Synthesis of new derivatives of pyridazino[6,1-*c*]pyrimido[5,4-*e*][1,2,4]triazine; a novel heterocyclic system

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Several derivatives of the novel pyridazino[6,1-*c*]pyrimido[5,4-*e*][1,2,4]triazine ring system have been synthesised through heterocyclisation of 5-bromo-2,4-dichloro-6-methylpyrimidine with 3-chloro-6-hydrazinylpyridazine followed by treatment with secondary amines in boiling ethanol.

Keywords: 1,2-dihydropyridazine-3,6-dione, heterocyclisation, 5-bromo-2,4-dichloro-6-methylpyrimidine, pyridazino[6,1-c]pyrimido[5,4-*e*][1,2,4]triazine

The pyridazine ring is widely present in biologically and pharmacologically active compounds.[1] Pyridazines are also of considerable interest because of their synthetic utility and applications in physical organic chemistry.[2,3] A number of pyridazine synthetic protocols, including cycloaddition reactions of 1,2,4,5-tetrazines with different dienophiles[4] and cyclocondensation of 1,4-dicarbonyl compounds with hydrazine,[5] have been reported in the literature.

Some synthetic routes for construction of fused heterocyclic pyridazines are found in the literature. Fused heterocyclic pyradizines possess a wide range of biological and pharmacological activity, such as monoamine oxidase inhibitory,[6] cytotoxic,[7] anthelmintic[8] and antiviral[9] activities.

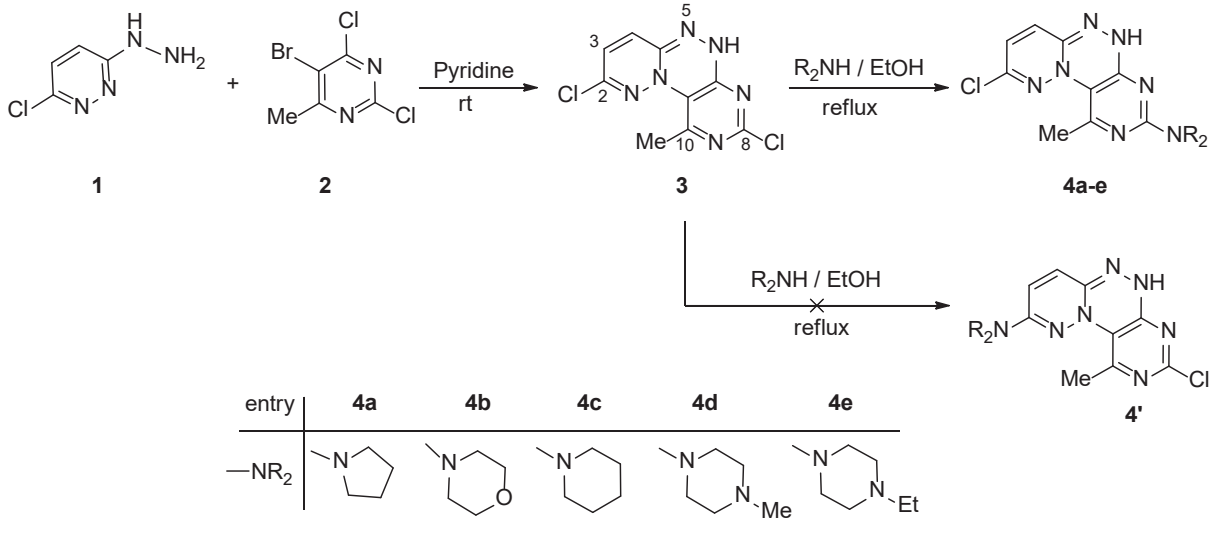
There are reviews dealing with the synthesis of condensed 1,2,4-triazines.[10] The chemistry of these heterocyclic compounds has been extensively studied. Condensation of the amidrazones with 1,2-dicarbonyl compounds provides one of the most straightforward syntheses of 1,2,4-triazines.[11] This heterocyclic moiety plays a vital role in many biological activities including antiviral,[12] antihypertensive,[13] blood-platelet aggregation, inhibitory,[14] analgesic[15] and antibacterial properties[16] as well as some anti-HIV and anticancer agents.[17]

Prompted by these findings and due to our interest in the synthesis of new derivatives of heterocyclic compounds with potential biological activities,[18] we report here a convenient synthesis of several derivatives of a novel heterocyclic system, pyridazino[6,1-*c*]pyrimido[5,4-*e*][1,2,4]triazine.

