A CONVENIENT APPROACH TO NOVEL PYRAZOLO[4,3-*E*]-1,2,4-TRIAZOLO[1,5-*C*]PYRIMIDINES

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Abstract : A series of new pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines **3a-i** have been synthesized through the condensation of 5-amino-4-iminopyrazolopyrimidines **1a-c** and several electrophilic species **2a-d.**
Keywords: pyrazolopyrimidines, cyclocendansation, pyrazolotriazolopyrimidines

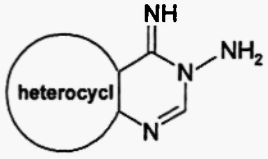
Introduction

Heterocycles including the pyrazolopyrimidine scaffold have often proved efficiency in different therapeutic areas as anxiolytics, antidepressants (1-4), analgesics (5-6), fungicides (7) and antibacterial (8). On another hand, heterocycles incorporating the 1,2,4-triazole nucleus, are used extensively in medicinal chemistry (9).

Referring to several reports claming that the fusion of a triazole ring to other heterocyclic scaffold could introduce modification of the biological properties of the parent molecule, we were interested in the synthesis of novel polycyclic molecules featuring a triazolic moiety fused onto the pyrazolopyrimidine ring-system and we report here an efficient access to novel pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines.

Results and discussion

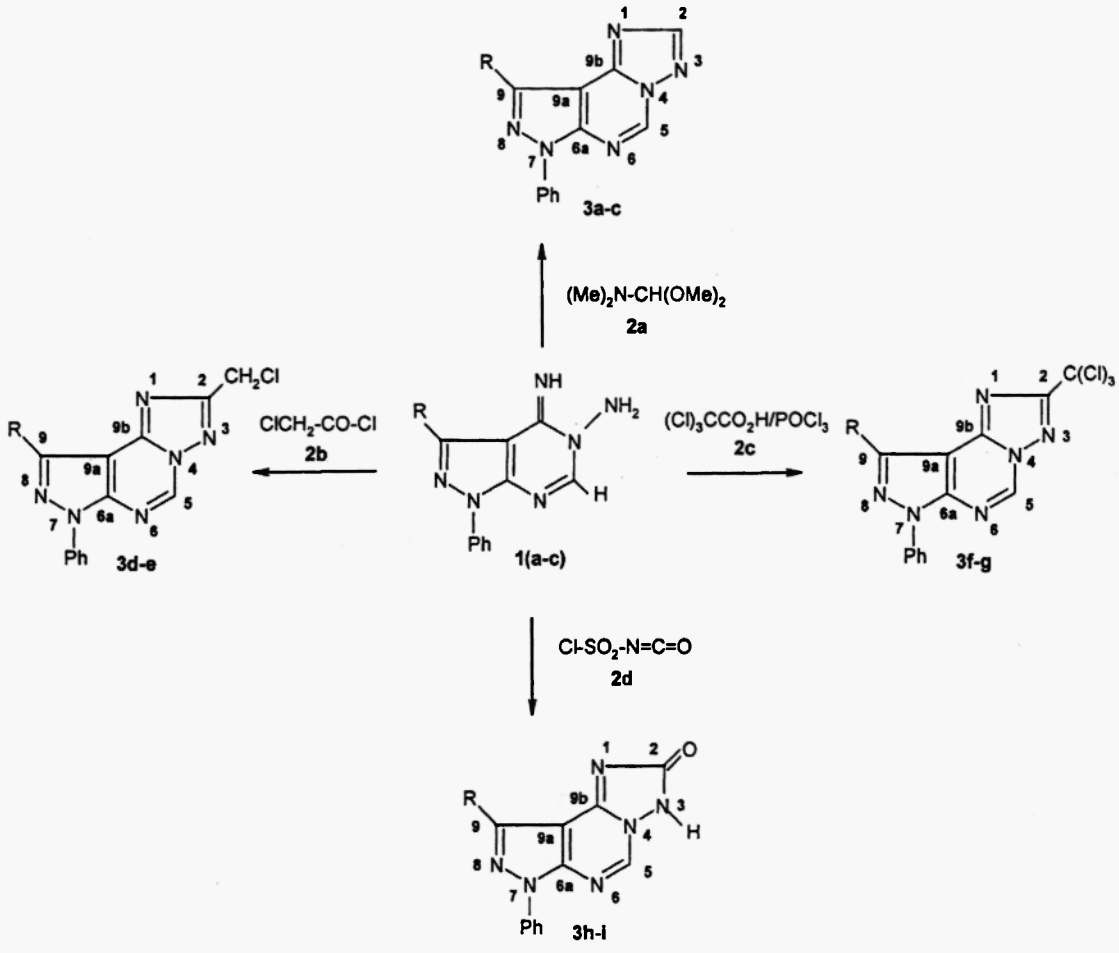
Our key intermediate was the *N,N*-binucleophile **A**, since such system constitutes a commonly used building block for the construction of a variety of polyheterocycles (10,11).



