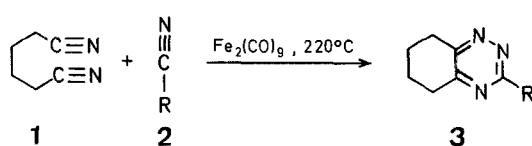


## Iron-Catalyzed Cocyclization of Adiponitriles with Nitriles: A New Synthesis of Fused 1,2,4-Triazines

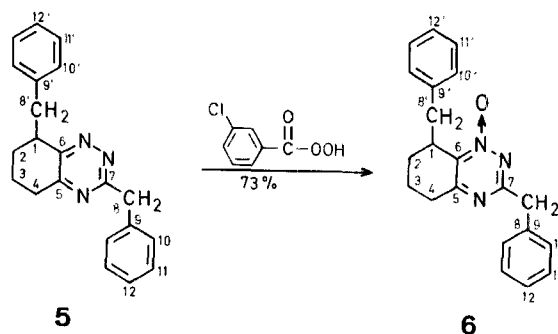
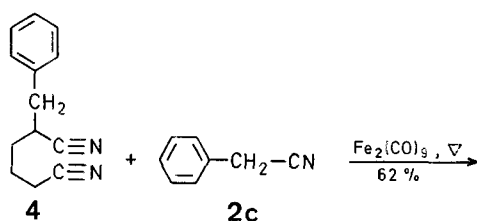
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1,2,4-Triazines, particularly when anelated, are commanding considerable current attention because of their biological activity<sup>1-7</sup> and other potential uses<sup>8</sup>, for example as synthetic intermediates<sup>9,10,11</sup>. We report here the ready chemo- and regiospecific construction of the 5,6,7,8-tetrahydrobenzo[1,2-*e*]-1,2,4-triazine nucleus from adiponitrile precursors (Scheme A, Table 1, Scheme B) by exploiting the ability of iron carbonyl to catalyze nitrile cyclotrimerizations<sup>12</sup>.



Scheme A



Scheme B

Several features in these transformations are noteworthy.

First, whereas adiponitrile cyclizes with itself quite effectively to give the trimer **3e**, and mononitriles, such as benzonitrile, also autocyclize but to the 1,3,5-triazines<sup>12</sup>, these types of products are formed in only trace quantities in the cocyclizations leading to **3a-d**.

Second, despite the comparatively stringent conditions, the yields are fairly good. However, functionalized systems other than **2b**, such as  $\text{NC-CH}_2\text{-COOC}_2\text{H}_5$ ,  $\text{NC-CH}_2\text{-O-CH}_2\text{C}_6\text{H}_5$ ,  $\text{NC-CH}_2\text{CH}_2\text{-O-CH}_2\text{C}_6\text{H}_5$ , and also  $\text{NC-(CH}_2\text{)}_n\text{-CN}$  ( $n = 1-3$ ) decomposed on attempted cyclization.

**Table 1.** 5,6,7,8-Tetrahydrobenzo-1,2,4-triazines **3** prepared (Scheme A)

| Product <sup>a</sup><br>No. | R   | Yield<br>[%] | m.p. [°C]<br>(solvent)                          | Molecular<br>Formula <sup>b</sup>                           |
|-----------------------------|---|--------------|---|---|
| <b>3a</b>                   | <i>n</i> -C <sub>4</sub> H <sub>9</sub>   | 42           | 139–140°<br>(acetone)                           | C <sub>11</sub> H <sub>17</sub> N <sub>3</sub><br>(191.3)   |
| <b>3b<sup>c</sup></b>       | —(CH <sub>2</sub> ) <sub>4</sub> —O—<br> <br>C <sub>6</sub> H <sub>5</sub> —CH <sub>2</sub> — | 64           | 143–144°<br>(C <sub>2</sub> H <sub>5</sub> OAc) | C <sub>18</sub> H <sub>23</sub> N <sub>3</sub> O<br>(297.4) |
| <b>3c</b>                   | —CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>  | 58           | 198–199°<br>(C <sub>2</sub> H <sub>5</sub> OAc) | C <sub>14</sub> H <sub>15</sub> N <sub>3</sub><br>(225.3)   |
| <b>3d<sup>14</sup></b>      | —C <sub>6</sub> H <sub>5</sub>  | 68           | 141–142°<br>(ether)                             | C <sub>13</sub> H <sub>13</sub> N <sub>3</sub><br>(211.3)   |
| <b>3e<sup>d</sup></b>       | —(CH <sub>2</sub> ) <sub>4</sub> —  | 71           | 231–232°<br>(C <sub>2</sub> H <sub>5</sub> OAc) | C <sub>18</sub> H <sub>24</sub> N <sub>6</sub><br>(324.4)   |

<sup>a</sup> Spectroscopic data (M.S., I.R., N.M.R.) are in full accord with the assigned structures.

<sup>b</sup> Satisfactory microanalyses obtained: C ± 0.25, H ± 0.13, N ± 0.09.

<sup>c</sup> Nitrile **2b<sup>a</sup>** was prepared from 1,4-dibromobutane by treatment first with the sodium salt of benzyl alcohol and benzyl alcohol in dimethyl sulfoxide at room temperature followed by sodium cyanide in dimethyl sulfoxide at 80°C; yield: 45%; b.p. 130–140°C/0.5 torr (Kugelrohr).

C<sub>12</sub>H<sub>15</sub>NO calc. C 76.16 H 7.99 N 7.40 (189.3) found 75.99 8.06 7.35

<sup>d</sup> The bistriazine **3e** was obtained by direct cyclization of adiponitrile.

