Synthesis of Heterocyclic Compounds, XXIII. Pyridines from Malononitrile Dimer and Benzylidene malononitriles

Luis Fuenes, Juan J. Vaquero
Departmento de Quimica Organica, Universidad de Alcalá de Henares, Madrid, Spain
José L. Soria

Departmento de Quimica Organica, Facultad de Quimica, Universidad Complutense, Madrid, Spain

In the reaction of malononitrile (1) with benzylidene malononitriles (2) and amines, from which the 1-dialkylaminopyridines (3) were isolated, we observed that malononitrile showed a great tendency to undergo dimerization. In the present work the intervention in that reaction of the malononitrile dimer in the formation of diethylammonium, pyrrolidinium, and piperidinium salts (4) of 2-amino-4-aryl-3,5-dicyano-6-dicyanomethylene-1,2-dihydropyridines (9) was described.

The intervention of 2-amino-1,1,3-tricyanopropene (5) in the formation of compounds 4 was indicated by the formation of a mixture of salts 4 and 7 from the reaction of 5, previously synthesized, with benzylidene malononitriles (2) and amine in chloroform/tetrahydrofuran. The reaction is initiated by a 1,4-addition of the 2-amino-1,1,3-tricyanopropene (5) to the corresponding benzylidene malononitrile (2) to afford the adduct 6 which cyclizes to 4 and 7 via intramolecular attack of the enamine nitrogen atom in the cyanoethyl moiety of 6. The salt mixture is oxidized completely to 4 by treatment with dichlorodicyanobenzorquinone (DDQ).

The structures assigned to the salts 4 and 1,2-dihydropyridines 9, liberated from 4 in acid medium, are based on the preparation of 9a (Ar = C₆H₅) by treatment of 2-amino-3,5-dicyano-6-ethylthio-4-phenylpyridine (8a) with malononitrile in ethanol/ethoxide, and subsequent liberation of 9a from the sodium salt thus formed.

The 1,4-dihydropyridine salts (7) can be isolated if tetrahydrofuran is used as reaction medium. Due the easy decomposition and readiness to oxidation of these compounds, we only describe the pyrrolidinium salt in which Ar = C₆H₅.

Meltng points are uncorrected. Infrared spectra were recorded on Perkin-Elmer 257 and 599 spectrometers. *H-N.M.R. spectra were recorded on a Varian T-60 apparatus. For the column chromatography, Merck 60 alumina was used.
Table. Compounds 4 and 9 prepared

<table>
<thead>
<tr>
<th>Product No.</th>
<th>R</th>
<th>Ar</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>Molecular formula&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1H-N.M.R. (DMSO-d&lt;sub&gt;6&lt;/sub&gt;) δ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>-&lt;CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-</td>
<td>68</td>
<td>243-244&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;</td>
<td>6.1-2.1 (m, 4H); 2.8-3.3 (m, 4H); 6.70 (br, 2H); 7.3 (m, 5H); 4.7-8.3 (br, 2H)</td>
</tr>
<tr>
<td>4b</td>
<td>-&lt;CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-</td>
<td>68</td>
<td>224-225&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>6.1-2.0 (m, 4H); 2.8-3.2 (m, 4H); 6.70 (br, 2H); 7.3 (m, 5H); 4.7-8.3 (br, 2H)</td>
</tr>
<tr>
<td>4c</td>
<td>-&lt;CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-</td>
<td>61</td>
<td>253-254&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;CN&lt;sub&gt;2&lt;/sub&gt;</td>
<td>6.1-2.0 (m, 4H); 2.9-3.3 (m, 4H); 6.70 (br, 2H); 7.28-7.32 (2m, 4H); 3.5-8.3 (br, 2H)</td>
</tr>
<tr>
<td>4d</td>
<td>-&lt;CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-</td>
<td>60</td>
<td>259-260&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>6.1-2.1 (m, 4H); 2.8-3.3 (m, 4H); 6.70 (br, 2H); 7.3-9.0 (m, 6H)</td>
</tr>
<tr>
<td>4e</td>
<td>-&lt;CH&lt;sub&gt;2&lt;/sub&gt;-</td>
<td>-</td>
<td>66</td>
<td>247-248&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;</td>
<td>6.1-2.1 (m, 4H); 2.8-3.3 (m, 4H); 6.70 (br, 2H); 7.3 (m, 5H); 3.7-6.3 (br, 2H)</td>
</tr>
<tr>
<td>4f</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>68</td>
<td>244-245&lt;sup&gt;c&lt;/sup&gt;</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;</td>
<td>6.1-2.1 (m, 4H); 2.8-3.3 (m, 4H); 6.70 (br, 2H); 7.3 (m, 5H); 4.5-6.4 (br, 2H)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Compounds 4 are recrystallized from chloroform/ethanol.