Results and discussion

In the present study, 1,2-dihydropyridazine-3,6-dione was initially prepared from the reaction of maleic anhydride with hydrazinum hydrochloride which was treated with $POCl_3$ and subsequently with hydrazine hydrate to give the corresponding 3-chloro-6-hydrazinyl pyridazine **1**.[19] In addition, 5-bromo-2,4-dichloro-6-methylpyrimidine **2** was synthesised according to the previously reported method.[20] Treatment of compound **1** as a binucleophile with compound **2** in pyridine at room temperature afforded 2,8-dichloro-10-methyl-6*H*-pyridazino[6,1-*c*]pyrimido[5,4-*e*][1,2,4]triazine **3**. The selective nucleophilic displacement of the 4-Cl substituent by the hydrazine NH_2 moiety proceeded smoothly following a similar reported procedure.[21,22] This phenomenon can be explained *via* the repulsive interaction between the lone pairs on the pyrimidine ring nitrogens and the NH_2 nucleophile with the result that substitution of the 2-Cl substituent requires a higher temperature than for the 4-Cl substituent. The treatment of compound **3** with some secondary amines in boiling EtOH generated various derivatives of the pyridazino[6,1-*c*]pyrimido[5,4-*e*][1,2,4]triazine **4a–e** system (Scheme 1).

The evidence which confirmed that 8-Cl substituent on compound **3** is substituted by the appropriate secondary amine was deduced *via* computational evaluations. Fukui indices, useful for resolving the ambiguity in the structure of products **4a–e**, make a comparison of their magnitudes for individual atoms in molecules.[23] For example, the nucleophilic substitution of pyrrolidine at C-8 or C-2 of precursor **3** would lead to the formation of structures **4a**



Scheme 1

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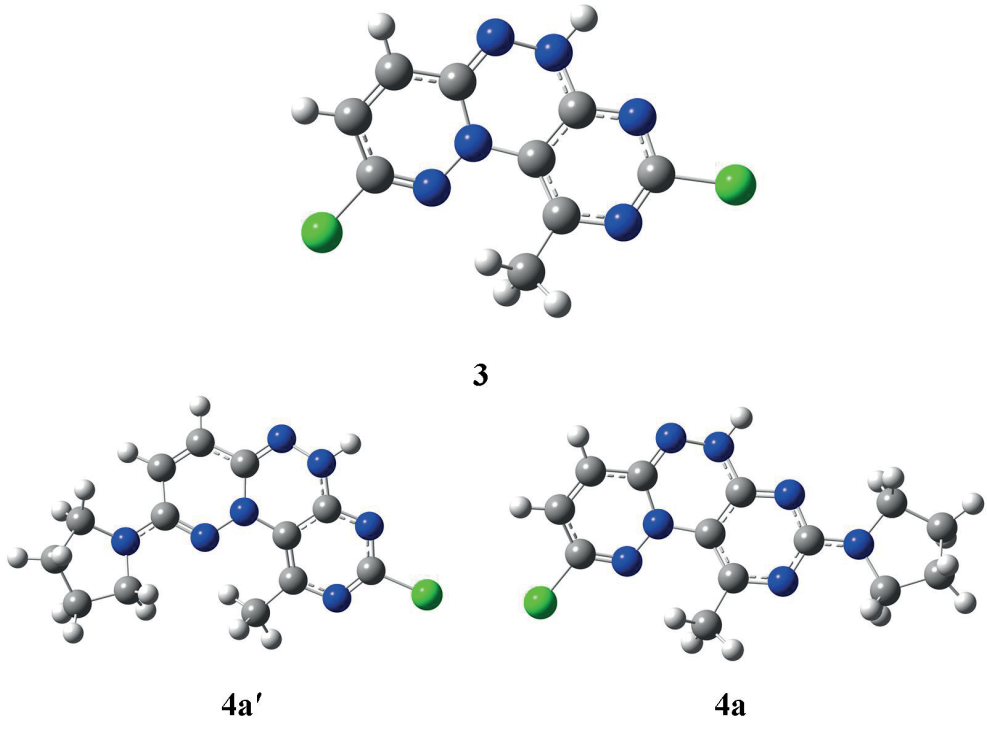

