Synthesis of pyrazolotriazolopyrimidine tri-fused heterocyclic compounds

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This paper uses basic-catalysed method to convert 1*H*-pyrazole-4-carboxamides into tri-fused heterocyclic systems containing two kinds of pyrazolotriazolopyrimidine framework. The synthesis of compounds **5–6** and reactions of them with some electrophiles have been investigated. Preliminary bioassay study showed that some compounds displayed high activity.

Keywords: pyrazoles, fused pyrazoles, fused 1,2,4-triazoles, fused pyrimidines

Pyrazole-fused heterocyclic compounds have been found to exhibit biological activity and have widely been used in the fields of pesticides and medicine.[1-4] Recently, pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives were reported to act as human A_3 adenosine receptor antagonists[5,6], 7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones as xanthine oxidase inhibitors[7], and 5,6-dihydro-9*H*-pyrazolo[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridine as PDE-IV inhibitors[8]. In this paper, we have undertaken the base-mediated synthesis of novel pyrazolotriazolopyrimidine compounds in order to test their bioactivity.

Based on our group's research[9],we oxidised 1-substituted 5-chloro-3-methylpyrazole-4-carboxaldehydes to the corresponding 1-substituted 5-chloro-3-methylpyrazole-4-carboxylic acids **1**. Then, with thionyl chloride, the corresponding 1-substituted 5-chloro-3-methylpyrazole-4-carbonyl chlorides **2** were obtained in high yields. **2** reacted with 3-substituted 5-aminotriazoles under different conditions; two kinds of product, **3** and **4**, were thereby obtained.[9] The procedure is shown in Scheme 1.

Compounds **3a, b** or **4a, b** were heated at 80 °C in DMSO with K_2CO_3, product **5a, b** and **6a, b**, respectively, were produced. In compounds **5** and **6**, there are five nitrogen atoms in the framework, a carbonyl group and an active hydrogen atom. Such substances we are optimistic may become lead compounds in drug discovery. In order to improve activity and solubility, we also synthesised N-substituted compounds **7** and **8** by reaction of **5** or **6** with some electrophilic reagents, as shown in Scheme 2.

Some preliminary bioassay studies have been made, which showed that some compounds display high activity. This aspect is under active investigation.

These protocols are especially attractive as they allow for the synthesis of tricyclic heterocyclic systems under mild conditions. The scope of this methodology is clearly capable of extension to the synthesis of other interesting heterocyclic compounds.

Experimental

Melting points were determined with a Yanaco model MP-500 apparatus. Mass spectra were obtained on an HP 5989 mass spectrometer (EI). Elemental analyses were carried out on a Yanaco MT-3 instrument. IR spectra were recorded on a Nicolet Magna-IR 750 spectrometer with Nic-Plan IR microscope-54183 ^{13}C NMR spectra were recorded on a Bruker AC-200Q spectrometer. ^1H NMR spectra were measured on a Bruker APX400 spectrometer using TMS as internal standard.

The reagents and solvents were available commercially and purified by conventional methods.

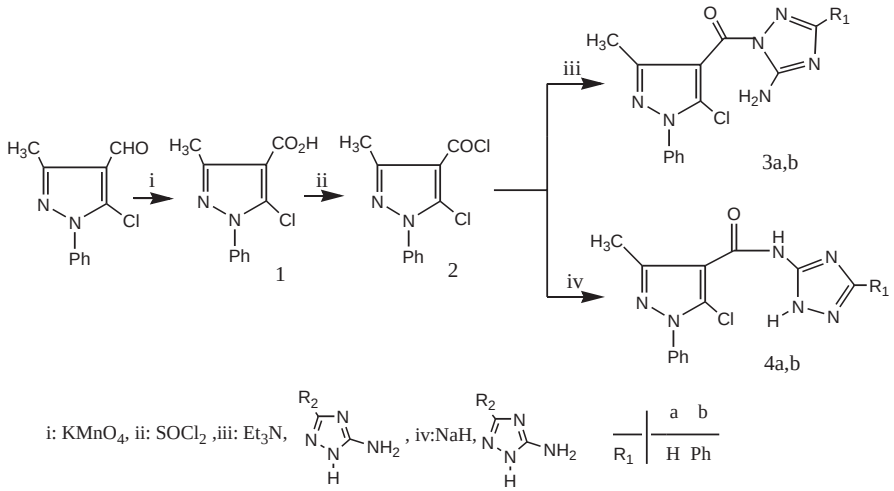
Compounds **3a,b** and **4a,b** were prepared according to the literature[9].

