Heterocycle Syntheses through Ternary Condensation of Terephthalaldehyde with Malononitrile and Some Nucleophiles

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The ternary condensation of terphthalaldehyde with malononitrile and some active methylene, and methyl group reagents are reported. Structures and different pathways are described.

The present work is in continuation of our programme aiming at developing an efficient procedure of multicomponent condensation for the syntheses of new heterocyclic derivatives of potential biological activity [1−6]. Based on the versatility of the activated cyano olefins as organic syntheses [1−9], we, herein, report on a convenient one-flask, high yield, unprecedented syntheses of some new heterocycles containing \(p\)-phenylenebis-derivatized moieties of naphtho[2,1-b]-4H-pyran, benzo[b]-4H-pyran, pyrano[3,2-d]pyrimidine, pyrano[2,3-c]pyrazole, phthalazine, quinazoline, 4H-thiopyran and 1,4-dihydropyridine.

Thus, it has been found that an ethanolic piperidine solution of terephthalaldehyde 1, malononitrile 2 and 2-naphthol 3 in a 1:2:2 molar ratio afforded product 4. The structure of 4 was established on the basis of elemental and spectral data (cf. Table I). The IR spectrum of 4 showed only one conjugated \(C=\text{N}\) absorption band at 2180 cm\(^{-1}\) and its 'H NMR spectrum showed a singlet signal for, together, the H-4 of the two pyran moieties. These spectral data indicate to a plane of symmetry in 4, thus, support its structure.

Formation of 4 is assumed to proceed via the initial formation of 1,4-bis(\(\alpha,\alpha\)-dicyanovinyl)-benzene 5, followed by the addition of 3 to both of the \(\beta\)-vinyl carbons in 5 to form the acyclic intermediate 6 which cyclizes to 7 that tautomerizes to 4 (Scheme 1).

Resorcinol, 8, reacted similarly under the same conditions to afford 1,4-bis-(2-amino-3-cyano-7-hydroxybenzo[b]pyran-4-yl)benzene 9 (Scheme 1).

Thiobarbituric acid 10 was subjected to the same reaction conditions to afford the \(\alpha\)-phenylenedipyrano[2,3-d]pyrimidine derivative 11 (Scheme 1).

The pyrazolin-5-one derivatives 12a, b afforded \(\alpha\)-phenylenedipyrano[2,3-c]pyrazole derivatives 13a, b. The IR spectrum of 13a revealed the presence of a conjugated cyano band at 2180 cm\(^{-1}\) and bands for the NH\(_2\) and NH functions in the region of 3420−3160 cm\(^{-1}\) and the absence of any absorption in the C=O region, indicating to the participation of the pyrazolone carbonyl group in the formation of the pyran moiety of 13. Also, the structure symmetry was concluded from its 'H NMR spectrum. It showed singlet signal(s) for the proton(s) of each pair of the CH\(_3\), pyran H-4, \(\text{NH}_2\) and \(\text{NH}\) functions, besides the singlet of the four aromatic protons (cf. Table I).

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Table I. Characterization data of the synthesized compounds.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Cryst. from (m.p. °C)</th>
<th>Colour</th>
<th>Mol. formula (Mol. wt.)</th>
<th>Found (%) (Calc.)</th>
<th>IR (cm⁻¹); ¹H NMR (δ)</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>4</td>
<td>Dioxane (&gt; 300)</td>
<td>Light buff</td>
<td>C₃₄H₃₈N₄O₂ (518.55)</td>
<td>78.73 (78.75)</td>
<td>3420–3200 (NH₂), 2180 (CN); 5.35 (s, 2H, 2pyran H-4), 7.1–8.1 (m, 2OH, Ar, 2NH₂)</td>
</tr>
<tr>
<td>9</td>
<td>Ethanol (210–212)</td>
<td>Yellow</td>
<td>C₃₄H₃₈N₄O₂ (450.43)</td>
<td>69.30 (69.32)</td>
<td>3370–3200 (NH₂), 2180 (CN)</td>
</tr>
<tr>
<td>11</td>
<td>Ethanol (230–232, dec.)</td>
<td>Buff</td>
<td>C₃₄H₃₈N₄O₂ (518.52)</td>
<td>50.93 (50.96)</td>
<td>3400–3150 (OH, NH₂), 2180 (CN)</td>
</tr>
<tr>
<td>13a</td>
<td>Ethanol (240–242)</td>
<td>Buff</td>
<td>C₃₄H₃₈N₄O₂ (426.43)</td>
<td>61.95 (61.96)</td>
<td>3420–3160 (NH₂-NH₂), 2180 (CN)</td>
</tr>
<tr>
<td>13b</td>
<td>Ethanol-water (190–192)</td>
<td>Brown</td>
<td>C₃₄H₃₈N₄O₂ (576.62)</td>
<td>70.55 (70.57)</td>
<td>3400, 3300 (NH₂), 2180 (CN)</td>
</tr>
<tr>
<td>19</td>
<td>Ethanol (&gt; 300)</td>
<td>Greenish</td>
<td>C₄₀H₃₈N₄O₂ (742.73)</td>
<td>67.88 (67.91)</td>
<td>3400, 3300 (NH₂), 2200 (CN), 1730 (C=O)</td>
</tr>
<tr>
<td>20</td>
<td>Ethanol (280–282)</td>
<td>Brown</td>
<td>C₃₄H₃₈N₄O₂ (630.73)</td>
<td>68.52 (68.55)</td>
<td>3400–3150 (NH₂), 2200 (CN)</td>
</tr>
<tr>
<td>26</td>
<td>Ethanol (200–202)</td>
<td>Yellowish</td>
<td>C₃₄H₃₈N₄O₂ (430.50)</td>
<td>55.79 (55.80)</td>
<td>3320, 3200 (NH₂), 2180 (CN); 4.2 (s, 2 thiopyran H-4), 6.9 (s, 8H, 4NH₂), 7.2 (s, 4H, Ar)</td>
</tr>
<tr>
<td>29</td>
<td>Ethanol (&gt; 300)</td>
<td>Brown</td>
<td>C₃₄H₃₈N₄O₂ (432.47)</td>
<td>55.54 (55.54)</td>
<td>3340, 3200 (NH₂, OH), 200 (CN), 1670–1650 (br, C=O)</td>
</tr>
</tbody>
</table>

