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Synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines

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Abstract Starting from 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones, a synthesis pathway to the tricyclic pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines is described. Reaction of 1,5-dihydro-4*H*-pyrazolo[3,4-*d*] pyrimidin-4-ones with phosphoryl chloride afforded the corresponding 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidines. Treatment of these compounds with hydrazine hydrate at reflux temperature gave the hydrazino derivatives, which were subsequently cyclized to the titled compounds on heating with orthoesters in ethanol.

Keywords Pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines; Phosphoryl chloride; Hydrazine hydrate; Triethylorthoesters; Cyclocondensation.

Introduction

Pyrazolotriazolopyrimidines are a class of fused heterocycles interesting from the view point of pharmacological activities [1–4]. There are few reports on the synthesis and chemistry of these compounds in literature [1, 2, 5–11]. The pyrazolo[4,3-*e*]-[1,2,4]triazolo[4,3-*c*]pyrimidine ring system is one of them that has not received much attention and very little is known about the synthesis and properties of these compounds [1, 10, 11]. Prompted by these findings and due to our interest in the synthesis of new heterocyclic compounds with potential biological activities [12–21], and in continuation of our work on the synthesis of new pyrazolotriazolopyrimidines [22], we report herein a convenient synthesis of some new pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **4a**–**4f** that might be of pharmacological importance.

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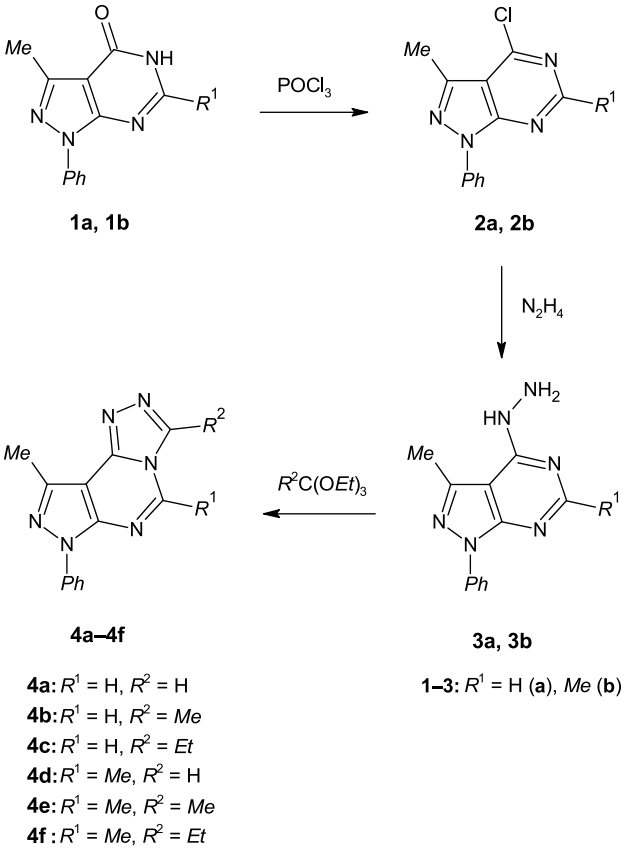
Results and discussion

Our approach is based on the use of 1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones **1a** and **1b** as the starting materials [23]. Reaction of these compounds with phosphoryl chloride gave the corresponding 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidines **2a** and **2b**. The chloro derivatives **2a** and **2b** were then stirred with hydrazine hydrate at room temperature to give the hydrazino derivatives **3a** and **3b**. The latter compounds subsequently underwent cyclocondensation with triethylorthoesters in ethanol on heating under reflux to give the desired tricyclic pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **4a**–**4f** (Scheme 1).