1-[(5'-Chloro-3'-methyl-1'-phenyl-1'H-pyrazol-4'-yl)carbonyl]-1H-1,2,4-triazol-5-amine (**3a**): white powder, yield 60%, m.p. 210–212 °C.

1-[(5'-Chloro-3'-methyl-1'-phenyl-1'H-pyrazol-4'-yl)carbonyl]-3-phenyl-1H-1,2,4-triazol-5-amine (**3b**): white powder, yield 43%, m.p. 220–222 °C.

5-Chloro-3-methyl-1-phenyl-N-(1',2',4'-triazol-3'-yl)-1H-pyrazole-4-carboxamide (**4a**): white powder, yield 95%, m.p. 293–295 °C.

5-Chloro-3-methyl-1-phenyl-N-(5'-Phenyl-1',2',4'-triazol-3'-yl)-1H-pyrazole-4-carboxamide (**4b**): white powder, yield 86%, m.p. 277–278 °C.



Scheme 1

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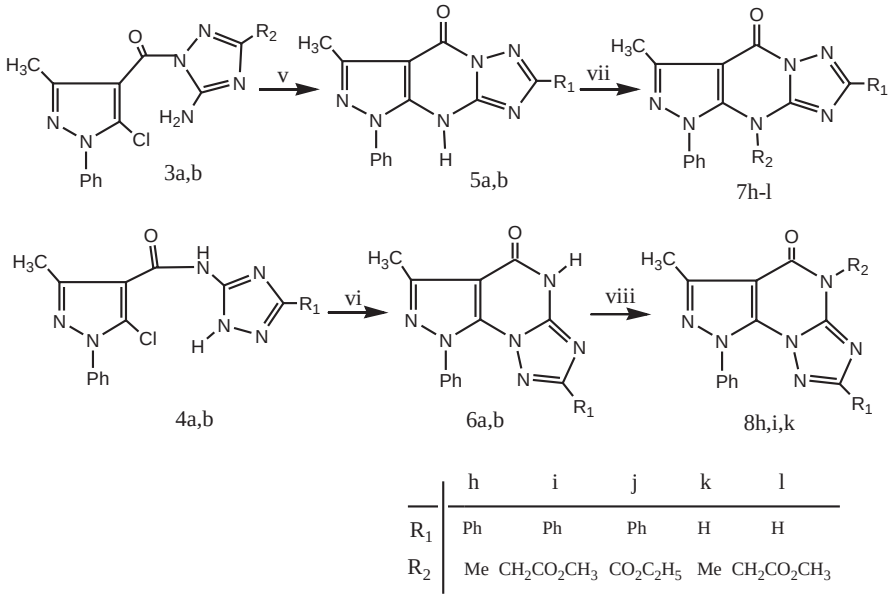

	h	i	j	k	l
R_1	Ph	Ph	Ph	H	H
R_2	Me	$CH_2CO_2CH_3$	$CO_2C_2H_5$	Me	$CH_2CO_2CH_3$

v, vi: K_2CO_3/DMSO, vii, viii: NaH/DMF,R_2X (R_2=Me,X=I, others X=Cl)

Scheme 2

Typical procedure for the preparation of 1,7-diphenyl-3-methyl-1H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4(9H)-one (**5b**): A solution of 1.52g (4 mmol) **3b**, 0.55g (4 mmol) K_2CO_3, in 20ml DMSO was stirred at 80 °C until compound **3b** was consumed (checked by TLC). The reaction mixture was cooled and water (50 ml) was added. The solution was acidified to pH 7 with 10% HCl. A white precipitate was obtained, which was dried and crystallised from DMF/ethanol, providing the desired product **5b** (0.86g 63%), m.p. >280 °C. IR: 3261 (NH), 1670 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 2.52 (s, 3H, 3-CH_3), 7.38–7.92 (m, 10H, 2Ph); MS: *m/z* 342(M^+, 100), 225 (29), 77 (86). Anal: calcd.for $C_{19}H_{14}N_6O$ (342.4): C, 66.66; H, 4.12; N, 24.55. Found: C, 66.35; H, 3.95; N, 24.49 %.

