Two approaches to a new heterocyclic system of pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine

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Dedicated to Prof. Alexander T. Balaban on the occasion of his 75th Birthday in recognition of his outstanding contributions to theoretical chemistry and chemistry of heterocyclic compounds
(received 26 May 04; accepted 13 Aug 04; published on the web 10 Dec 04)

Abstract
Derivatives of a new heterocyclic system, viz. pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine 5, have been synthesized by coupling imidoesters of 1-substituted-5-aminocarbonitriles 2 with acylhydrazides. The thermal recyclization of 1-substituted-4-(2-acylhydrazin-1-yl)pyrazolo[3,4-d]-pyrimidines 7 is found to be an alternative approach to the heterocyclic system 5.

Keywords: 2,7-Disubstituted pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidines, bis-heterocyclization, carboxylic acids hydrazides

Introduction

The imidoesters 2 obtained by coupling 5-amino-1H-pyrazole-4-carbonitriles 1 with triethyl orthoformate react with amines to form a heterocyclic pyrazolo[3,4-d]pyrimidine system,1,2 the compounds of which display interesting chemical properties1-6 and possess a wide spectrum of biological activities.7-11 We have presumed that by employing hydrazides as the amine components of this reaction, the cascade heterocyclization 2→3→4→5 may occur to afford derivatives of a new heterocyclic system of pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine 5.1 Indeed, it has been shown that the imidoesters 2 react with hydrazides under prolonged reflux in bromobenzene to give compounds 5 in about 50% yield. The reaction mechanism illustrated in

1 A preliminary communication on this transformation has been made in the form of the conference report.12
Scheme 1 has been confirmed by isolation of the intermediates 3a and 4a in the reaction of imidoester 2 (R = H) with 4-methoxybenzoic acid hydrazide under milder conditions. Subsequent heating of a bromobenzene solution of pyrazolopyrimidine 4a smoothly converts it to the final product 5a.

Scheme 1

Results and Discussion

The amidrazone 3a is obtained by short-term reflux of an ethanolic solution of the imidoester 2 (R = H) and 4-methoxybenzoylhydrazine taken in equimolar amounts. The IR-spectrum of 3a contains the bands characteristic of the stretching vibrations of nitrile (2200 cm⁻¹), carbonyl (1675 cm⁻¹), amidine (1650 cm⁻¹) and imino (3060, 3330, 3355 cm⁻¹) groups. Both the initial molecular ion peak M₁⁺ (284) and that of the ion M₂⁺ (266) related to the pyrazolotriazolopyrimidine 5a formed by elimination of a molecule of water from 3a in the gas phase appear in the mass spectrum of the amidrazone 3a. Heating a dimethylformamide solution of the amidrazone 3a gives rise to 4-iminopyrazolopyrimidine 4a, the IR-spectrum of which does not contain a νCN vibration band, whereas νCO and νNH vibration bands appear at 1650 and 3115, 3200 cm⁻¹, respectively. The cyclization of 4a to 5a, via elimination of a molecule of water, proceeds upon reflux in bromobenzene for 3-4 hours. The structure of pyrazolotriazolopyrimidine 5a was supported by its ¹H NMR spectrum that contained signals for a methoxy substituent (3.85 ppm), two doublets (AB-quartet J 8.7 Hz) for aryl protons (7.1 and...
8.2 ppm) and a sharp singlet (9.5 ppm) for the H₅ proton in the pyrimidine ring. At room temperature, the signals (8.6 and 14.4 ppm, DMSO-d₆) of, respectively, CH and NH protons of the pyrazole ring, are substantially broadened, which is due to the fast prototropic exchange process associated with migration of a NH proton between the two nitrogen atoms.

With the goal of the synthesis of derivatives of another heterocyclic system of pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine 8 isomeric to 5 we have prepared a series of 4-acylhydrazinopyrazolo[3,4-d]pyrimidines 7 by coupling 6-chloropyrazolo[3,4-d]pyrimidines 6 with acylhydrazines and studying their cyclization reactions. The energy preference of the amino form of the acylhydrazines 7 over the possible imino tautomer is confirmed by their ¹H NMR spectra (DMSO-d₆, 20°C) which exhibit broadened AB quartet signals for the vicinal NH protons appearing at 9.5 – 11.0 ppm. Dehydration of the acylhydrazines 7 occurs under severe conditions on heating their melts and gives rise not to the expected pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidines 8, but to the isomeric pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]-pyrimidines 5 (Scheme 2). The identity of the products of the dehydration of acylhydrazines 7 with those obtained by cyclization of the intermediate imines 4 was confirmed by comparison of their IR and ¹H NMR spectra.