**Table 2.** <sup>13</sup>C-Chemical Shift Values in ppm for **5** and **6**

| Carbon <sup>a</sup> | <b>5</b>           | <b>6</b>           |
|---------------------|--------------------|--------------------|
| 1                   | 45.49              | 38.78              |
| 2                   | 27.53 <sup>b</sup> | 28.61 <sup>b</sup> |
| 3                   | 24.80 <sup>b</sup> | 25.21 <sup>b</sup> |
| 4                   | 39.06              | 38.87              |
| 5                   | 168.00             | 157.23             |
| 6                   | 159.84             | 150.74             |
| 7                   | 173.67             | 162.47             |
| 8                   | 113.29             | 114.68             |
| 8'                  | 46.95              | 46.63              |
| 9                   |                    |                    |
| 9                   | 139.25, 139.92     | 136.29, 139.40     |
| 10                  |                    |                    |
| 10'                 | 129.12, 129.19     | 129.10, 129.20     |
| 11                  |                    |                    |
| 11'                 | 128.09, 128.21     | 128.18, 128.24     |
| 12                  |                    |                    |
| 12'                 | 125.88, 126.06     | 126.04, 126.45     |

<sup>a</sup> For the numbering, see Scheme B.

<sup>b</sup> Assignment uncertain.

Third, the cyclization of 1-benzyl-1,4-dicyanobutane (**4**) [from adiponitrile: lithium diisopropylamide, tetrahydrofuran, –20° to 0°C, benzyl bromide, 0°C to r.t., yield: 77%; b.p. 190–200°C/0.5 torr (Kugelrohr)] and benzyl cyanide gave only the 3,8-regioisomer (**5**). The structure of **5** was assigned based on a comparison of its <sup>13</sup>C-N.M.R. spectrum with that of the analogous N-1-oxide (**6**)<sup>1,13</sup>. Oxidation at N-1 causes a relatively large upfield shift for the methine carbon

resonance ( $\Delta\delta = -6.7$  ppm) reflecting the  $\gamma$ -syn-relationship<sup>1</sup>.

Fourth, extreme caution should be exercised when handling the 1,2,4-triazines **3,5**, and **6**! Three laboratory workers developed skin rashes when exposed to these materials, one severely so, and over his entire body.

### 3,8-Dibenzyl-5,6,7,8-tetrahydro-1,2,4-benzo[1,2-*e*]triazine (**5**):

1-Benzyl-1,4-dicyanobutane (**4**; 0.99 g, 5 mmol), benzyl cyanide (0.59 g, 5 mmol), and nonacarbonyldiiron (0.38 g, 1 mmol) are heated for 18 h at 220°C under nitrogen. The mixture is extracted with hot methanol (3 × 20 ml), the solution is filtered, and the methanol evaporated. The residue is chromatographed on Kieselgel 60 using ethyl acetate as eluent ( $R_F = 0.26$ ); yield: 0.97 g (62%). Recrystallization from acetone affords pale yellow crystals; m.p. 132–133°C.

C<sub>21</sub>H<sub>21</sub>N<sub>3</sub> calc. C 79.97 H 6.71 N 13.32 (315.4) found: 79.69 6.81 13.17

M.S. (70 eV):  $m/e = 315$  (M<sup>+</sup>, 54%).

I.R. (Nujol):  $\nu = 3020, 3010, 1655, 1580, 1490, 725, 695$  cm<sup>-1</sup>.

<sup>1</sup>H-N.M.R. (CDCl<sub>3</sub>/TMS<sub>int</sub>):  $\delta = 1.76$ – $1.93$  (m, 2H);  $2.08$ – $2.29$  (m, 2H);  $2.44$ – $2.52$  (m, 2H);  $2.70$  (dd,  $J = 10$  Hz, 14 Hz, 1H);  $3.36, 3.43$  (AB,  $J = 4$  Hz, 2H);  $4.17$  (s, 2H);  $7.20$ – $7.44$  ppm (m, 10H).

### 3,8-Dibenzyl-5,6,7,8-tetrahydrobenzo[1,2-*e*]1,2,4-triazine 1-Oxide (**6**):

A solution of **5** (0.16 g, 0.5 mmol) and *m*-chloroperoxybenzoic acid (0.22 g, 80%, 1 mmol) in dichloromethane (5 ml) is heated to reflux for 72 h. The reaction mixture is diluted with ether (20 ml) and washed with aqueous sodium hydrogen carbonate (2 × 20 ml) and water (20 ml). The organic layer is dried with magnesium sulfate, the solvent evaporated, and the residue chromatographed on Kieselgel 60 using ethyl acetate/methanol (3:1) as eluent ( $R_F = 0.43$ ); yield: 0.12 g (73%). Recrystallization from ethyl acetate affords white crystals; m.p. 123°C (decomp.).

C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O calc. C 76.11 H 6.39 N 12.68 (331.4) found 76.08 6.57 12.15

M.S. (70 eV):  $m/e = 331$  (M<sup>+</sup>, 4%).

I.R. (Nujol):  $\nu = 3040, 3020, 1655, 1650, 1640, 1555, 1490, 745, 705$  cm<sup>-1</sup>.

<sup>1</sup>H-N.M.R. (CDCl<sub>3</sub>, TMS<sub>int</sub>):  $\delta = 1.73$ – $2.24$  (m, 4H);  $2.38$ – $2.62$  (m, 2H);  $2.69$  (dd,  $J = 10$  Hz, 15 Hz, 1H);  $3.21, 3.36$  (AB,  $J = 4$  Hz, 2H);  $4.45$  (s, 2H);  $7.11$ – $7.52$  ppm (m, 10H).

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