMR) data (see Section 3).

To provide a decisive evidence for this rearrangement, the products **6a**, **6k** and **6l** were compared with authentic samples prepared by an alternative synthesis.[1] Thus, in our hands, treatment



Scheme 3.

of **1** with 1 equiv quantity of each of benzoyl chloride, acetic anhydride and formic acid gave products, [1] which proved identical in all respects (mp, mixed mp, IR and ^{1}H NMR spectra) with those obtained above from base-catalyzed rearrangement of **5a**, **5k**, and **5l**, respectively (Scheme 1). This finding confirms the base-catalyzed rearrangement of **5** into **6** (Scheme 1). A further evidence for the rearrangement of **5** into **6** is provided by comparison of the ^{1}H NMR spectrum of **5l** with that of **6l**. For example, the ^{1}H NMR spectrum of **5l** reveals the triazole C3–H proton signal at δ 8.88, whereas that of **6l** shows the C2–H proton signal at δ 8.47. This feature is consistent with the literature reports, which indicate that the C3–H proton of *s*-triazolo[4,3-*c*]pyrimidine is more deshielded than that of C2–H of *s*-triazolo[1,5-*c*]pyrimidine.[20] The driving force for the observed rearrangement is the fact that [1,2,4]triazolo[1,5-*c*]pyrimidine ring system is thermodynamically more stable than its isomer namely [1,2,4]triazolo[4,3-*c*]pyrimidine.[21]

In conclusion, we have presented a facile strategy for the general synthesis of the title compounds **5** and **6**. Such new heterocycles will be evaluated in pharmacological assays to determine their activities as xanthine oxidase inhibitors and human adenosine antagonists.

3. Experimental

3.1. General

All melting points were determined on an electrothermal Gallenkamp apparatus. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz) in $CDCl_3$. The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. The starting 5-amino-1,3-diphenyl-4,5-dihydro-4-imino-1*H*-pyrazolo[3,4-*d*]pyrimidine **1** was prepared according to a literature method.[1] The 2-phenyl-, 2-methyl- and 2-unsubstituted derivatives of 7,9-diphenylpyrazolo[4,3-*e*][1,2,4]triazolo[1,5-c]pyrimidines (**6a**, **6k**, **6l**) were also prepared as previously described from **1** and the respective one-carbon atom cyclizing agents.[1]

3.2. 4-Hydrazino-1,3-diphenylpyrazolo[3,4-*d*]pyrimidine (2)

3.2.1. *Method A*

To 5-amino-1,3-diphenyl-4-imino-4,5-dihydro-1*H*-pyrazolo[3,4-*d*] pyrimidine **1** (1.51 g, 5 mmol) in ethanol (30 mL) was added hydrazine hydrate (80%, 8.5 mL). The mixture was stirred at room temperature for 24 h. The solid that precipitated was filtered and crystallized from dioxane to give **2** as white solid, yield 1.3 g (83%), mp 204 °C.

3.2.2. Method B

To 1,3-diphenyl-4-cyano-5-ethoxymethyleneaminopyrazole (1.58 g, 5 mmol) in ethanol was added hydrazine hydrate (10 mL, 80%). The mixture was stirred at room temperature for 24 h and then the solid that precipitated was filtered and crystallized from dioxane to give **2** (1.3 g, 83%) as white solid, mp 204 °C; IR ν (KBr) 3420, 3307 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.03 (s, 2H, NH_2), 5.33 (s, 1H, NH), 7.33–8.24 (m, 10H, ArH), 8.58 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 303 (M^++1, 26), 302 (M^+, 100), 287 (36), 272 (41), 194 (16), 170 (16), 143 (20), 104 (21), 77 (84). Anal. Calcd for $C_{17}H_{14}N_6$ (302.34): C, 67.54; H, 4.67; N, 27.80. Found: C, 67.60; H, 4.34; N, 27.65%.

3.3. Aldehyde *N*-(1,3-diphenylpyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazones 4a–l

3.3.1. General procedure

To a mixture of 4-hydrazino-1,3-diphenylpyrazolo[3,4-*d*]pyrimidine **2** (1.51 g, 5 mmol) and the appropriate aldehyde **3** (5 mmol) in ethanol (50 mL), few drops of acetic acid were added and the reaction mixture was refluxed for 2 h and then cooled. The precipitate, formed upon cooling, was filtered off, washed with water and then with ethanol and finally crystallized from the appropriate solvent to give the corresponding hydrazone derivative **4**.