A

For this purpose and as described in scheme 1, our approach to the target system **3** was based on compound's **1** intramolecular cyclization. Thus the construction of the triazolo-pyrimidine squeleton was accomplished through the incorporation of a carbon-unit using readily available electrophilic species **2** namely *N,N*-dimethylformamide acetal, chloroacetyl chloride, trichloroacetyl chloride and chlorosylfonylisocyanate.

Our trials to optimise the reaction conditions showed that best yields were reached on heating equimolar amounts of reactants **1a-c** and **2a-d** in dry solvents. Under these conditions, the reaction progress monitored by thin layer chromatography revealed in all cases the formation of a sole product which was, on the basis of its spectral data, assigned as the pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine **3** (Scheme-1).



	3a	3b	3c	3d	3e	3f	3g	3h	3i
R	H	Me	Et	H	Et	H	Me	Me	Et

Scheme-1

From a mechanistic point of view, the reaction process is assumed to follow a two-steps pathway (10-11). Primely, an addition of the free amino group of the pyrazolopyrimidine **1** take place attacks the electrophilic site of compound **2**. The non-isolable so formed intermediate spontaneously cyclised to afford the expected pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine **3**. In all case these products were isolated as colourless crystals. All the examined compounds showed correct molecular peak ($M^{+\cdot}$). Furthermore NMR spectra provide evidence to the suggested condensation reaction, thus ^1H NMR spectra exhibited set of signals relative to aromatic and alkyl groups protons for which chemical shifts and multiplicities were in good agreement with the proposed structure (see experimental section). Unambiguous proofs for the obtained tricyclic systems aroused from their

^{13}C data, particularly the high shift-values attributed to the quaternary carbons C_2 (154.4-170.6 ppm) is in complete agreement with the strong deshielding effects caused by the nitrogens proximity (12-13).

Conclusion

The synthesis we have described above illustrates a simple and efficient method for the preparation of a series of novel pyrazolo[4,3-*e*]-1,2,4-triazol[1,5-*c*]pyrimidines **3a-i** in good yield *via* the cyclocondensation of 4-imino-5-aminopyrazolo[3,4-*d*]pyrimidines **1a-c** with electrophiles 2a-d.

Experimental

Melting points were taken on a Buchi-510 capillary melting point apparatus. Infrared spectra (potassium bromide) were run on a Perkin-elmer IR-197 infrared spectrometer. ^1H and ^{13}C nmr spectra were recorded on a Brüker spectrometer AC-300 using $CDCl_3$ and DMSO-d_6 as solvents. Mass spectra were obtained with an Automass Multi Thermo Finnigan (electron impact mode, 70 eV) and a MR-SX102 spectrometer using FAB^+ technical. All the reactions were followed by TLC using aluminum sheets of Merck silica gel 60 F_{254}, 0.2 mm. The starting materials **1a-c** were prepared according to the literatures (14-16).

7-Phenylpyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyri-midine 3a : To a solution of **2a** (1mmol) in dry toluene (50 mL), DMFDMA was added (4 mmol). The reaction mixture was heated for 15 min. After cooling, the precipitate formed is filtered, dried and crystallized from ethanol to afford **3a** : (yield = 93%); mp: 164 °C ; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.41-8.13 (m, $5H_{arom}$), 8.45 (s, 1H, H_9) , 8.61 (s, 1H, H_5), 9.21 (s, 1H, H_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm): 102.9 (C_{9a}), 122.4-138.6 ($C_{arom.}$, C_5), 143.1-148.4 (C_{6a}, C_9, C_{9b}), 154.4 (C_2); IE m/z (rel. Int.%) 236 [$M^{+\cdot}$] (100), 210 (11), 182 (13), 77 (46), 51 (22).