![Scheme 2](image)

The decisive evidence for the pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine structure 5 of the compounds prepared by dehydration of the acylhydrazines 7 is provided by an X-ray determination of the molecular and crystal structure of compound 5g obtained from 7g (Figure 1).
Figure 1. Perspective view and atom labeling of the X-ray crystal structure of 5g.

The bond lengths in the tricyclic system are the following: C(2)-N(2) 1.318, C(3)-N(3) 1.322, C(5)-N(5) 1.324, C(7)-N(4) 1.301 Å, C(2)-N(3) 1.360, C(3)-N(2) 1.375, C(6)-N(4) 1.362, C(6)-N(6) 1.361, C(7)-N(2) 1.375 Å. The dihedral angles C(6)N(6)-C(14)C(19) and C(1)O(1)-C(8)C(13) are 34.9° and 20.6°, respectively.

Of certain interest is the mode of crystal packing for compound 5g. Due to the formation of a network of C-HN bonds, the molecules of 5g are assembled in the crystal in almost planar layers. The attractive π-π stacking interaction between the neighboring layers of the tricyclic aromatic systems of 5g is manifested by their almost parallel (the dihedral angle between the planes is 5.5°) orientation (Figures 2 and 3).

Figure 2. The layered crystal packing of molecules 5g. The N…H distances in the C-H…N hydrogen bridges are 2.54, 2.29 and 2.55 Å for N(1)…H(5)-C(5), N(3)…H(3)-C(7) and N(5)H(9)-C(9), respectively.
**Figure 3.** A fragment of the crystal structure of compound 5g. The shortest distance between the nearly parallel layers of the molecules is that between the N(5) and C(6) atoms of the five-membered heterocyclic moiety.

**Conclusions**

Two new routes to the preparation of derivatives of a new fused heterocyclic system of pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine 5 have been elaborated. The heterocyclization of the acylhydrazines 7 involves a rearrangement 7→5, the direction of which is opposite to that of the base-catalyzed Dimroth rearrangement. It is suggested here that the initial step of the 7→5 rearrangement involves tandem migration of hydride and an acyl group (B→C). The 1-acyl-1-hetaryldyrazine (C) undergoes cleavage of the N-N bond with the intermediate formation of the tight ionic pair (D) of the resonance-stabilized anion and the aminium cation, which then quenches to the N-amine E. The mechanism of the last stage is similar to that operating in the N-amination of nitrogen heterocycles with hydroxylaminosulfuric acid. The subsequent dehydration of E affords the final product (Scheme 3).

![Scheme 3](image)
**Experimental Section**

**General Procedures.** NMR spectra were recorded on a Varian Unity-300 spectrometer (300 MHz) using DMSO and CDCl$_3$ as solvents. IR spectra were recorded on a Specord 71 spectrophotometer in nujol or KBr tablets. Mass spectra were obtained on a Kratos instrument using an ionization energy of 71 eV and a directing voltage of 1.75 kV. Single-crystal X-ray diffraction experiments were carried out with a Bruker SMART 1000 CCD area detector using graphite monochromated Mo-K$_\alpha$ radiation ($\lambda = 0.71073$ Å), $\omega$-scans with a 0.3° step in $\omega$ and 10s per frame exposure, $2\theta < 58^\circ$) at 120 K. A total of 12416 reflections were measured, 4436 ($R_{int} = 0.0531$). The structures were solved by direct method and refined by the full-matrix least-squares against $F^2$ in anisotropic (for no-hydrogen atoms) approximation. The hydrogen atom positions were calculated and were refined isotropically in riding model approximation. The final refinements were converged to $R_1 = 0.0576$ (from 3549 unique reflections with $I > 2\sigma(I)$) and $wR_2 = 0.1693$ (from all 4436 unique reflections; the number of the refined parameters is 244. All calculations were performed on an IBM PC/AT using the SHELXTL software.$^{13}$

Crystal data for 5g. Colorless plate C$_{19}$H$_{13}$ClN$_6$O (M = 376.80), monoclinic, space group $P2_1/c$ (no. 14), $a = 19.047(7)$Å, $b = 12.206(5)$Å, $c = 7.226(3)$Å, $\beta = 93.292(8)^\circ$, $V = 1677(1)$Å$^3$, $Z = 4$, $d_{calc} = 1.492$ g cm$^{-3}$, $\mu = 0.252$ mm$^{-1}$, $F(000) =$, crystal size 0.07 × 0.40 × 0.50 mm.

