Studies with Alkylheteroaromatic Carbonitriles: A Novel Synthesis of Pyrazolo[2',3':3,4]benzo[c]-1,2,4-triazine

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Alkylheteroatomic Carbonitriles, Thienopyrazolotriazines

A novel synthesis of derivatives of the title ring system by reacting methylpyrazolo[5,1-c]-1,2,4-triazin-6-carbonitriles (9) with sulphur and subsequent treatment of the resulting thienopyrazolotriazines with acetylated double bond system is described.

As a part of biological chemistry programme samples of substituted pyrazolo[2',3':3,4]benzo[c]-1,2,4-triazines (1) were required. Literature survey revealed that derivatives of this ring system have never been reported although pyrazolo[2',3':3,4]-naphtho[c]-1,2,4-triazines (2) have been synthesized earlier via coupling of diazotized 5-amino-pyrazoles with α-naphthol or β-naphthylamine [1]. Attempts to prepare 1 in a similar manner have resulted in formation of the coupling products 3 and 4 [2].

Thus, we have investigated methylpyrazolo[5,1-c]-1,2,4-triazine-6-carbonitriles (9a-c) as starting materials for the synthesis of the required compounds. Recently, a general approach for the synthesis of benzoazines from methylazinylcarbonitriles has been reported [3–5]. Compounds 9a-c could be synthesized by reacting the diazocompounds (6a–c) with 3-aminocrotonitrile (7). The intermediates (8) could not be isolated.

In contrast to the reported formation of benzoazines in the reacting of methylazinylcarbonitriles with benzilidene malonitriles (11a) the reaction of 9a-c with arylidenemalononitriles (11a–c) resulted in the formation of the ylide derivatives (12a–i) via the Michael adducts (10a–i). Compounds 12a–i were also formed from reaction of 9a-c with aromatic aldehydes.

Compounds 9a–c reacted with elemental sulphur to yield the thienopyrazolo[3',4':6,7]pyrazolo[5,1-c]-1,2,4-triazines (13a–c) which is another example of the Gewald reaction.

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based on spectral data. The behaviour of 13, thus parallels that of similar systems [4].

Compound 13a–c also reacted with N-phenylmaleimide to yield the polynuclear pyrazolotriazine derivatives (19a–c).

Experimental

All melting points are uncorrected. IR spectra were obtained (KBr) on a Pye Unicam 1000 spectrophotometer and on a Shimadzu IR 200. 1H NMR spectra were measured on a Varian EM 390–90 MHz in DMSO using TMS as internal standard and chemical shifts are expressed as δ ppm. Analytical data were obtained from the analytical data unit at Cairo University.

7-Methyl-2,3-disubstituted pyrazolo[5,1-c]-1,2,4-triazine-6-carbonitriles (9a–c): general procedure

A solution of the diazonium salt 6a, b or c (prepared from 0.01 mol of aminopyrazole 5a–c and the appropriate quantities of sodium nitrite and hydrochloric acid) was added to 0.01 mol of 3-aminocrotononitrile (7) in 150 ml ethanol and
Table I. List of synthesized compounds.

