Reaction of Malononitrile and Ethyl Cyanoacetate: a Novel Synthesis of Polyfunctional Pyridine Derivatives

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Malononitrile, Ethyl Cyanoacetate, Pyridine Derivatives

Malononitrile reacts with ethyl cyanoacetate to give a polyfunctional substituted pyridine derivative 5. The latter compound reacts with aniline, hydrazines and aromatic aldehydes to give condensed products. The active methylene of 5 couples with benzenediazonium chloride to give the phenylhydrazone derivative which cyclises readily to give a pyrido[2,3-d]pyridazine derivative. 5 reacts with trichloroacetonitrile, and carbon disulphide to give fused heterocyclic derivatives.

Polyfunctional substituted pyridines are versatile reagents specially as precursors for synthesis of the fused heterocyclic pyridine derivatives [1, 2]. In a recent article we have reported for the synthesis and the chemistry of 2-pyridothione derivatives using cyanothioacetamide as starting material [3]. In continuation of this program we report here for the synthesis of a new polyfunctional pyridine derivative starting with malononitrile (1) and ethyl cyanoacetate (2). The latter two reagents were reported by Junek et al. [4] to react together in sodium ethoxide solution to give ethyl 2-cyano-3-amino crotonoate. However, we found that fusion of the two reagents together in 2:1 molar ratio in presence of a catalytic amount of piperidine, a product of molecular formula C5H11N2O2 was obtained. Structure 5 was proposed for the reaction product based on IR spectrum which revealed the presence of two amino stretching bands at 3450–3200 cm⁻¹, two cyano stretching bands at 2225, 2220 cm⁻¹ and an ester carbonyl group at 1720 cm⁻¹. 1H NMR data revealed the presence of a singlet at δ 3.01 ppm for CH₂ group and the presence of four D₂O exchangeable protons for two NH₂ groups at δ 7.35 and 7.58 ppm. A logical mechanism for this reaction is based on formation of malononitrile in the basic medium [5] to give compound 3, the latter inturn reacts with ethyl cyanoacetate to give ethyl α-(2,4-diamino-3,5-dicyano-6-pyridinyl)acetate (5). Such pyridine formation finds parallism with the reported literature [6]. This reaction sequence is strictly confirmed via direct fusion of equimolecular amounts of malononitrile dimer (3) with ethyl cyanoacetate in presence of piperidine where 5 was obtained again but in a better yield. However, it is worthy to mention here that preparation of 5 via the former method is much more favourable for the easyness of the procedure, simplicity of the starting materials and saving of time. However, the chemistry of 5 presents further confirmation for the proposed structure.

The reactivity of the ethyl carboxylate group of 5 towards amines and hydrazines finds parallism to the reported literature [7]. Thus, 5 condenses with aniline and hydrazines to give the anilide and hydrazide derivatives 6a–c, respectively. The structures of 6a–c were identified based on analytical and spectral data.

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The active methylene group of the side chain in 5 found to yield arylidine derivatives 7a, b on condensation with benzaldehyde and salicylaldehyde respectively (cf. Table II).

5 couples with benzenediazonium chloride to form the phenylhydrazone derivative 8. The latter readily cyclises in alcoholic sodium hydroxide solution to give the pyrido[2,3-d]pyridazine derivative 9. Structures of compounds 7a, b; 8 and 9 were established based on analytical and spectral data (cf. Table II).

Refluxing 5 in acetic/hydrochloric acid mixture gives a product identified as pyrido[4,3-b]pyridine derivative 11 based on analytical and spectral data. It seems that 11 formed via cyclisation of the non isolable intermediate 10. Moreover, 11 was also obtained on treating compound 6a under the same conditions mentioned for cyclisation of 5.

5 reacts also with trichloroacetonitrile to give a pyrido[4,3-b]pyridine derivative 13, which is logically formed through cyclisation of the non isolable intermediate 12 followed by hydrolysis of the trichloromethyl group as reported [8]. Moreover, compound 13 found to condense with hydrazine hydrate to give a pyrazolo[3′,4′:7,8]pyrido[3,2-c]pyridine derivative 14. Structures of compounds 13, 14 were identified based on analytical and spectral data (cf. Tables I and II).