**5-Amino-1H-pyrazole-4-carbonitriles (1)** were prepared by coupling ethoxymethylene-malodinitrile with hydrazine hydrate and the corresponding monosubstituted hydrazines according to the previously described procedure.$^4$ By treatment of 5-amino-1H-pyrazole-4-carbonitriles 1 with ethyl orthoformate, imidoesters 2 were prepared following a literature method.$^2$ Chloropyrazolopyrimidines 6 were obtained by the method described by Robins.$^{3,4}$

**5-[2-(4-Methoxyphenyl)-1-hydrazinomethylidenamino]-1H-pyrazolecarbonitrile (3a).** To a solution of imidoester 2a (0.082 g, 0.5 mmol) in 2 ml of ethanol a solution 4-methoxybenzoyl hydrazine (0.083 g, 0.5 mmol) in 1 ml of ethanol was added and the reaction mixture was allowed to stand at room temperature for 1 h. The precipitate formed was filtered off, washed with ethanol and water and dried (0.060 g, 0.21 mmol, 42.3 %): m.p. 304 – 306 °C; IR ($\nu$, cm$^{-1}$): 3555, 3330, 3060, 2200, 1673, 1650. Anal. Calcd. for C$_{13}$H$_{12}$N$_6$O$_2$: C, 54.92; H, 4.23; N, 29.58. Found: C, 54.71; H, 4.35; N, 29.63.

**4-Amino-5-(4-methoxyphenylcarboxamido)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidine (4a).** A suspension of carbonitrile 3a (0.060 g, 0.21 mmol) in 2 ml of DMF was heated to reflux for 10 min. The precipitate formed was filtered off, washed with hexane and dried (0.050 g, 0.17 mmol, 92 %): m.p. 345 – 346 °C; IR (v, cm$^{-1}$): 3284; 3235, 3200, 3115, 1650. Anal. Calcd. for C$_{13}$H$_{12}$N$_6$O$_2$: C, 54.92; H, 4.23; N, 29.58. Found: C, 55.12; H, 4.35; N, 29.71.

**2-(4-Methoxyphenyl)-7H-pyrazolo[4,3-e]triazolo[1,5-c]pyrimidine (5a).** A suspension of pyrimidine 4a (0.100 g, 0.35 mmol) in 2 ml of bromobenzene was refluxed for 10 h, then cooled to room temperature and the formed colorless precipitate was filtered off, washed with ethanol, and dried (0.060 g, 0.225 mmol, 64 %): m. p. 274 – 275 °C; IR (v, cm$^{-1}$): 3167, 3100, 1650; $^1$H
NMR (δ, ppm, DMSO): 3.85 (s, 3H), 7.1 (d, 2H), 8.2 (d, 2H), 8.6 (s, 1H), 14.4 (s, 1H). Molecular ion m/e 266. Anal. Calcd. for C_{13}H_{10}N_{6}O: C, 58.65; H, 3.76; N, 31.58. Found: C, 58.78; H, 3.83; N, 31.46.

**General procedure for the preparation of 2,7-disubstituted 7H-pyrazolo[4,3-e][1,2,3]-triazolo[1,5-c]pyrimidine 7b-i**

A suspension of equimolar amounts of 1-substituted 4-chloro-pyrazolopyrimidines 6 and the corresponding acylhydrazine in ethanol was refluxed for 0.5 – 1.0 h. On heating, the suspension passes into solution and a precipitate of 2,7-disubstituted 7H-pyrazolo[4,3-e][1,2,3]-triazolo[1,5-c]pyrimidine 7b-i is gradually formed. It was filtered off, washed with ethanol and water and crystallized from DMF.

1-(1-Methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-(4-phenylcarboxamido)hydrazine (7b).

Yield 69%; m. p. 245–246 ºC; ¹H NMR (δ, ppm, DMSO-d₆): 3.95 (s, 1H), 7.4 – 8.2 (m, 6H), 9.8 – 11.0 (m, 2H). Anal. Calcd. for C_{13}H_{12}N_{6}O: C, 58.21; H, 4.48; N, 31.34. Found: C, 58.42; H, 4.54; N, 31.26.

1-(1-Methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-(4-methoxyphenylcarboxamido)hydrazine (7c).