5a, **6a** and **6b** were prepared in the same method as **5b**.

1-Phenyl-3-methyl-1H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4(9H)-one (**5a**): white powder, m.p. >270 °C, yield 81 %. IR: 3243 (NH), 1682 cm^{-1} (C=O). ^{1}H NMR (400 MHz, DMSO-d_6): 2.68 (s, 3H, 3-CH_3), 7.52–7.66 (m, 5H, Ph); MS: *m/e* 266 (M^+, 100). Anal. calcd. for $C_{13}H_{10}N_6O$ (266.3): C, 58.64; H, 3.78; N, 31.56. Found: C, 58.37; H, 3.64; N, 31.33 %.

1-Phenyl-3-methyl-1H-pyrazolo[4,3-e][1,2,4]triazolo[2,3-a]pyrimidin-4(5H)-one (**6a**): white solid, m.p.>280 °C, yield 76 %. IR: 3103 (NH), 1696 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 2.72 (s, 3H, 3-CH_3), 7.48–7.87 (m, 5H, Ph); MS *m/e* 266 (M^+, 100). Anal. calcd.for $C_{13}H_{10}N_6O$ (266.3): C, 58.64; H, 3.78; N, 31.56. Found: C, 58.45; H, 3.71; N, 31.24 %.

1,8-Diphenyl-3-methyl-1H-pyrazolo[4,3-e][1,2,4]triazolo[2,3-a]pyrimidin-4(5H)-one (**6b**): white solid, m.p. >280 °C, yield 81 %; IR: 3118 (NH), 1681 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 2.51(s, 3H, 3-CH_3), 7.38–7.91 (m, 10H, 2Ph); MS *m/e* 342 (M^+, 100), 225 (29), 149 (11), 77 (86), 51 (24). Anal. calcd.for $C_{19}H_{14}N_6O$ (342.4): C, 66.66; H, 4.12; N, 24.55. Found: C, 66.47; H, 4.40; N, 24.50.

Typical procedure for the preparation of 1,7-diphenyl-3,9-dimethyl-1H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (**7h**): 50% NaH (0.096 g, 2 mmol) was added to a stirred solution of **5b** (0.40 g, 1.2 mmol) in dry DMF (10 ml). After 2h stirring at room temperature, methyl iodide (0.6 ml) was added and stirring was continued at room temperature until compound **5b** was consumed (checked by TLC). Then water (50ml) was added and the solution was acidified to pH 7 with 10% HCl. A white precipitate was filtered off, dried and crystallised from ethyl acetate. The desired product **7h** (0.36g, 84 %) was obtained, m.p. 258–260 °C. IR 1685 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 2.67 (s, 3H, 3-CH_3), 3.77 (s, 3H, N-CH_3), 7.37–7.98 (m, 10H, 2Ph). Anal. calcd.for $C_{20}H_{16}N_6O$ (356.4): C, 67.40; H, 4.53; N, 23.58. Found: C, 67.56; H, 4.61; N, 23.43 %.

Compounds **7i–l, 8h, i, k** were prepared in a similar method to **7h**.

1,7-Diphenyl-3-methyl-9-(methoxycarbonylmethyl)-1H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (**7i**): white solid, m.p. 170–172 °C, yield 64 %. IR: 1752, 1691 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 2.67 (s, 3H, 3-CH_3), 3.81 (s, 3H, OCH_3), 5.28 (s, 2H, N-CH_2-), 7.40–7.77 (m, 10H, 2Ph). Anal. calcd. for $C_{22}H_{18}N_6O_3$ (414.4): C, 63.76; H, 4.38; N, 20.28. Found: C, 63.36; H, 4.26; N, 20.36 %.