5 found to react with carbon disulphide in aqueous ammonium hydroxide solution at room temperature...
Table II. IR and $^1$H NMR of compounds listed in Table I.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IR [cm$^{-1}$] (selected bands)</th>
<th>$^1$H NMR [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3350, 3200 (2NH$_2$); 2950 (CH$_3$, CH$_2$); 2225, 2220 (2CN); 1710 (ester CO); 1650 ($\delta$NH$_2$)</td>
<td>1.68 (t, 3H, CH$_3$); 3.85 (s, 2H, CH$_2$); 4.58 (q, 2H, CH$_2$); 5.70 (s, 2H, NH$_2$); 7.23 (s, 2H, NH$_2$)</td>
</tr>
<tr>
<td>6a</td>
<td>3450–3300 (NH, NH); 3050 (CH aromatic); 2980 (CH$_2$); 2225, 2220 (2CN); 1650–1630 (NH$_2$, (NH deformation)</td>
<td>4.10 (s, 2H, CH$_2$); 4.99 (s, 2H, NH$_2$); 6.59 (s, 2H, 2NH$_2$); 7.33 (s, 5H, C$_6$H$_5$); 10.34 (s, br, 1H, NH)</td>
</tr>
<tr>
<td>6b</td>
<td>3400–3200 (3NH$_2$ and NH); 2980 (CH$_2$); 2225, 2220 (2CN); 1690 (CO)</td>
<td>3.80 (s, 2H, CH$_2$); 5.70 (s, 2H, NH$_2$); 7.53 (m, 4H, 2NH$_2$); 8.71 (s, br, 2NH)</td>
</tr>
<tr>
<td>6c</td>
<td>3350–3220 (2NH$_2$ and NH); 2225–2220 (2CN); 1685 (CO); 1640 ($\delta$NH$_2$)</td>
<td>3.92 (s, 2H, CH$_2$); 5.68 (s, 2H, NH$_2$); 7.50 (s, 2H, NH$_2$); 8.89–9.0 (2s, br, 2NH)</td>
</tr>
<tr>
<td>7a</td>
<td>3350, 3200 (2NH$_2$); 3010 (ylidene CH); 2225, 2210 (2CN); 1720 (ester CO); 1640, 1610 ($\delta$NH$_2$ and C=C)</td>
<td>1.70 (t, 3H, CH$_3$); 4.59 (q, 2H, CH$_2$); 5.75 (s, 2H, NH$_2$); 7.23 (s, 2H, NH$_2$); 7.35–7.38 (m, 6H, ylidene CH and C$_6$H$_5$)</td>
</tr>
<tr>
<td>7b</td>
<td>3450 (OH); 3300, 3250 (2NH$_2$); 2225, 2220 (2CN); 1650 ($\delta$NH$_2$)</td>
<td>1.70 (t, 3H, CH$_3$); 4.89 (s, 2H, CH$_2$); 5.76 (s, 2H, NH$_2$); 7.29 (s, 2H, NH$_2$); 7.35–7.40 (m, 5H, CH, C$_6$H$_5$); 10.10 (s, 1H, OH)</td>
</tr>
<tr>
<td>8</td>
<td>3350, 3310 (2NH$_2$); 2220, 2215 (2CN); 1720 (ester CO); 1660 ($\delta$NH$_2$)</td>
<td>Insoluble in common $^1$H NMR solvents</td>
</tr>
<tr>
<td>9</td>
<td>3450, 3300 (2NH$_2$); 2220 (CN); 1720–1690 (ester CO and exocyclic CO); 1620 ($\delta$NH$_2$)</td>
<td>Insoluble in common $^1$H NMR solvents</td>
</tr>
<tr>
<td>11</td>
<td>3450–3300 (NH$_2$, NH); 2980 (CH$_2$); 2220 (CN); 1680, 1700 (2CO); 1630 (NH$_2$, NH deformation)</td>
<td>4.57 (s, 2H, CH$_2$); 5.75 (s, 2H, NH$_2$); 6.89 (s, 2H, NH$_2$); 10.00 (s, br, 1H, NH)</td>
</tr>
<tr>
<td>13</td>
<td>3500 (OH); 3450–3300 (NH$_2$, NH); 2985 (CH$_2$, CH$_2$); 2220 (CN); 1680 (ester CO); 1630 (NH$_2$, deformation)</td>
<td>Insoluble in common $^1$H NMR solvents</td>
</tr>
<tr>
<td>14</td>
<td>3450–3200 (NH$_2$, NH); 2220 (CN); 1680 (ring CO); 1630 (NH$_2$, NH deformation)</td>
<td>Insoluble in common $^1$H NMR solvents</td>
</tr>
<tr>
<td>16</td>
<td>3450–3300 (NH$_2$, NH); 2980 (CH$_2$, CH$_2$); 2220 (CN); 1630 (NH$_2$, NH deformation); 1200 (C=S)</td>
<td>1.65 (t, 3H, CH$_3$); 4.25 (q, 2H, CH$_2$); 5.25 (s, 2H, NH$_2$); 7.01 (s, 2H, NH$_2$); 10.23 (s, br, 1H, NH)</td>
</tr>
</tbody>
</table>

Formulation of 16 is assumed to take place through cyclisation of the non isolable adduct 15.