Yield 78%, m. p. 228–230 ºC; ¹H NMR (δ, ppm, DMSO-d₆): 3.80 (s, 3H), 3.90 (s, 3H), 7.0 – 8.5 (m, 6H), 11.0 – 11.2 (d, 1H), 12.2 (s, 1H). Anal. Calc. for C_{14}H_{14}N_{6}O: C, 56.37; H, 4.70; N, 28.19. Found: C, 56.48; H, 4.91; N, 28.31.

1-(1-Benzyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-(4-phenylcarboxamido)hydrazine (7d).

Yield 73%; m. p. 230–232 ºC; ¹H NMR (δ, ppm, DMSO-d₆): 5.50 (s, 1H), 7.2 – 8.0 (m, 10H), 8.12 (s, 1H), 8.38 (s, 1H), 11.5 (d, 1H), 12.5 (s, 1H). Anal. Calc. for C_{19}H_{16}N_{6}O: C, 66.28; H, 4.65; N, 24.42. Found: C, 66.41; H, 4.72; N, 24.36.

1-(1-Benzyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-(4-p-methoxyphenylcarboxamido)hydrazine (7e).

Yield 73%; m. p. 217–219 ºC; ¹H NMR (δ, ppm, DMSO-d₆): 3.80 (s, 3H), 5.6 (d, 2H), 7.1 – 8.5 (m, 12H), 11.1 (s, 1H). Anal. Calcd. for C_{20}H_{18}N_{6}O_{2}: C, 64.17; H, 4.81; N, 22.46. Found: C, 64.53; H, 4.68; N, 22.72.

1-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-(4-methoxyphenylcarboxamido)hydrazine (7f).

Yield 69%; m. p. 233–235 ºC; ¹H NMR (δ, ppm, DMSO-d₆): 3.90 (s, 3H), 7.0 – 8.6 (m, 11H), 9.8 – 11.6 (m, 2H). Anal. Calcd. for C_{19}H_{16}N_{6}O_{2}: C, 63.34; H, 4.45; N, 23.33. Found: C, 63.27; H, 4.51; N, 23.15.

1-(1-Phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-(4-chlorophenoloxacylcarboxamido)hydrazine (7g).

Yield 86%; m. p. 218–220 ºC; ¹H NMR (δ, ppm, DMSO-d₆): 3.90 (s, 3H), 7.0 – 8.6 (m, 11H), 9.8 – 11.6 (m, 2H). Anal. Calcd. for C_{19}H_{16}N_{6}O_{2}: C, 63.34; H, 4.45; N, 23.33. Found: C, 63.27; H, 4.51; N, 23.15.

1-(1-(4-Methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-2-(4-phenylcarboxamido)hydrazine (7h).

Yield 89 %, M. p. 263–265 ºC. ¹H NMR (δ, ppm, DMSO-d₆): 2.50 (s, 3H), 7.2 – 8.2 (m, 11H), 10.0 – 11.1 (m, 2H). Anal. Calcd. for C_{19}H_{16}N_{6}O: C, 66.28; H, 4.65; N, 24.42. Found: C, 66.41; H, 4.70; N, 24.65.

**General procedure for the preparation of 2,7-disubstituted-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidines 5b-i**

**Method (a).** A bromobenzene solution of equimolar amounts of imidoester 2 (R = Me, CH₂Ph, Ph, C₆H₄Me-₆) and the corresponding acylhydrazine was refluxed for 5 – 10 h, allowed to reach room temperature and the precipitate formed was filtered off, washed with ethanol, dried and crystallized from DMF.

**Method (b).** 4-Acylhydrazino derivatives of pyrazolo[3,4-d]pyrimidines 7b-i were melted in an open vessel until evaporation of the eliminated water ceased. The remaining solid was crystallized from DMF. The melting points and yields of compounds 5a-i obtained by the methods (a) and (b) are given in **Table 1**.

**Table 1. Melting points and yields of derivatives of 7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]-pyrimidine 5 synthesized by the methods (a) and (b)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>M. p., °C</th>
<th>Yield by method (a)</th>
<th>Yield by method (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>274-275</td>
<td>64</td>
<td>-</td>
</tr>
<tr>
<td>5b</td>
<td>247-249</td>
<td>45</td>
<td>75</td>
</tr>
<tr>
<td>5c</td>
<td>242-243</td>
<td>39</td>
<td>65</td>
</tr>
<tr>
<td>5d</td>
<td>278-280</td>
<td>42</td>
<td>65</td>
</tr>
<tr>
<td>5e</td>
<td>208-209</td>
<td>54</td>
<td>76</td>
</tr>
<tr>
<td>5f</td>
<td>233-235</td>
<td>43</td>
<td>72</td>
</tr>
<tr>
<td>5g</td>
<td>190-192</td>
<td>58</td>
<td>70</td>
</tr>
<tr>
<td>5h</td>
<td>282-283</td>
<td>38</td>
<td>66</td>
</tr>
<tr>
<td>5i</td>
<td>310-311</td>
<td>56</td>
<td>71</td>
</tr>
</tbody>
</table>