Fig. 1 The optimised structures of precursor **3** and products **4a** and **4a'** using the B3LYP/6-311+g(2d,p) level of theory.

Table 1 Fukui indices,[a] dual-descriptor and NPA atomic charges of C-2 and C-8 of precursor **3**

No. of carbon	f_C^-	f_C^+	f_C^0	Dual-descriptor	NPA charge (neutral)	NPA charge (anion)	NPA charge (cation)
C-2	0.0562	0.0258	0.041	−0.0304	0.1575	0.1317	0.2137
C-8	0.0147	0.0494	0.0321	0.0346	0.4266	0.3772	0.4413

[a] f_C^-, f_C^+ and f_C^0 are nucleophilicity, electrophilicity and radical characteristic, respectively.

and **4a'** respectively (Scheme 1 and Fig. 1). The thermodynamic stability of **4a** and **4a'** isomers has been demonstrated through DFT calculations. Optimisation and frequency calculations were performed using the Gaussian 09 package[24] both at the B3LYP level of theory,[25] with 6-311+g(2d,p) basis set for all atoms and no symmetric restrictions. Figure 1 shows the optimised structures of precursor **3** and those of the isomeric products **4a** and **4a'**.

The comparisons of Gibbs free energies with optimised structures of **4a** and **4a'** at 298 K revealed that **4a** is more thermodynamically favourable than **4a'**. (5.82 kcal mol^{-1}) Moreover, three single point calculations for condensed Fukui indices were carried out on the optimised structure of the precursor with neutral, net +1 charge and net –1 charge at the same level of theory [B3LYP/6-311+g(2d,p)]. This calculation was done using the recently-developed UCA-FUKUI software[26] by imprinting two-electron integrals and Natural Population Analysis (NPA)[27] on the output of single point calculations.

Table 1 represents Fukui indices, dual-descriptor and NPA atomic charges of C-2 and C-8 on the model of precursor **3**. Because C-8 shows higher magnitude of f_C^+ compared with those calculated for C-2 in precursor **3**, therefore, C-8 is more susceptible to nucleophilic substitution. Moreover, the Daul-Descriptor, as a new developed index was calculated in which a positive value is a good indicator for the given atom to suffer a nucleophilic attack in comparison with negative ones.[28,29] Thus, C-8 in precursor **3** provided a positive amount in contrast with a negative amount for C-2. In addition, C-8 has greater positive atomic charge than C-2 in all anionic, neutral and cationic models of precursor **3** structure and demonstrated that the formations of compounds **4a–e** are preferred.

Beside the correct elemental analyses, the spectral data of compounds **4a–e** are in agreement with the assigned structures. For instance, the IR spectrum of compound **4b** showed the stretching vibration band for the NH group at ν_{max} 3417 cm^{-1}. The ^{1}H NMR spectrum showed a singlet signal at 2.35 ppm due to the methyl protons, whilst the signals from the morpholine moiety were at δ 3.66 and 3.81 ppm. Two doublets at 6.52 and 6.59 ppm due to the hydrogens of the pyridazine moiety and a signal at 8.59 ppm corresponding to the NH group were also present. The corresponding rather high field chemical shifts of the pyridazine core have also been previously reported in the literature with similar structures.[30,31] The mass spectrum of **4b** showed a molecular ion peak at *m/z* 319 (M^+, containing ^{35}Cl) consistent with the molecular formula of $C_{13}H_{14}ClN_7O$.