*3.3.2. Benzaldehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4a**)*

Yellow crystals (yield 1.6 g, 86%), mp 177–178 °C (dioxane); IR ν (KBr) 3332, 3057, 1637 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.34–8.18 (m, 16H, ArH and NH), 8.08 (s, 1H, –N=CH), 8.36 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 391 (M^++1, 19), 390 (M^+, 57), 388 (17), 313 (56), 286 (100), 259 (14), 104 (17), 91 (16), 77 (92). Anal. Calcd for $C_{24}H_{18}N_6$ (390.45): C, 73.83; H, 4.65; N, 21.52. Found: C, 73.95; H, 4.76; N, 21.48%.

*3.3.3. p-Tolualdehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4b**)*

Yellow crystals (yield 1.9 g, 88%), mp 213–215 °C (dioxane); IR ν (KBr) 3264, 3053, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.38 (s, 3H, CH_3), 7.17–8.19 (m, 15H, ArH and NH), 8.06 (s, 1H, –N=CH), 8.47 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 406 (M^++2, 1), 405 (M^++1, 17), 404 (M+, 38), 313 (26), 286 (100), 194 (20), 103 (11), 91 (14). Anal. Calcd for $C_{25}H_{20}N_6$ (404.48): C, 74.24; H, 4.98; N, 20.78. Found: C, 74.12; H, 4.90; N, 20.72%.

*3.3.4. p-Chlorobenzaldehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4c**)*

Yellow crystals (yield 1.8 g, 87%), mp 231–232 °C (dioxane); IR ν (KBr) 3262, 3058, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.33–8.18 (m, 15H, ArH and NH), 8.09 (s, 1H, –N=CH), 8.31 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 426 (M^++2, 14), 425 (M^++1, 15), 424 (M^+, 38), 286 (100), 259 (9), 104 (6), 77 (43). Anal. Calcd for $C_{24}H_{17}ClN_6$ (424.90): C, 67.84; H, 4.03; N, 19.78. Found: C, 67.62; H, 4.28; N, 19.72%.

*3.3.5. p-Methoxybenzaldehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4d**)*

Yellow crystals (yield 1.93 g, 92%), mp 187–188 °C (dioxane); IR ν (KBr) 3261, 3056, 2962, 1502 cm^{-1}; ^1H NMR ($CDCl_3$), δ (ppm): 3.70 (s, 3H, CH_3), 6.87–8.18 (m, 15H, ArH and NH), 8.02 (s, 1H, –N=CH), 8.31 (s, 1H, pyrimidine); MS *m*/*z* (%): 421 (M^++1, 14), 420 (M^+, 33), 286 (100), 259 (12), 90 (11), 77 (38). Anal. Calcd for $C_{25}H_{20}N_6O$ (420.48): C, 71.41; H, 4.79; N, 19.99. Found: C, 71.37; H, 4.51; N, 19.87%.

*3.3.6. p-Nitrobenzaldehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4e**)*

Orange crystals (yield 1.95 g, 90%), mp 289–290 °C (dioxane); IR ν (KBr) 3319, 1633 cm^{-1}; ^1H NMR ($CDCl_3$), δ (ppm): 7.22–8.32 (m, 15H, ArH and NH), 8.35 (s, 1H, –N=CH), 8.72 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 436 (M^++1, 16), 435 (M^+, 100), 313 (58), 286 (95), 102 (14), 91 (9), 77 (48). Anal. Calcd for $C_{24}H_{17}N_7O_2$ (435.45): C, 66.20; H, 3.94; N, 22.52. Found: C, 66.04; H, 3.82; N, 22.31%.

*3.3.7. p-Dimethylaminobenzaldehyde N-(1,3-diphenylpyrazolo[3,4-d] pyrimidin-4-yl)hydrazone (**4f**)*

Yellow crystals (yield 1.84 g, 85%), mp 141–142 °C (dioxane); IR ν (KBr) 3305, 2893, 1637 cm^{-1}; ^1H NMR ($CDCl_3$), δ (ppm): 3.01 (s, 6H, CH_3), 6.65–7.56 (m, 15H, ArH and NH), 8.16 (s, 1H, –N=CH), 8.19 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 434 (M^++1, 11), 433 (M^+, 35), 286 (100), 146 (66), 118 (10), 77 (35). Anal. Calcd for $C_{26}H_{23}N_7$ (433.52): C, 72.04; H, 5.35; N, 22.62. Found: C, 72.17; H, 5.44; N, 22.38%.