The structural assignment of the new compounds **2**–**4** is based upon spectroscopic and microanalytical data. For example, the ^{1}H NMR spectrum of **4d** did not show the NH_2 and NH signals of the precursor **3b** at $\delta = 4.75$ and 8.68 ppm, but instead showed a sharp ^{1}H signal at $\delta = 9.53$ ppm belonging to the triazole ring indicating the formation of the tricyclic **4d**. The IR spectrum was devoid of the NH_2 and NH absorption bands at $\bar{\nu} = 3375$,



Scheme 1

3330, and 3265 cm^{-1} of the precursor. The MS of **4d** showed a molecular ion peak at $m/z = 264$ (M^+) corresponding to the molecular formula $C_{14}H_{12}N_6$.

In conclusion, we describe the synthesis of new pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **4a–4f** through cyclocondensation of hydrazino derivatives **3a–3b** with triethylorthoesters in boiling ethanol.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 ev. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer and the results were found to agree satisfactorily with the calculated values.

*General procedure for the synthesis of 4-chloro-1H-pyrazolo-[3,4-d]pyrimidines **2a** and **2b***

1,5-Dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones **1a** and **1b** (5 mmol) and 20 cm^3 $POCl_3$ were heated under reflux for 5.0 h. After the completion of the reaction (monitored by TLC, $CHCl_3$:*Me*OH, 95:5), the solvent was evaporated *in vacuo*, ice–water was added, and the mixture extracted with chloroform. The chloroform layer was separated and evaporated to dryness to give **2a** and **2b** in 73 and 70% yields.

4-Chloro-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2a**, $C_{12}H_9ClN_4$)

Mp 91–93°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 2.70$ (s, CH_3), 7.30–8.20 (m, 5H-phenyl), 8.92 (s, 1H, CH-6) ppm; MS: m/z (%) = 246 [$M^+ + 2$] (12), 244 [M^+] (35), 210 (28), 182 (22), 153 (31), 102 (37), 91 (25), 77 (100).

4-Chloro-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]-pyrimidine (**2b**, $C_{13}H_{11}ClN_4$)

Mp 85–87°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 2.65$ (s, CH_3), 2.83 (s, CH_3), 7.25–8.20 (m, 5H-phenyl) ppm; MS: m/z (%) = 260 [$M^+ + 2$] (18), 259 (33), 258 [M^+] (53), 257 (100), 222 (23), 196 (34), 152 (12), 102 (20), 91 (17), 77 (81).

*General procedure for the synthesis of 4-hydrazino-1H-pyrazolo[3,4-d]pyrimidines **3a** and **3b***

A mixture of 3 mmol **2a** or **2b** and 10 cm^3 hydrazine hydrate was stirred at room temperature for 10.0 h. After the completion of the reaction (monitored by TLC, $CHCl_3$:*Me*OH, 95:5), the precipitate was filtered off and recrystallized from ethanol to give **3a** and **3b** in 95% and 89% yields.

4-Hydrazino-3-methyl-1-phenyl-1H-pyrazolo[3,4-d]-pyrimidine (**3a**, $C_{12}H_{12}N_6$)

Mp 218–220°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 2.62$ (s, CH_3), 4.63 (broad, NH_2), 7.20–8.25 (m, 5H-phenyl), 8.32 (s, 1H, CH-6), 8.80 (broad, NH) ppm; IR (KBr): $\bar{\nu} = 3380$, 3315, and 3250 (NH_2, NH) cm^{-1}; MS: m/z (%) = 240 [M^+] (17), 239 (51), 238 (92), 224 (32), 183 (28), 154 (12), 103 (36), 91 (29), 77 (100).

4-Hydrazino-3,6-dimethyl-1-phenyl-1H-pyrazolo[3,4-d]-pyrimidine (**3b**, $C_{13}H_{14}N_6$)

Mp 225–227°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 2.49$ (s, CH_3), 2.60 (s, CH_3), 4.75 (broad, NH_2), 7.15–8.20 (m, 5H-phenyl), 8.68 (broad, NH) ppm; IR (KBr): $\bar{\nu} = 3375$, 3330, and 3265 (NH_2, NH) cm^{-1}; MS: m/z (%) = 254 [M^+] (11), 253 (35), 252 (100), 238 (21), 197 (19), 153 (16), 102 (23), 91 (15), 77 (73).