Conclusions

In summary, various interesting fused-ring heterocyclic derivatives containing the pyridazino[6,1-*c*]pyrimido[5,4-*e*][1,2,4]triazine system were synthesised. The synthetic approach starts from the S_NAr reaction of 3-chloro-6-hydrazinylpyridazine **1** with 5-bromo-2,4-dichloro-6-methyl pyrimidine **2** as a binucleophile to give 2,8-dichloro-10-methyl-6*H*-pyridazino[6,1-*c*]pyrimido[5,4-*e*][1,2,4]triazine **3** which was further treated with various secondary amines to give the desired products **4a–e**.

Experimental

Melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on Avatar 370 FT-IR Thermo Nicolet spectrophotometer and only noteworthy absorptions are

listed. The ^{1}H NMR (300 MHz) and the ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance DRX-400 Fourier transformer spectrometer. Chemical shifts are reported in ppm downfield from TMS as an internal standard. The mass spectra were recorded on a Varian Mat CH-7 at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA 1112 microanalyser.

*Synthesis of 2,8-dichloro-10-methyl-6*H*-pyridazino[6,1-*c*]pyrimido-[5,4-*e*][1,2,4]triazine* **3:** *general procedure*

A solution of compound **1** (0.14 g, 1 mmol) and 5-bromo-2,4-dichloro-6-methylpyrimidine **(2)** (0.24 g, 1 mmol) in pyridine (5 mL) was stirred at room temperature for 1 h. After the completion of the reaction which was monitored by TLC using $CHCl_3$:MeOH (9:1), the resulting solid was filtered off, washed with water (2 × 10 mL) and recrystallised from EtOH to give the product as an orange powder; yield 65%; m.p. 185 °C; IR (KBr disc) (ν_{max} cm^{-1}): 3394, 3023, 2920, 2836, 1643, 833; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 7.17 (d, 1H, ArH), 7.85 (d, 1H, ArH), 8.91 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.7, 114.6, 115.4, 120.9, 125.5, 127.1, 129.9, 143.1, 145.0; MS (*m/z*): 268 (M^+), 270 ($M^+ + 2$), 272 ($M^+ + 4$). Anal. calcd for $C_9H_6Cl_2N_6$: C, 40.17; H, 2.25; N, 31.23; found: C, 40.01; H, 2.20; N, 31.17%.

Synthesis of compounds **4a–e***; general procedure*

The appropriate secondary amine (1.5 mmol) was added to a mixture of compound **3** (1 mmol, 0.27g) and Et_3N (1 mL) in EtOH (5 mL), and the solution was heated under reflux for 12 h. After the completion of the reaction, the solvent was removed under reduced pressure and the resulting solid product was filtered off, washed with water (2 × 10 mL) and recrystallised from EtOH.

*2-Chloro-10-methyl-8-(pyrrolidin-1-yl)-6*H*-pyridazino[6,1-c]pyrimido[5,4-e][1,2,4]triazine* (**4a**): Light yellow powder; yield 75%; m.p. 200–202 °C; IR (KBr disc) (ν_{max} cm^{-1}): 3419, 3203, 2923, 2852, 1616, 778; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86 (m, 4H, CH_2), 2.34 (s, 3H, CH_3), 3.44 (t, *J* = 6.4 Hz, 4H, CH_2N), 6.51 (d, *J* = 5.9 Hz, 1H, ArH), 6.57 (d, *J* = 5.9 Hz, 1H, ArH), 8.54 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 29.5, 46.8, 111.0, 126.7, 134.0, 138.0, 148.1, 153.1, 158.1, 159.3; MS (*m/z*): 303 (M^+), 305 ($M^+ + 2$). Anal. calcd for $C_{13}H_{14}ClN_7$: C, 51.40; H, 4.65; N, 32.28; found: C, 51.34; H, 4.60; N, 32.22%.