*3.3.8. Cinnamaldehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4g**)*

Yellow crystals (yield 1.83 g, 88%), mp 189–190 °C (dioxane); IR ν (KBr) 3322, 3053, 1634 cm^{-1}; ^1H NMR ($CDCl_3$), δ (ppm): 6.85–7.05 (m, 2H, CH=CHPh), 7.29–8.22 (m, 16H, ArH and NH), 8.06 (s, 1H, –N=CH), 8.33 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 417 (M^++1, 8), 416 (M^+, 32), 413 (10), 339 (33), 286 (100), 129 (18), 115 (25), 102 (15), 77 (90). Anal. Calcd for $C_{26}H_{20}N_6$ (416.49): C, 74.98; H, 4.84; N, 20.18. Found: C, 74.75; H, 4.75; N, 20.11%.

*3.3.9. 1-Naphthaldehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4h**)*

Yellow crystals (yield 1.87 g, 85%), mp 211–212 °C (dioxane); IR ν (KBr) 3326, 3056, 1635 cm^{-1}; ^1H NMR ($CDCl_3$), δ (ppm): 7.39–8.55 (m, 18H, ArH and NH), 8.04 (s, 1H, –N=CH), 8.31(s, 1H, pyrimidine-H); MS *m*/*z* (%): 441 (M^++1, 9), 440 (M^+, 30), 313 (20), 286 (100), 153 (14), 127 (17), 77 (38). Anal. Calcd for $C_{28}H_{20}N_6$ (440.51): C, 76.35; H, 4.58; N, 19.08. Found: C, 76.15; H, 4.45; N, 18.93%.

*3.3.10. 2-Furanaldehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4i**)*

Yellow crystals (yield 1.56 g, 82%), mp 191–192 °C (dioxane); IR ν (KBr) 3393, 3042, 1636 cm^{-1}; ^1H NMR ($CDCl_3$), δ (ppm): 6.49–8.14 (m, 14H, ArH and NH), 8.01 (s, 1H, –N=CH), 8.24 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 380 (M^+, 38), 287 (54), 286 (100), 195 (5), 194 (31), 77 (35). Anal. Calcd for $C_{22}H_{16}N_6O$ (380.41): C, 69.46; H, 4.24; N, 22.09. Found: C, 69.63; H, 4.13; N, 22.22%.

*3.3.11. 2-Thiophenaldehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4j**)*

Yellow crystals (yield 1.70 g, 86%), mp 192–193 °C (dioxane); IR ν (KBr) 3326, 3053, 1634 cm^{-1}; ^1H NMR ($CDCl_3$), δ (ppm): 7.06–8.12 (m, 14H, ArH and NH), 7.99 (s, 1H, –N=CH), 8.31 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 398 (M^++2, 8), 397 (M^++1, 18), 396 (M^+, 65), 286 (100), 259 (11), 96 (11), 77 (62). Anal. Calcd for $C_{22}H_{16}N_6S$ (396.48): C, 66.65; H, 4.07; N, 21.20. Found: C, 66.59; H, 4.14; N, 20.94%.

*3.3.12. 2-Acetaldehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4k**)*

Yellow crystals (yield 1.41 g, 86%), mp 209–210 °C (dioxane); IR ν (KBr) 3248, 3066, 2930, 1640 cm^{-1}; ^1H NMR ($CDCl_3$), δ (ppm): 1.79 (d, *J*=5.7, 3H, CH_3), 6.38 (q, *J*=5.7, 1H, –N=CH), 7.45–8.45 (m, 11H, ArH and NH), 7.67 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 330 (M^++2, 1), 329 (M^++1, 3), 328 (M^+, 15), 313 (85), 104 (11), 77 (100). Anal. Calcd for $C_{19}H_{16}N_6$ (328.38): C, 69.50; H, 4.91; N, 25.59. Found: C, 69.32; H, 4.85; N, 25.67%.