9-Methyl-7-phenylpyrazolo[4,3-*e*]-1,2,4-triazolo-[1,5-*c*]pyrimidine 3b : prepared from **2b** (1mmol), DMFDMA (4mmol) in dry toluene (50 ml) according to the procedure described for **3a** : (yield = 90%); mp: 168 °C ; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 2.82 (s, 3H, $-CH_3$), 7.32-8.08 (m, $5H_{arom}$), 8.37 (s, 1H, H_5), 9.13 (s, 1H, H_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm): 13.8 ($\underline{C}H_3$), 103.6 (C_{9a}), 122.1-138.5 ($C_{arom.}$, C_5), 143.3-148.3 (C_{6a}, C_9, C_{9b}), 155.3 (C_2); IE m/z (rel. Int.%) 250 [$M^{+\cdot}$] (100), 222 (10), 182 (67), 77 (37), 51 (20).

9-Ethyl-7-phenylpyrazolo[4,3-*e*]-1,2,4-triazolo-[1,5-*c*]pyrimidine 3c : prepared from **2c** (1mmol), DMFDMA (4mmol) in dry toluene (50 ml) according to the procedure described for **3a** : (yield = 87%); mp: 173 °C ; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 1.55 (t, 3H, $\underline{CH_3}$-CH_2-), 3.25 (q, 2H, -$\underline{CH_2}$-CH_3), 7.36-8.12 (m, $5H_{arom}$), 8.41

(s, 1H, H_5), 9.18 (s, 1H, H_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm): 13.1 ($\underline{C}H_3$-CH_2-), 22.1 (-$\underline{C}H_2$-CH_3), 102.9 (C_{9a}), 122.2-138.5 ($C_{arom.}$, C_5), 146.1-149.1 (C_{6a}, C_9, C_{9b}), 155.3 (C_2); IE m/z (rel. Int.%) 264 [M^+] (33), 222 (45), 103 (16), 77 (100), 51 (34).

2-Chloromethyl-7-phenylpyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine 3d : To a solution of pyrazolopyrimidines **2a** (1mmol) in DMF (50 mL), chloroacetyl chloride was added (1.1 mmol). The reaction mixture was boiled at reflex for 4 h and after cooling poured into ice-water (50 mL) to give a with solid which was crystallized from ethanol to give **3d** : (yield = 76%); mp: 183 °C ; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 4.87 (s, 2H, -$\underline{CH_2}$-Cl), 7.43-8.15 (m, $5H_{arom}$), 8.58 (s, 1H, H_9), 9.19 (s, 1H, H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm): 37.8 (-$\underline{C}H_2$-Cl), 104.4 (C_{9a}), 122.8-138.7 ($C_{arom.}$, C_5), 146.7-149.1 (C_{6a}, C_9, C_{9b}), 164.8 (C_2); FABMS m/z : 284 [MH^+]

9-Ethyl-2-chloromethyl-7-phenylpyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine 3e : prepared from **2c** (1mmol) and chloroacetyl chloride (1.1 mmol) according to the procedure described for **3d** : (yield = 74%); mp: 185 °C ; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 1.53 (t, 3H, $\underline{CH_3}$-CH_2-), 3.25 (q, 2H, CH_2-$\underline{CH_2}$-), 4.87(s, 2H, -$\underline{CH_2}$-Cl), 7.36-8.10 (m, $5H_{arom}$), 9.14 (s, 1H, H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm): 12.9 ($\underline{C}H_3$-CH_2-), 22.1 (CH_3-$\underline{C}H_2$-), 37.4 ($\underline{C}H_2$-Cl), 102.5 (C_{9a}), 122.3-138.4 ($C_{arom.}$, C_5), 146.4-164.5 (C_{6a}, C_9, C_{9b}), 170.6 (C_2); FABMS m/z : 312 [MH^+]