1,7-Diphenyl-3-methyl-9-ethoxycarbonyl-1H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (**7j**): white solid, m.p. 234–236 °C, yield 55 %. IR: 1676, 1696 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 1.45 (t, 3H, CH_3), 2.68 (s, 3H, 3-CH_3), 4.46 (q, 2H, OCH_2), 7.40–8.18 (m, 10H, 2Ph); MS *m/e* 414 (M^+, 1), 342 (49), 225 (13), 143 (11), 103 (26), 77 (100), 51 (35). Anal. calcd.for $C_{22}H_{18}N_6O_3$ (414.4): C, 63.76; H, 4.38; N, 20.28. Found: C, 63.90; H, 4.52; N, 20.34 %.

1-Phenyl-3,9-dimethyl-1H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one (**7k**): white solid, m.p. 210–212 °C, yield 88 %. IR 1696 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 2.70 (s, 3H, 3-CH_3), 3.76 (s, 3H, NCH_3), 7.42–7.90 (m, 5H, Ph). Anal. calcd.for $C_{14}H_{12}N_6O$ (280.3): C, 59.99; H, 4.32; N, 29.98. Found: C, 60.27; H, 4.37; N, 29.69 %.

1-*Phenyl-3-methyl-9-(methoxycarbonylmethyl)-1H-pyrazolo[3,4-d][1,2,4]triazolo[1,5-a]pyrimidin-4-one* (**7l**): white solid, m.p. 194–195 °C, yield 66 %. IR: 1752, 1694 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 2.67 (s, 3H, 3-CH_3), 3.81 (s, 3H, OCH_3), 5.01 (s, 2H, N-CH_2), 7.44–7.84 (m, 5H, Ph). Anal. calcd.for $C_{16}H_{14}N_6O_3$ (338.3): C, 56.80; H, 4.17; N, 24.84. Found: C, 56.77; H, 4.18; N, 24.60.

1,8-Diphenyl-3,5-dimethyl-1H-pyrazolo[4,3-e][1,2,4]triazolo[2,3-a]pyrimidin-4-one (**8h**): white solid, yield 87 %, m.p. 257–259 °C. IR: 1695 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 2.68 (s, 3H, 3-CH_3), 3.79 (s, 3H, N-CH_3), 7.40–7.97 (m, 10H, 2Ph). Anal. calcd.for $C_{20}H_{16}N_6O$ (356.4): C, 67.40; H, 4.53; N, 23.58. Found: C, 67.27; H, 4.33; N, 23.52 %.

1,8-Diphenyl-3-methyl-9-(methoxycarbonylmethyl)-1H-pyrazolo[4,3-e][1,2,4]triazolo[2,3-a]pyrimidin-4-one (**8i**): white solid, m.p. 171–172 °C, yield 67%. IR: 1752, 1704 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 2.63 (s, 3H, 3-CH_3), 3.80 (s, 3H, OCH_3), 5.26 (s, 2H, N-CH_2), 7.36–7.75 (m, 10H, 2Ph). Anal. calcd.for $C_{22}H_{18}N_6O_3$ (414.4): C, 63.76; H, 4.38; N, 20.28. Found: C, 63.47; H, 4.33; N, 20.11 %.

1-Phenyl-3,9-dimethyl-1H-pyrazolo[4,3-e][1,2,4]triazolo[2,3-a]pyrimidin-4-one (**8k**): white solid, m.p. 211–213 °C, yield 82%. IR: 1707 cm^{-1} (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): 2.68 (s, 3H, 3-CH_3), 3.81 (s, 3H, OCH_3), 5.02 (s, 2H, N-CH_2), 7.40–7.82 (m, 5H, Ph). Anal. calcd.for $C_{14}H_{12}N_6O$ (280.3): C, 59.99; H, 4.32; N, 29.98. Found: C, 59.78; H, 4.35; N, 29.73 %.

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