*3.3.13. 2-Formaldehyde N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazone (**4l**)*

Yellow crystals (yield 1.27 g, 81%), mp 194–195 °C (dioxane); IR ν (KBr) 3330, 3058, 1655 cm^{-1}; ^1H NMR ($CDCl_3$), δ (ppm): 5.37 (s,

2H, –N=CH_2), 7.25–8.49 (m, 11H, ArH and NH), 7.52 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 316 (M^++2, 5), 315 (M^++1, 5), 314 (M^+, 15), 287 (49), 127 (9), 104 (10), 77 (100). Anal. Calcd for $C_{18}H_{14}N_6$ (314.35): C, 68.78; H, 4.49; N, 26.74. Found: C, 68.83; H, 4.37; N, 26.63%.

3.4. 3-Substituted-7,9-diphenylpyrazolo[4,3-*e*][1,2,4]triazolo-[4,3-*c*]pyrimidines 5a–l

3.4.1. General procedure

To a solution of the appropriate hydrazone **4** (1 mmol) in ethanol (25 mL) was added a solution of ferric chloride (2 M, 2 mL) and the mixture was stirred at room temperature for 12 h. The precipitated solid was filtered off, washed with water and then with ethanol and finally crystallized from DMF–EtOH to give the respective 3-substituted-7,9-diphenylpyrazolo[4,3-*e*][1,2,4]triazolo [4,3-*c*]-pyrimidine.

3.4.2. 3,7,9-Triphenylpyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5a**)

White crystals (yield 0.3 g, 78%), mp 233–234 °C; IR *ν* (KBr) 3063, 1626 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 7.42–8.90 (m, 15H, ArH), 8.95 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 390 (M^++2, 5), 389 (M^++1, 23), 388 (M+, 100), 103 (7), 77 (21). Anal. Calcd for $C_{24}H_{16}N_6$ (388.44): C, 74.21; H, 4.15; N, 21.64. Found: C, 73.97; H, 4.16; N, 21.34%.

3.4.3. 7,9-Diphenyl-3-(p-tolyl)pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5b**)

White crystals (yield 0.31 g, 82%), mp 259–260 °C; IR *ν* (KBr) 3054, 2917, 1623 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 2.51 (s, 3H, CH_3), 7.43–8.91 (m, 14H, ArH), 8.95 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 404 (M^++2, 5), 403 (M^++1, 37), 402 (M^+, 100), 103 (17), 77 (48). Anal. Calcd for $C_{25}H_{18}N_6$ (402.46): C, 74.61; H, 4.51; N, 20.88. Found: C, 74.43; H, 4.55; N, 20.64%.

3.4.4. 7,9-Diphenyl-3-(p-chlorophenyl) pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5c**)

White crystals (yield 0.34 g, 80%), mp 254–255 °C; IR *ν* (KBr) 3058, 1624 cm^{-1} ^1H NMR ($CDCl_3$): *δ* 7.55–8.88 (m, 14H, ArH), 8.92 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 424 (M^++2, 30), 423 (M^++1, 30), 422 (M^+, 100), 153 (10), 103 (19), 77 (68). Anal. Calcd for $C_{24}H_{15}ClN_6$ (422.88): C, 68.17; H, 3.58; N, 19.87. Found: C, 68.10; H, 3.40; N, 19.76%.

3.4.5. 7,9-Diphenyl-3-(p-methoxyphenyl)pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5d**)

White grey crystals (yield 0.33 g, 81%), mp 199–200 °C; IR *ν* (KBr) 3064, 2934, 1626 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 3.93 (s, 3H, CH_3), 7.31–8.91 (m, 14H, ArH), 8.93 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 420 (M^++2, 4), 419 (M^++1, 26), 418 (M^+, 100), 209 (9), 103 (20), 77 (50). Anal. Calcd for $C_{25}H_{18}N_6O$ (418.46): C, 71.76; H, 4.34; N, 20.08. Found: C, 71.43; H, 4.47; N, 19.94%.

3.4.6. 7,9-Diphenyl-3-(p-nitrophenyl)pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5e**)

Orange brown crystals (yield 0.32 g, 75%), mp 213–214 °C; IR *ν* (KBr) 3059, 1634 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 7.49–9.24 (m, 14H, ArH), 9.28 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 435 (M^++2, 69), 434 (M^++1, 45), 433 (M^+, 75), 286 (100), 259 (16), 156 (15), 103 (21), 77 (60). Anal. Calcd for $C_{24}H_{15}N_7O_2$ (433.43): C, 66.51; H, 3.49; N, 22.62. Found: C, 66.38; H, 3.35; N, 22.48%.