<sup>b</sup> Satisfactory microanalyses obtained: C ± 0.35, H ± 0.17, N ± 0.31, Cl ± 0.02.

<sup>c</sup> 100% yield from salt 4.

Diethylammonium, Pyrroldinium, and Piperidinium Salts of 2-Amino-4-aryl-3,5-dicyano-6-dicyanomethylpyridines 4; General Procedure:

A solution of 2-amino-1,1,3-tricyanopropene (5; 0.66 g, 5 mmol) in tetrahydrofuran (6 ml) is slowly added to a stirred mixture of the corresponding benzylidenemalonitrile 2 (5 mmol) in chloroform (40 ml). The mixture is maintained for 45 min at 35-40 °C and the crude product (mixture of 4 and 7) is separated by filtration. This mixture is dissolved in tetrahydrofuran (20 ml) and treated dropwise with a solution of DDQ in tetrahydrofuran (6-7 ml of a solution of DDQ (0.9 g, 4 mmol) in tetrahydrofuran (50 ml) with stirring for 1 h at room temperature. Salt 4 precipitates and is filtered. The isolation of 4 that remains in the filtrate is achieved by passage through an alumina column (12 g) using acetone as eluent.

Pyrroldinium Salt of 1,4-Dihydropyridine (7a):

To a solution of benzylidenemalonitrile (0.77 g, 5 mmol) and pyrrolidine (0.36 g, 5 mmol) in tetrahydrofuran (15 ml) is added slowly and with stirring for 1 h to 0 °C, a solution of 2-amino-1,3-tricyanopropene (5; 0.66 g, 5 mmol) in tetrahydrofuran (15 ml). When the addition is complete, the mixture is left stirring for 5 h, after which time a precipitate of 7a has separated; yield: 0.95 g (53%). Recrystallization from water gives a white product; m.p. 212-213 °C. C<sub>7</sub>H<sub>12</sub>N<sub>2</sub> calc. C 67.21 H 5.36 N 27.44 found C 67.46 H 5.37 N 27.88

<sup>1</sup>H-N.M.R. (KBr): δ = 3.470, 3.420, 3.360, 3.340 (N-CH<sub>2</sub>-stretch); 2.200, 2.170, 2.160 (C=CH<sub>2</sub>-stretch); 1.655, 1.595, 1.490 cm<sup>-1</sup> (N-H bending, C=C and C=N stretch).
6-Amino-4-ethyl-3,5-dicyano-2-dicyanomethylene-1,2-dihydropyridines

9: General Procedure:
A solution of 4 (0.05 mol) in ethanol (20 ml) is poured over a water/ice mixture weakly acidified by hydrochloric acid. The yellow precipitate formed in each case is recrystallized from dimethylformamide/water.

Product 9a: from 2-Amino-3,5-dicyano-6-ethylthio-4-phenylpyridine (8):
From a mixture of 8 (1.12 g, 4 mmol) and malononitrile (1; 0.33 g, 5 mmol) in absolute ethanol/sodium ethoxide (30 ml, 5 mmol) is heated for 6 h and reflux and allowed to stand for 12 h at room temperature, a precipitate (0.6 g) of the sodium salt of 2-amino-3,5-dicyano-6-dicyanomethylene-1,2-dihydropyridine (9) is formed. Removal of the solvent in vacuo leaves an oily material which is treated with chloroform and a few drops of ethanol to afford 0.28 g more of the salt. Recrystallization from ethanol gives the pure compound: yield: 0.80 g (68%); m.p. > 340°C.

(324.3) found 58.95 2.75 25.67

I.R. (KBr): ν = 3470, 3360 (N–H stretch); 2220, 2200, 2160 (C≡N); 1620, 1580, 545, 1505, 1495 cm⁻¹ (N–H bending, C=C and C≡N stretching).

1H-N.M.R. DMSO-d₆ δ = 6.66 (br, 2H); 7.3 ppm (m, 5H).

Product 9a is isolated from the above sodium salt as described for the salt 4 above.

Received: October 7, 1981