Experimental

Melting points are uncorrected, IR spectra were recorded (KBr) on a Pye-Unicam SP-1000. $^1$H NMR spectra were obtained on an EM-90 MHz spectrometer in DMSO using TMS as internal standard and chemical shifts are expressed as ppm. Analytical data were performed by the microanalytical data Unit at Cairo University.

*Preparation of ethyl
a-(2,4-diamino-3,5-dicyano-6-pyridinyl)acetate (5)*

Method (A)

A mixture of malononitrile (1) (1 mol) and ethyl cyanooacetate (0.05 mol) containing $\frac{1}{2}$ ml of to give a thiopyrano[4,3-b]pyridine derivative 16.
piperidine is heated in an oil bath at 140 °C for 40 min then left to cool. The product, so formed, is boiled in ethanol (100 ml) then collected by filtration (cf. Tables I and II for data).

**Method (B)**

An equimolecular amounts (0.1 mol) of malononitrile dimer (3) and ethylcyanoacetate is heated in an oil bath at 140 °C for 30 min. The solid product, so obtained, is boiled with (70 ml) ethanol then collected by filtration.

**Reaction of 5 with hydrazine and phenyl hydrazine to give the hydrazide derivatives 6a and 6b, respectively**

To a suspension of compound 5 (0.01 mol) in 30 ml ethanol each of hydrazine hydrate or phenylhydrazine (0.01 mol) is added. The whole mixture is boiled under reflux for 2 h then poured into ice/water containing few drops of hydrochloric acid. The solid product, so formed is collected by filtration (cf. Table I and II).

**Reaction of 5 with benzaldehyde and salicylaldehyde to give arylidine derivatives 7a and 7b, respectively**

To a solution of compound 5 in DMF (30 ml) containing ½ ml of piperidine, each of benzaldehyde or salicylaldehyde (0.01 mol) is added. The reaction mixture is heated under reflux for 1½ h then poured into ice/water mixture. The solid product, so formed, is collected by filtration (cf. Tables I and II).

**Coupling of 5 with benzenediazonium chloride to give the phenylhydrazine derivative 8**

A solution of benzenediazonium chloride (prepared by adding sodium nitrite (0.01 mol) to the appropriate quantity of aniline in hydrochloric acid) is added to a stirred solution of 5 (0.01 mol) in ethanol (50 ml) and 5 ml (5%) sodium hydroxide solution. The mixture is left at room temperature for 15 min. The solid obtained is collected by filtration (cf. Tables I and II).

Cyclisation of 8 to give the pyrido[2,3-d]pyrazine derivative (9)

A solution of 8 (0.01 mol) in 50 ml of ethanol containing 2 pellets of sodium hydroxide is heated under reflux for 3 h then evaporated in vacuo. The remaining product is triturated with water containing few drops of hydrochloric acid. The so formed solid product is collected by filtration (cf. Tables I and II).

**Cyclisation of 5 or 6a to pyrido[4,3-b]pyridine derivative (11)**

A solution of compound 5 (0.01 mol) or 10 (0.01 mol) in acetic acid (30 ml) and hydrochloric acid (5 ml) mixture is heated under reflux for 6 h then left to cool. The reaction product is precipitated on adding sodium hydroxide solution (0.1 N) till pH 7 then collected by filtration (cf. Tables I and II).

**Reaction of 5 with trichloroacetonitrile to give 13**

To a solution of compound 5 (0.01 mol) in DMF (30 ml) trichloroacetonitrile (0.01 mol) is added together with ½ ml of triethylamine. The reaction mixture is left at room temperature overnight then poured into ice/water containing few drops of hydrochloric acid. The solid product, so formed is collected by filtration (cf. Tables I and II).

**Reaction of 13 with hydrazine hydrate to give 14**

To a solution of compound 13 in (0.01 mol) in DMF (30 ml) hydrazine hydrate (0.01 mol) is added. The reaction mixture is heated under reflux for 1 h then left to cool. The reaction product is precipitated on pouring into dilute hydrochloric acid/ice mixture then collected by filtration (cf. Tables I and II).

**Reaction of compound 5 with carbodisulphide to give 16**

To a suspension of compound 5 (0.01 mol) in ammonium hydroxide (20%, 100 ml), carbodisulphide (0.01 mol) is added. The reaction mixture is left at room temperature overnight with constant stirring. The solid product, so formed, is collected by filtration (cf. Tables I and II).