3.4.7. 7,9-Diphenyl-3-(p-dimethylaminophenyl)pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5f**)

Yellow crystals (yield 0.34 g, 80%), mp 257–258 °C; IR *ν* (KBr) 3059, 2860, 1609 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 3.08 (s, 6H, CH_3), 7.55–8.93 (m, 14H, ArH), 8.98 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 433 (M^++2, 5), 432 (M^++1, 34), 431 (M^+, 100), 145 (9), 77 (11). Anal. Calcd for $C_{26}H_{21}N_7$ (431.50): C, 72.37; H, 4.91; N, 22.72. Found: C, 72.14; H, 4.73; N, 22.78%.

3.4.8. 7,9-Diphenyl-3-(cinnamyl)pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5g**)

White grey crystals (yield 0.33 g, 81%), mp277–278 °C; IR *ν* (KBr) 3054, 1625 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 6.83–6.96 (m, 2H, CH=CHPh), 7.42–8.26 (m, 15H, ArH), 8.89 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 416 (M^++2, 22), 415 (M^++1, 48), 414 (M^+, 90), 413 (100), 128 (14), 77 (41). Anal. Calcd for $C_{26}H_{18}N_6$ (414.47): C, 75.35; H, 4.38; N, 20.28. Found: C, 75.17; H, 4.48; N, 20.64%.

3.4.9. 7,9-Diphenyl-3-(1-naphthyl)pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5h**)

White-green crystals (yield 0.36 g, 83%), mp 256–257 °C; IR *ν* (KBr) 3053, 1624 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 7.51–8.96 (m, 17H, ArH), 8.52 (s, 1H, pyrimidine-H). MS *m*/*z* (%): 440 (M^++2, 14), 439 (M^++1, 50), 438 (M^+, 59), 437 (100), 219 (19), 153 (23), 127 (18), 77 (99). Anal. Calcd for $C_{28}H_{18}N_6$ (438.50): C, 76.70; H, 4.14; N, 19.17. Found: C, 76.79; H, 4.08; N, 19.51%.

3.4.10. 7,9-Diphenyl-3-(2-furyl)pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5i**)

White grey crystals (yield 0.30 g, 80%), mp 265–266 °C; IR *ν* (KBr) 3059, 1623 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 6.72–8.86 (m, 13H, ArH), 9.48 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 380 (M^++2, 6), 379 (M^++1, 26), 378 (M^+, 100), 103 (10), 77 (48). Anal. Calcd for $C_{22}H_{14}N_6O$ (378.40): C, 69.83; H, 3.73; N, 22.21. Found: C, 70.08; H, 3.72; N, 22.06%.

3.4.11. 7,9-Diphenyl-3-(2-theinyl)pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5j**)

White-brown crystals (yield 0.33 g, 85%), mp 241–242 °C; IR *ν* (KBr) 3067, 1621 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 7.31–8.89 (m, 13H, ArH), 9.12 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 396 (M^++2, 4), 395 (M^++1, 25), 394 (M^+, 75), 197 (12), 129 (12), 103 (25), 77 (100). Anal. Calcd for $C_{22}H_{14}N_6S$ (394.46): C, 66.99; H, 3.58; N, 21.31. Found: C, 67.25; H, 3.49; N, 21.47%.

3.4.12. 7,9-Diphenyl-2-methylpyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5k**)

White crystals (yield 0.25 g, 78%), mp 227–228 °C; IR *ν* (KBr) 3060, 2927, 1598 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 2.98 (s, 3H, CH_3), 7.37–8.23 (m, 10H, ArH), 8.87 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 327 (M^++1, 9), 326 (M^+, 6), 302 (47), 273 (13), 142 (15), 104 (11), 77 (100). Anal. Calcd for $C_{19}H_{14}N_6$ (326.36): C, 69.93; H, 4.32; N, 25.75. Found: C, 70.03; H, 4.11; N, 26.03%.