2-Trichloromethyl-7-phenylpyrazolo[4,3-*e*]-1,2,4-triazolo[1, 5-*c*]pyrimidine 3f : A mixture of **2a** (1mmol), trichloroacetic acid (1.5 mmol) and $POCl_3$ (15 ml) was reflexed for 5 h and after cooling poured into ice-water (100 mL) to give a with solid which was crystallized from dioxane to give **3f** : (yield = 65%); mp: 175 °C ; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.35-8.05 (m, $5H_{arom}$), 8.56 (s, 1H, H_9), 9.16 (s, 1H, H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm): 88.8 (-$\underline{C}(Cl)_3$), 104.4 (C_{9a}), 122.9-138.6 ($C_{arom.}$, C_5), 146.1-149.7 (C_{6a}, C_9, C_{9b}), 167.6 (C_2); FABMS m/z : 352 [MH^+]

9-Methyl-2-trichloromethyl-7-phenylpyrazolo-[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine 3g : prepared from **2b** (1mmol), trichloroacetic acid (1.5 mmol) and $POCl_3$ (15 ml) according to the procedure described for **3f** : (yield = 67%); mp: 178 °C ; ^1H NMR (300 MHz, $CDCl_3$) δ(ppm): 2.83 (s, 3H, -CH_3), 7.33-8.03 (m, $5H_{arom}$), 9.10 (s, 1H, H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm): 14.3 (-$\underline{C}H_3$), 88.7 (-$\underline{C}(Cl)_3$), 103.8 (C_{9a}), 122.6-138.8 ($C_{arom.}$, C_5), 144.2-150.2 (C_{6a}, C_9, C_{9b}), 167.7 (C_2); FABMS m/z : 366 [MH^+]

9-Methyl-7-phenylpyrazolo[4,3-*e*]-1,2,4-triazolo-[1,5-*c*]pyrimidine-2-one 3h : a solution of **2b** (1mmol) in dry CH_2Cl_2 (50 mL), chlorosulfonyle isocyanate was added (1.1 mmol) dropwise with stirring. The reaction mixture was heated for 30 min. After cooling, the precipitate formed is filtered, dried and crystallized from ethanol to afford **3h** : (yield = 70%); mp: 174 °C ; ^{1}H NMR (300 MHz, DMSO-d_6) δ(ppm): 2.63 (s, 3H, -CH_3), 7.33-8.07 (m, 5H_{arom}), 9.29 (s, 1H, H_5), 12.37 (s, **NH**) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ(ppm): 13.8 (-$\underline{C}H_3$), 102.4 (C_{9a}), 121.6-139.5 ($C_{arom.}$, C_5), 142.7-147.8 (C_{6a}, C_9, C_{9b}), 170.4 (C_2); IE m/z (rel. Int.%) 266 [M^+] (77), 265 (18), 142 (12), 77 (100), 51 (22).

9-Ethyl-7-phenylpyrazolo[4,3-*e*]-1,2,4-triazolo-[1,5-*c*]pyrimidine-2-one 3i : prepared from **2c** (1mmol), chlorosulfonyle isocyanate (1.1 mmol) in dray CH_2Cl_2 (50 ml) according to the procedure described for **3h** : (yield = 81%); mp: 182 °C ; ^{1}H NMR (300 MHz, DMSO-d_6) δ(ppm): 1.41 (t, 3H, $\underline{CH_3}$-CH_2-), 3.05 (q, 2H, CH_3-$\underline{CH_2}$-), 7.35-8.09 (m, 5H_{arom}), 9.33 (s, 1H, H_5), 12.65 (s, **NH**) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ(ppm): 13.2 ($\underline{C}H_3$-CH_2-), 21.9 (CH_3-$\underline{C}H_2$-), 101.7 (C_{9a}), 121.8-139.6 ($C_{arom.}$, C_5), 147.1-148.2 (C_{6a}, C_9, C_{9b}), 170.4 (C_2); IE m/z (rel. Int.%) 286 [$M^{+\cdot}$] (42), 279 (23), 265 (18), 77 (100), 51 (41).

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