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

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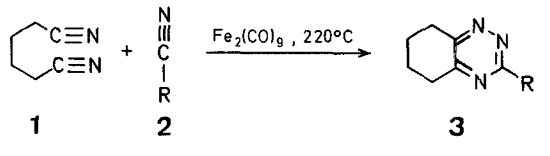
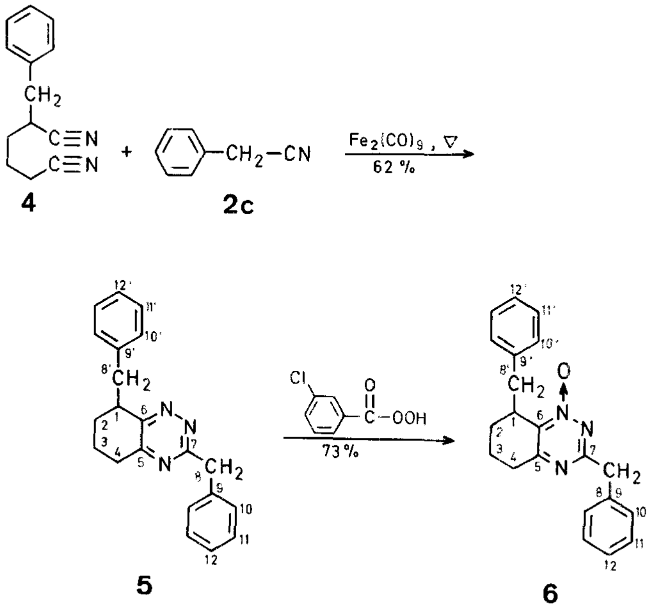
1,2,4-Triazines, particularly when anelated, are commanding considerable current attention because of their biological activity[1-7] and other potential uses[8], for example as synthetic intermediates[9,10,11]. We report here the ready chemo- and regiospecific construction of the 5,6,7,8-tetrahydrobenzo[1,2-*e*]-1,2,4-triazine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



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[12], 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 $NC—CH_2—COOC_2H_5$, $NC—CH_2—O—CH_2C_6H_5$, $NC—CH_2CH_2—O—CH_2C_6H_5$, and also $NC—(CH_2)_n—CN$ ($n = 1–3$) decomposed on attempted cyclization.

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

Product[a] No.	R	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[b]
3a	$n\text{-}C_4H_9$	42	139–140° (acetone)	$C_{11}H_{17}N_3$ (191.3)
3b[c]	$-(CH_2)_4-O$ $C_6H_5-CH_2$	64	143–144° (C_2H_5OAc)	$C_{18}H_{23}N_3O$ (297.4)
3c	$-CH_2C_6H_5$	58	198–199° (C_2H_5OAc)	$C_{14}H_{15}N_3$ (225.3)
3d[14]	$-C_6H_5$	68	141–142° (ether)	$C_{13}H_{13}N_3$ (211.3)
3e[d]	$-(CH_2)_4-$	71	231–232° (C_2H_5OAc)	$C_{18}H_{24}N_6$ (324.4)

[a] Spectroscopic data (M.S., I.R., N.M.R.) are in full accord with the assigned structures.

[b] Satisfactory microanalyses obtained: C ±0.25, H ±0.13, N ±0.09.

[c] Nitrile **2b**[a] 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).

$C_{12}H_{15}NO$	calc.	C 76.16	H 7.99	N 7.40
(189.3)	found	75.99	8.06	7.35

[d] The bistriazine **3e** was obtained by direct cyclization of adiponitrile.

Table 2. ^{13}C-Chemical Shift Values in ppm for **5** and **6**

Carbon[a]	**5**	**6**
1	45.49	38.78
2	27.53[b]	28.61[b]
3	24.80[b]	25.21[b]
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

[a] For the numbering, see Scheme **B**.

[b] 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 ^{13}C-N.M.R. spectrum with that of the analogous N-1-oxide (**6**)[1,13]. Oxidation at N-1 causes a relatively large upfield shift for the methine carbon resonance ($\Delta\delta = -6.7$ ppm) reflecting the *γ-syn*-relationship[1].

Fourth, *extreme caution should be exercized 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 affors pale yellow crystals; m.p. 132°–133 °C.

$C_{21}H_{21}N_3$	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^+, 54%).

I.R. (Nujol): $\nu = 3020, 3010, 1655, 1580, 1490, 725, 695\,cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.76$–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.)

$C_{21}H_{21}N_3O$	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^+, 4%).

I.R. (Nujol): $\nu = 3040, 3020, 1655, 1650, 1640, 1555, 1490, 745, 705\,cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$, TMS_{int}): $\delta = 1.73$–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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