3.4.13. 7,9-Diphenylpyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (**5l**)

White crystals (yield 0.25 g, 80%), 274–276 °C; IR *ν* (KBr) 3039, 1624 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 7.45–8.84 (m, 10H, ArH), 8.88 (s, 1H, triazole-CH), 9.00 (s, 1H, pyrimidine-H). MS *m*/*z* (%): 313 (M^++1, 11), 312 (M^+, 81), 129 (10), 103 (17), 77 (100). Anal. Calcd for $C_{18}H_{12}N_6$ (312.34): C, 69.22; H, 3.87; N, 26.91. Found: C, 68.96; H, 3.65; N, 27.06%.

3.5. 2-Substituted-7,9-diphenylpyrazolo[4,3-*e*][1,2,4]triazolo-[1,5-*c*]pyrimidines 6a–l

3.5.1. General procedure

To a solution of the appropriate **5** (1 mmol) in ethanol (50 mL) was added sodium acetate (0.164 g, 2 mmol) and the mixture was refluxed for 6 h and then cooled. The precipitated solid was filtered off, washed with water and then with ethanol and finally crystallized from dimethylformamide to give the respective 2-substituted-7,9-diphenylpyrazolo[3,4-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine.

*3.5.2. 2,7,9-Triphenylpyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (**6a**)*

White crystals (yield 0.33 g, 86%), mp 223–225 °C (lit. mp 222 °C);[1] IR ν (KBr) 3061, 1634 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.42–8.91 (m, 15H, ArH), 9.22 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 388 (M^+, 100), 387 (39), 104 (5), 77 (50). Anal. Calcd for $C_{24}H_{16}N_6$ (388.44): C, 74.21; H, 4.15; N, 21.64. Found: C, 74.16; H, 4.97; N, 21.35%.

*3.5.3. 7,9-Diphenyl-2-(p-tolyl)pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (**6b**)*

White crystals (yield 0.31 g, 79%), mp 271–272 °C; IR ν (KBr) 3056, 2916, 1632 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 7.34–8.91 (m, 14H, ArH), 9.19 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 404 (M^++2, 5), 403 (M^++1, 28), 402 (M^+, 100), 77 (12). Anal. Calcd for $C_{25}H_{18}N_6$ (402.46): C, 74.61; H, 4.51; N, 20.88. Found: C, 74.48; H, 4.43; N, 21.03%.

*3.5.4. 7,9-Diphenyl-2-(p-chlorophenyl)pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (**6c**)*

White crystals (yield 0.35 g, 83%), mp 298–300 °C; IR ν (KBr) 3058, 1629 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45–8.88 (m, 14H, ArH), 9.22 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 424 (M^++2, 40), 423 (M^++1, 42), 422 (M^+, 100), 421 (34), 77 (37). Anal. Calcd for $C_{24}H_{15}ClN_6$ (422.88): C, 68.17; H, 3.58; N, 19.87. Found: C, 68.40; H, 3.46; N, 19.94%.

*3.5.5. 7,9-Diphenyl-2-(p-methoxyphenyl)pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (**6d**)*

White crystals (yield 0.33 g, 81%), mp 283–284 °C; IR ν (KBr) 3059, 2834, 1633 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.92 (s, 3H, CH_3), 7.06–8.91 (m, 14H, ArH), 9.19 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 420 (M^++2, 5), 419 (M^++1, 30), 418 (M^+, 100), 417 (20), 77 (21). Anal. Calcd for $C_{25}H_{18}N_6O$ (418.46): C, 71.76; H, 4.34; N, 20.08. Found: C, 71.60; H, 4.28; N, 20.20%.

*3.5.6. 7,9-Diphenyl-2-(p-nitrophenyl)pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (**6e**)*

Yellow crystals (yield 0.36 g, 85%), mp 346–348 °C; IR ν (KBr) 3083, 1631 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.43–8.86 (m, 14H, ArH), 9.37 (s, 1H, pyrimidine-H). MS *m*/*z* (%): 435 (M^++2, 32), 434 (M^++1, 88), 433 (M^+, 100), 432 (16), 386 (14), 77 (60). Anal. Calcd for $C_{24}H_{15}N_7O_2$ (433.43): C, 66.51; H, 3.49; N, 22.62. Found: C, 66.74; H, 3.59; N, 22.46%.