Formation of 13 is assumed to proceed via initial condensation of terephthalaldehyde 1 with 2 moles of malononitrile 2, or with 2 moles of the pyrazolone 12, affording the ylidenes 5 or 16, respectively. This is followed by the Michael addition of the other active methylene reagent to the ylidenic bond in 5 or 16, leading to an acyclic intermediate 14 which cyclizes to 15 that tautomerizes to give the final product 13 (Scheme 2).

When active methyl-heterocycles pyridazine 17 and pyrimidine 18 were reacted with 1 and 2 in refluxing 1,4-dioxane, in the presence of catalytic amount of piperidine 1,4-bis-[(8-amino-7-cyano-4-ethoxycarbonyl-1(2H)-oxo-2-phenyl)-1,2-dihydrophthalazin-6-yl]benzene 19 and 1,4-bis-[(5-amino-6-cyano-2-phenyl-4(2H)-thioxo)-3,4-dihydroquinazolin-7-yl]benzene 20 were obtained.
Formation of 26 is rationalized in terms of the initial condensation of 1 with two mole ratios of 2 or cyanothioacetamide 25 affording the arylidenecyano olefin 5 or 27, respectively. Following, the other remaining active methylene compound undergoes Michael addition to each of the β-vinylic carbons in 5 or 27 forming the acyclic intermediate 28 which cyclizes to 26, (Scheme 4).

On the other hand, refluxing ethanolic piperidine solution of terephthalaldehyde 1, malononitrile 2 and cyanothioacetamide 25 in 1:2:2 molar proportions afforded the corresponding 1,4-bis-[3,5-dicyano-2-hydroxy-6-mercapto-1,4-dihydropyridin-4-yl]benzene 29.

The formation of 29 is rationalized in terms of the initial formation of the kinetically controlled reaction product 26, followed by its rearrangement to the thermodynamically controlled reaction product 29 (Scheme 4).

**Experimental**

All melting points were uncorrected. IR (KBr) spectra were recorded on Shimazu 408 spectrophotometer. 1H NMR spectra were recorded in DMSO-d6 on a 90 MHz varian EM-390 Spectrometer with Me4Si as an internal standard and chemical shifts are expressed as δ values. Analytical data were obtained from the Microanalytical Data Unit at Cairo University.

The data of synthesized new derivatives are listed in Table I.

**General procedure for the synthesis of compounds 4, 9, 11, 13a,b and 26**

A mixture of 1 (0.01 mol), 2 (0.02 mol) and the appropriate compound (0.02 mol) of either 3, 8, 10, 12a,b or 25, respectively, in absolute ethanol
(70 ml) and catalytic amount of piperidine was stirred at room temperature (30–35 °C).

In order to complete the reaction, stirring was continued for 3 h even if a solid precipitate was formed after a shorter reaction time. The deposited solid, or that obtained after concentration of the reaction mixture to half of its volume and trituration with water, was filtered and crystallized from the appropriate solvent.

**General procedure for the synthesis of compounds 19 and 20**

A mixture of 1 (0.01 mol), 2 (0.02 mol) and (0.02 mol) of either 17 or 18 in dioxane (50 ml) containing catalytic amount of piperidine, was refluxed for 3 h. The solid deposited on cooling, or obtained after concentration of the reaction mixture to half of its volume and trituration with water, was filtered and crystallized from the appropriate solvent.

**Synthesis of compound 27**

A: By reaction 1, 2 and 25. To a suspension of 1 (0.01 mol) and 2 (0.02 mol) in ethanol (50 ml) was added 25 (0.02 mol) and 2 drops of piperidine. The reaction mixture was refluxed for 4 h, then concentrated to its half volume, cooled and triturated with water containing few drops of acetic acid. The solid obtained was filtered, washed with water, dried and crystallized from ethanol.

B: From 26: To a solution of 26 (0.7 g) in ethanol (30 ml) was added 3 drops of piperidine and 0.5 ml of water. The reaction mixture was refluxed for 6–7 h, concentrated to its half volume, cooled and then treated as in method A.

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