2-Phenyl-7-methyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (5b). ¹H NMR (δ, ppm, DMSO-d₆): 4.20 (s, 3H), 7.5 – 8.3 (m, 5H), 8.40 (s, 1H). Anal. Calc. for C₁₃H₁₀N₆: C, 62.40; H, 4.01; N, 33.60 Found: C, 62.30; H, 4.00; N, 33.75.

2-(4-Methoxyphenyl-7-methyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (5c). ¹H NMR (δ, ppm, DMSO-d₆): 3.9 (s, 3H), 4.2 (s, 3H), 7.0 – 8.0 (m, 4H), 8.40 (s, 1H). Anal. Calc. for C₁₄H₁₂N₆O: C, 60.04; H, 4.30; N, 30.00. Found: C, 60.30; H, 4.10; N, 29.91.

2-Phenyl-7-benzyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (5d). NMR ¹H (δ, ppm, DMSO-d₆): 5.70 (s, 2H), 7.3 – 8.3 (m, 10H), 8.40 (s, 1H). Anal. Calc. for C₁₉H₁₄N₆: C, 69.94; H, 4.30; N, 25.77 Found: C, 69.50; H, 4.15; N, 25.80.

2-(4-Methoxyphenyl-7-benzyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (5e). ¹H NMR (δ, ppm, DMSO-d₆): 3.90 (s, 3H), 5.70 (s, 2H), 7.0 – 7.4 (m, 9H), 8.40 (s, 1H). Anal. Calc. for C₂₀H₁₆N₆O: C, 67.42; H, 4.49; N, 23.60. Found: C, 67.50; H, 4.20; N, 23.59.
2-(4-Methoxyphenyl-7-phenyl-7\textsubscript{H}-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (5f). \textsuperscript{1}H NMR (\(\delta\), ppm, DMSO-\(d_6\)): 7.4 – 8.4 (m, 12H), 8.60 (s, 1H), 9.20 (s, 1H). Anal. Calc. for C\textsubscript{19}H\textsubscript{14}N\textsubscript{6}O: C, 66.66; H, 4.03; N, 24.56. Found: C, 66.50; H, 4.10; N, 24.60.

2-(4-Chlorophenoxymethyl-7-phenyl-7\textsubscript{H}-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (5g). \textsuperscript{1}H NMR (\(\delta\), ppm, DMSO-\(d_6\)): 5.4 (s, 2H), 7.0 – 8.2 (m, 9H), 8.50 (s, 1H), 9.20 (s, 1H). Anal. Calc. for C\textsubscript{19}H\textsubscript{13}N\textsubscript{6}OCl: C, 60.56; H, 3.45; N, 22.31; Cl, 9.43. Found: C, 60.72; H, 3.56; N, 22.46; Cl, 9.62.

2-Phenyl-7-(4-methylphenyl)-7\textsubscript{H}-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (5h). \textsuperscript{1}H NMR (\(\delta\), ppm, DMSO-\(d_6\)): 2.40 (s, 3H), 7.4 – 8.4 (m, 9H), 8.60 (s, 1H), 9.20 (s, 1H). Anal. Calc. for C\textsubscript{19}H\textsubscript{14}N\textsubscript{6}: C, 69.94; H, 4.30; N, 25.77 Found: C, 70.15; H, 4.16; N, 25.91.

2-(4-Methylphenyl)-7-(4-methylphenyl)-7\textsubscript{H}-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (5i). \textsuperscript{1}H NMR (\(\delta\), ppm, DMSO-\(d_6\)): 2.40 (s, 6H), 7.3 – 8.2 (m, 8H), 8.60 (s, 1H), 9.20 (s, 1H). Anal. Calc. for C\textsubscript{20}H\textsubscript{16}N\textsubscript{6}: C, 70.59; H, 4.71; N, 24.71 Found: C, 70.72; H, 4.83; N, 24.93.

Acknowledgments

This work was supported by Grants N. Sh. 945. 03. 2003 from Ministry of Education and Science RF and REC-004 from CRDF and Ministry of Education and Science RF.

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