*3.5.7. 7,9-Diphenyl-2-(p-dimethylaminophenyl)pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (**6f**)*

White crystals (yield 0.36 g, 84%), mp 308–310 °C; IR ν (KBr) 3056, 2897, 1609 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.09 (s, 6H, CH_3), 6.37–8.92 (m, 14H, ArH), 9.17 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 432 (M^++1, 89), 431 (M^+, 80), 424 (25), 422 (100), 403 (34), 216 (18), 77 (31). Anal. Calcd for $C_{26}H_{21}N_7$ (431.50): C, 72.37; H, 4.91; N, 22.72. Found: C, 72.20; H, 4.86; N, 22.59%.

*3.5.8. 7,9-Diphenyl-2-(cinnamyl)pyrazolo[3,4-e][1,2,4]triazolo[1,5-c]pyrimidine (**6g**)*

White crystals (yield 0.33 g, 80%), mp 251–252 °C; IR ν (KBr) 3062, 1625 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.25–7.30 (m, 2H, CH=CHPh), 7.33–8.85 (m, 15H, ArH), 9.15 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 415 (M^++1, 21), 414 (M^+, 92), 413 (100), 337 (11), 128 (12), 77 (27). Anal. Calcd for $C_{26}H_{18}N_6$ (414.47): C, 75.35; H, 4.38; N, 20.28. Found: C, 75.39; H, 4.62; N, 20.34%.

*3.5.9. 7,9-Diphenyl-2-(1-naphthyl)pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine (**6h**)*

White crystals (yield 0.35 g, 80%), mp 249–250 °C; IR ν (KBr) 3055, 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45–9.43 (m, 17H, ArH), 9.23 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 440 (M^++2, 30), 439 (M^++1, 92), 438 (M^+, 100), 437 (38), 219 (22), 153 (25), 127 (17), 77 (72). Anal. Calcd for $C_{28}H_{18}N_6$ (438.50): C, 76.70; H, 4.14; N, 19.17. Found: C, 76.79; H, 3.95; N, 19.03%.

*3.5.10. 7,9-Diphenyl-2-(2-furyl)pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (**6i**)*

White crystals (yield 0.30 g, 78%), mp 254–255 °C; IR ν (KBr) 3065, 1623 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.63–8.82 (m, 13H, ArH), 9.21 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 380 (M^++2, 4), 379 (M^++1, 28), 378 (M^+, 100), 377 (29), 77 (46). Anal. Calcd for $C_{22}H_{14}N_6O$ (378.40): C, 69.83; H, 3.73; N, 22.21. Found: C, 69.56; H, 3.46; N, 22.14%.

*3.5.11. 7,9-Diphenyl-2-(2-thienyl)pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine **(6j)***

White crystals (yield 0.32 g, 82%), mp 277–278 °C; IR ν (KBr) 3068, 1632 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.20–8.85 (m, 13H, ArH), 9.45 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 396 (M^++2, 8), 395 (M^++1, 33), 394 (M^+, 100), 393 (38), 77 (22). Anal. Calcd for $C_{22}H_{14}N_6S$ (394.46): C, 66.99; H, 3.58; N, 21.31. Found: C, 67.10; H, 3.49; N, 21.09%.

*3.5.12. 7,9-Diphenyl-2-methylpyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (**6k**)*

White crystals (yield 0.25 g, 78%), mp 182–183 °C (lit. mp 185 °C);[1] IR ν (KBr) 3062, 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.71 (s, 3H, CH_3), 7.34–8.78 (m, 10H, ArH), 9.11 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 327 (M^++1, 29), 326 (M^+, 100), 325 (32), 77 (29). Anal. Calcd for $C_{19}H_{14}N_6$ (326.36): C, 69.93; H, 4.32; N, 25.75. Found: C, 69.81; H, 4.17; N, 25.62%.

*3.5.13. 7,9-Diphenylpyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (**6l**)*

White crystals (yield 0.25 g, 80%), mp 234–235 °C (lit. mp 233 °C);[1] IR ν (KBr) 3068, 1632 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.44–8.76 (m, 10H, ArH), 8.47 (s, 1H, triazole-CH), 9.23 (s, 1H, pyrimidine-H); MS *m*/*z* (%): 313 (M^++1, 18), 312 (M^+, 79), 311 (38), 156 (14), 127 (22), 77 (100). Anal. Calcd for $C_{18}H_{12}N_6$ (312.34): C, 69.22; H, 3.87; N, 26.91. Found: C, 69.08; H, 3.96; N, 26.67%.

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