*General procedure for the synthesis of pyrazolo[4,3-e]-[1,2,4]triazolo[4,3-c]pyrimidines **4a–4e***

To a solution of 2 mmol **3a** or **3b** in 10 cm^3 ethanol 3 mmol of the respective triethylorthoester was added. The reaction mixture was heated under reflux for 6.0 h. After the completion of the reaction (monitored by TLC, $CHCl_3$:*Me*OH, 95:5), the mixture was cooled to room temperature. The crude product was collected and recrystallized from ethanol to give **4a–4e** in high yields.

9-Methyl-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]-pyrimidine (**4a**, $C_{13}H_{10}N_6$)
Yield 80%; mp 260–263°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 2.74$ (s, CH_3), 7.35–8.15 (m, 5H-phenyl), 9.32 (s, 1H, CH-5), 9.43 (s, 1H, CH-3) ppm; MS: m/z (%) = 250 [M^+] (9), 249 (10), 248 (34), 242 (33), 224 (100), 208 (26), 154 (21), 103 (34), 91 (21), 77 (97).

3,9-Dimethyl-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo-[4,3-c]pyrimidine (**4b**, $C_{14}H_{12}N_6$)
Yield 74%; mp 255–257°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 2.71$ (s, CH_3), 2.82 (s, CH_3), 7.30–8.20 (m, 5H-phenyl), 9.23 (s, 1H, CH-5) ppm; MS: m/z (%) = 264 [M^+] (2), 263 (4), 262 (22), 261 (100), 235 (4), 224 (6), 153 (13), 102 (19), 91 (7), 77 (60).

3-Ethyl-9-methyl-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo-[4,3-c]pyrimidine (**4c**, $C_{15}H_{14}N_6$)
Yield 72%; mp 228–230°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 1.41$ (t, $J = 7.0$ Hz, CH_3), 2.72 (s, CH_3), 3.19 (q, $J = 7.0$ Hz, CH_2), 7.35–8.30 (m, 5H-phenyl), 9.26 (s, 1H, CH-5) ppm; MS: m/z (%) = 278 [M^+] (3), 277 (28), 276 (98), 252 (12), 224 (12), 152 (10), 103 (22), 91 (17), 77 (100).

5,9-Dimethyl-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo-[4,3-c]pyrimidine (**4d**, $C_{14}H_{12}N_6$)
Yield 75%; mp 238–240°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 2.72$ (s, CH_3), 2.92 (s, CH_3), 7.30–8.20 (m, 5H-phenyl), 9.53 (s, 1H, CH-3) ppm; MS: m/z (%) = 264 [M^+] (14), 263 (81), 262 (100), 238 (10), 221 (20), 154 (19), 103 (26), 91 (11), 77 (94).

3,5,9-Trimethyl-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo-[4,3-c]pyrimidine (**4e**, $C_{15}H_{14}N_6$)
Yield 70%; mp 198–199°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 2.66$ (s, CH_3), 2.94 (s, CH_3), 3.02 (s, CH_3), 7.35–8.20 (m, 5H-phenyl) ppm; MS: m/z (%) = 278 [M^+] (3), 277 (13), 276 (62), 275 (75), 266 (34), 251 (18), 238 (34), 222 (11), 154 (10), 103 (19), 91 (18), 77 (100).

3-Ethyl-5,9-dimethyl-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]-triazolo[4,3-c]pyrimidine (**4f**, $C_{16}H_{16}N_6$)
Yield 68%; mp 180–182°C; ^{1}H NMR (100 MHz, *DMSO*-d_6): $\delta = 1.45$ (t, $J = 7.0$ Hz, CH_3), 2.68 (s, CH_3), 3.03 (s, CH_3), 3.25 (q, $J = 7.0$ Hz, CH_2), 7.25–8.20 (m, 5H-phenyl) ppm; MS: m/z (%) = 292 [M^+] (2), 291 (7), 290 (56), 289 (100), 274 (16), 154 (5), 103 (22), 91 (7), 77 (80).

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