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<tr>
<td>9a</td>
<td>160</td>
<td>EtOH</td>
<td>88</td>
<td>C₁₃H₁₀N₂ (235.25)</td>
<td>66.3/65.9; 3.8/3.6; 29.7/29.4</td>
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<td></td>
<td>C₁₃H₁₀N₂ (235)</td>
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<td>EtOH</td>
<td>83</td>
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<td>60.6/60.3; 3.9/3.9; 35.3/35.0</td>
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<td>9c</td>
<td>135</td>
<td>EtOH</td>
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<td>C₁₄H₁₁N₂ (173.18)</td>
<td>55.4/55.7; 4.0/4.0; 40.4/40.3</td>
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<td>EtOH/DMF</td>
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<td>C₂₀H₁₄N₂ (323.36)</td>
<td>74.2/73.9; 4.0/3.8; 21.6/21.3</td>
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<td></td>
<td>C₂₀H₁₄N₂ (323)</td>
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<td>C₁₇H₁₂N₂O (289.30)</td>
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<td>C₁₇H₁₂N₂Cl (295.28)</td>
<td>61.0/60.7; 3.4/3.1; 23.7/23.5</td>
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<td>90</td>
<td>C₁₃H₁₀N₂S (267.32)</td>
<td>58.4/58.2; 3.3/3.2; 26.2/26.0</td>
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<td>C₁₄H₁₁N₂S (309.36)</td>
<td>54.3/54.1; 3.5/3.2; 31.6/31.2</td>
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<td>C₁₁H₇N₂S (205.25)</td>
<td>46.8/46.6; 3.4/3.3; 34.1/33.8</td>
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<td>C₁₅H₁₃N₂ (286.3)</td>
<td>67.1/66.8; 3.5/3.5; 29.3/29.0</td>
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<td></td>
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<td>C₁₅H₁₃N₂ (286)</td>
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<td>17b</td>
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<td>EtOH/DMF</td>
<td>81</td>
<td>C₁₇H₁₄N₂ (328.28)</td>
<td>62.1/61.9; 3.6/3.4; 34.1/34.2</td>
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<td>17c</td>
<td>&gt;300</td>
<td>EtOH/DMF</td>
<td>71</td>
<td>C₁₇H₁₄N₂ (328.28)</td>
<td>58.9/58.7; 3.5/3.3; 37.4/37.3</td>
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<td>19a</td>
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<td>78</td>
<td>C₁₅H₁₃N₂O₂ (406.41)</td>
<td>67.9/67.7; 3.4/3.2; 20.6/20.5</td>
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<td>19b</td>
<td>&gt;300</td>
<td>EtOH/DMF</td>
<td>81</td>
<td>C₁₅H₁₃N₂O₂ (448.43)</td>
<td>64.2/64.0; 3.6/3.4; 24.9/24.7</td>
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<tr>
<td>19c</td>
<td>&gt;300</td>
<td>EtOH</td>
<td>65</td>
<td>C₁₅H₁₃N₂O₂ (344.32)</td>
<td>62.7/62.5; 3.5/3.4; 24.4/24.2</td>
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</table>
3.09 g sodium acetate. The reaction mixture was stirred at room temperature for 1 h. The solid product, so formed, was washed with water and recrystallized from the proper solvent, (cf. Tables I and II).

7-Methyl-2,3-disubstituted pyrazolo[5,1-c]-1,2,4-triazine-6-carbonitriles (12a-c): general procedure

To a solution of 9a, b, or c (0.01 mol) in absolute ethanol (50 ml) the appropriate 11a,b or c (0.01 mol) in absolute ethanol (50 ml) the appropriate