*2-Chloro-10-methyl-8-(morpholin-4-yl)-6*H*-pyridazino[6,1-c]pyrimido[5,4-e][1,2,4]triazine* (**4b**): Light yellow powder; yield 61%; m.p. 205–206 °C; IR (KBr disc) (ν_{max} cm^{-1}): 3417, 2918, 2849, 799; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 3.66 (m, 4H, CH_2N), 3.81 (m, 4H, CH_2O), 6.52 (d, *J* = 5.8 Hz, 1H, ArH), 6.59 (d, *J* = 5.8 Hz, 1H, ArH), 8.59 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.5, 48.6, 66.1, 111.0, 126.7, 134.0, 138.0, 148.1, 153.1, 158.1, 159.3; MS (*m/z*): 319 (M^+), 321 ($M^+ + 2$). Anal. calcd for $C_{13}H_{14}ClN_7O$: C, 48.83; H, 4.41; N, 30.66; found: C, 48.77; H, 4.38; N, 30.57%.

*2-Chloro-10-methyl-8-(piperidin-1-yl)-6*H*-pyridazino[6,1-c]pyrimido[5,4-e][1,2,4]triazine* (**4c**): Light yellow powder; yield 65%; m.p. 206–207 °C; IR (KBr disc) (ν_{max} cm^{-1}): 3212, 2953, 2924, 2852, 1640; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.52 (m, 4H, CH_2), 1.61 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 3.69 (t, *J* = 6.3 Hz, 4H, CH_2N), 6.53 (d, *J* = 5.8 Hz, 1H, ArH), 6.62 (d, *J* = 5.8 Hz, 1H, ArH), 8.65 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.5, 30.1, 31.2, 59.6, 111.3, 126.8, 134.2, 138.3, 148.0, 153.3, 158.2, 159.0; MS (*m/z*): 317 (M^+), 319 ($M^+ + 2$). Anal. calcd for $C_{14}H_{16}ClN_7$: C, 52.91; H, 5.07; N, 30.85; found: C, 52.83; H, 4.98; N, 30.75%.

*2-Chloro-10-methyl-8-(4-methylpiperazin-1-yl)-6*H*-pyridazino[6,1-c]pyrimido[5,4-e][1,2,4]triazine* (**4d**): Brown powder; yield 66%; m.p. 220–222 °C; IR (KBr disc) (ν_{max} cm^{-1}): 3395, 3143, 2918, 2849; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 2.72 (s, 3H, CH_3N), 3.29 (t, *J* = 6.3 Hz, 4H, CH_2N), 3.69 (t, *J* = 6.3 Hz, 4H, CH_2N), 6.49 (d, *J* = 5.8 Hz, 1H, ArH), 6.54 (d, *J* = 5.8 Hz, 1H, ArH), 8.02 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5, 43.7, 46.2, 54.9, 120.0, 142.0, 142.0, 143.1, 144.1, 145.0, 150.0, 153.0; MS (*m/z*): 332 (M^+), 334 ($M^+ + 2$). Anal. calcd for $C_{14}H_{17}ClN_8$: C, 50.53; H, 5.15; N, 33.67; found: C, 50.45; H, 5.04; N, 33.58%.

*2-Chloro-8-(4-ethylpiperazin-1-yl)-10-methyl-6*H*-pyridazino[6,1-c]pyrimido[5,4-e][1,2,4]triazine* (**4e**): Light yellow powder; yield 59%; m.p. 210–212 °C; IR (KBr disc) (ν_{max} cm^{-1}): 3396 3444, 2850, 1347; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, *J* = 5.3 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.23 (q, *J* = 5.3 Hz, 2H, CH_2N), 3.27 (t, *J* = 6.3 Hz, 4H, CH_2N), 3.66 (t, *J* = 6.3 Hz, 4H, CH_2N), 6.48 (d, *J* = 5.8 Hz, 1H, ArH), 6.52 (d, *J* = 5.8 Hz, 1H, ArH), 8.36 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 24.5, 43.2, 46.5, 54.1, 120.9, 142.7, 142.9, 143.8, 144.6, 145.9, 151.2, 153.7; MS (*m/z*): 346 (M^+), 348 ($M^+ + 2$). Anal. calcd for $C_{15}H_{19}ClN_8$: C, 51.95; H, 5.52; N, 32.31; found: C, 51.89; H, 5.47; N, 32.25%.

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