<table>
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<th>Compd. No.</th>
<th>IR [cm⁻¹]</th>
<th>¹H NMR [ppm]</th>
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<tbody>
<tr>
<td>9a</td>
<td>2220 (CN)</td>
<td>3.15 (s, 3H, CH₃), 7.2–8.15 (m, 6H, aromatic protons and pyrazole H-4).</td>
</tr>
<tr>
<td>9b</td>
<td>2220 (CN)</td>
<td>– – –</td>
</tr>
<tr>
<td>9c</td>
<td>2210 (CN)</td>
<td>2.6 (s, 3H, pyrazole CH₃), 3.0 (s, 3H, triazine CH₃), 7.5 (s, H, pyrazole H-4).</td>
</tr>
<tr>
<td>12a</td>
<td>2180 (CN)</td>
<td>6.8–8.2 (br, 13H, 12 aromatic protons and pyrazole H-4).</td>
</tr>
<tr>
<td>12b</td>
<td>2160 (CN)</td>
<td>3.8 (s, 3H, OCH₃), 6.8–8.2 (m, 12H, aromatic protons and pyrazole H-4).</td>
</tr>
<tr>
<td>12c</td>
<td>2170 (CN)</td>
<td>6.8–8.4 (m, 12H, aromatic protons and pyrazole H-4).</td>
</tr>
<tr>
<td>12d</td>
<td>2165 (CN)</td>
<td>2.7 (s, 3H, CH₃), 6.8–8.2 (br, 12H, aromatic protons).</td>
</tr>
<tr>
<td>12e</td>
<td>2170 (CN)</td>
<td>2.65 (s, 3H, CH₃), 3.7 (s, 3H, OCH₃), 6.8–8.3 (m, 11H, aromatic protons).</td>
</tr>
<tr>
<td>12f</td>
<td>2170 (CN)</td>
<td>2.65 (s, 3H, CH₃), 6.8–8.2 (m, 11H, aromatic protons).</td>
</tr>
<tr>
<td>12g</td>
<td>2205 (CN)</td>
<td>3.1 (s, 3H, CH₃), 6.8–8.2 (m, 8H, aromatic protons and pyrazole H-4).</td>
</tr>
<tr>
<td>12h</td>
<td>2210 (CN)</td>
<td>3.15 (s, 3H, CH₃), 3.8 (s, 3H, OCH₃), 6.8–8.2 (m, 7H, aromatic protons and pyrazole H-4).</td>
</tr>
<tr>
<td>12i</td>
<td>2200 (CN)</td>
<td>– – –</td>
</tr>
<tr>
<td>13a</td>
<td>3100–3200 (br, NH₂)</td>
<td>7.0–8.2 (m, 7H, aromatic protons), 8.9 (br, 2H, NH₂)</td>
</tr>
<tr>
<td>13b</td>
<td>3250, 3365 (NH₂)</td>
<td>2.7 (s, 3H, CH₃), 7.6–8.1 (m, 6H, aromatic protons), 9.2 (br, 2H, NH₂)</td>
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<tr>
<td>13c</td>
<td>3150, 3350 (NH₂)</td>
<td>3.0 (s, 3H, CH₃), 6.4 (s, 1H, pyrazole H-3), 7.6 (s, 1H, thiophene H-8), 9.1 (s, 2H, NH₂)</td>
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<td>17a</td>
<td>2300 (CN), 3260, 3290 (NH₃)</td>
<td>7.5 (br, 2H, NH₂), 7.6–8.9 (m, 8H, aromatic protons and pyrazole H-3).</td>
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<td>2290 (CN), 3350 (br, NH₂)</td>
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<td>17c</td>
<td>2200 (CN), 3200–3380 (br, NH₂)</td>
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<tr>
<td>19a</td>
<td>3200–3500 (br, NH₂), 1700 (CO)</td>
<td>7.4 (br, 2H, NH₂), 7.6–8.4 (m, 12H, aromatic protons and pyrazole H-3).</td>
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<tr>
<td>19b</td>
<td>3250–3500 (br, NH₂), 1690 (CO)</td>
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<td>3280–3480 (br, NH₂), 1700 (CO)</td>
<td>3.0 (s, 3H, CH₃), 7.5 (br, 2H, NH₂), 7.65–8.5 (m, 12H, aromatic protons and pyrazole H-3).</td>
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</tbody>
</table>

Table II. IR and ¹H NMR of newly prepared compounds.
mol) and anhydrous triethylamine (1 ml) were added. The reaction mixture was refluxed for 5 h and then evaporated in vacuo. The remaining products were poured on ice acidified by dilute hydrochloric acid up to pH 4. The solid product, so formed, was then collected by filtration and recrystallized from the proper solvent (cf. Tables I and II).

2,3-Disubstituted thieno[3',4':6,7]pyrazolo[5,1-c]-1,2,4-triazine-6-amines (13a–c): general procedure

To a suspension of 9a, b or c (0.01 mol) in absolute ethanol (50 ml) elemental sulphur (0.3 g, 0.01 mol) and anhydrous triethylamine (1 ml) were added. The reaction mixture was refluxed for 3 h and then evaporated in vacuo. The remaining product was poured on ice, acidified by dilute hydrochloric acid up to pH 4. The solid product, so formed is then collected by filtration and recrystallized from the proper solvent, (cf. Tables I and II).

Reaction of 13 with activated double bond systems (17a–c) and (19a–c): general procedure

To a suspension of 13a, b or c (0.01 mol) in dioxane/acetic acid mixture (50 ml) the appropriate quantity of either acrylonitrile or N-phenylmaleimide was added (0.01 mol). The reaction mixture was refluxed for 5 h and then poured on ice cold water. The solid product, so formed is then collected by filtration and recrystallized from the proper solvent (cf. Tables I and II).

Reaction of 13 with activated double bond systems (17a–c) and (19a–c): general procedure

To a suspension of 13a, b or c (0.01 mol) in dioxane/acetic acid mixture (50 ml) the appropriate quantity of either acrylonitrile or N-phenylmaleimide was added (0.01 mol). The reaction mixture was refluxed for 5 h and then poured on ice water. The solid product, so formed is then collected by filtration and recrystallized from the proper solvent (cf. Tables I and II).