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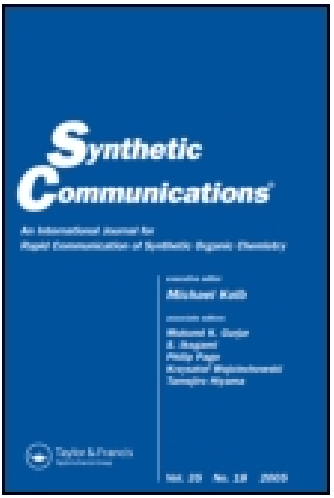

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A Convenient Procedure for the Preparation of 2-Dimethylamino-4,6-Bis[(5-Tetrazolyl)Phenyl]-1,3,5-Triazines

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SYNTHETIC COMMUNICATIONS, 27(1), 127-134 (1997)

A CONVENIENT PROCEDURE FOR THE PREPARATION OF 2-DIMETHYLAMINO-4,6-BIS[(5-TETRAZOLYL)PHENYL]-1,3,5-TRIAZINES

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Abstract: A two-step method has been developed for converting dicyanobenzenes to 2-dimethylamino-4,6-bis[(5-tetrazolyl)phenyl]-1,3,5-triazines (*ortho*, *metha*, and *para* isomers) *via* 4,6-bis(cyanophenyl)-2-dimethylamino-1,3,5-triazines in reasonable total yields.

The tetrazolyl residue is an important structural subunit of a variety of pharmacologically active compounds[1-5] and it also shows non-bilogical applications[6]. Sometime ago we developed a procedure for 4,6-bis(4-cyanophenyl)-2-dimethylamino-1,3,5-triazine (**2c**) which was a substrate for the synthesis of dicationic diaryltriazines[7]. Such a type of dinitriles was usually obtained by conversion of the bis-bromo compounds by treatment of copper(I) cyanide in quinoline or pyridine at reflux temperatures[8-10].

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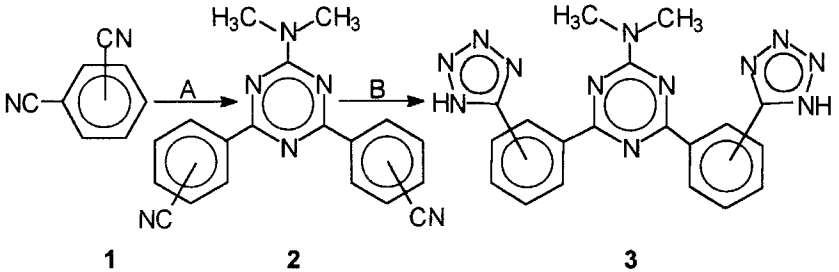
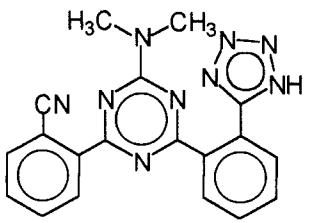
In the present communication I would like to report the syntheses of 2- and 3-cyanophenyl derivatives **2a-b** which were accomplished in one-step process by the reaction of 1,2- or 1,3-dicyanobenzenes **1a-b** and 1,1-dimethylguanidine sulfate in the presence of sodium hydride (Scheme). The above bisnitriles, sodium azide and ammonium chloride were heated in DMF[5] to afford **3**. In the case of the reaction of *ortho*-cyano substituted aromatic bisnitrile **2a** with sodium azide, because of steric hindrance, the mono-substitution product **4** was also obtained, as illustrated in Scheme. All the synthesized new derivatives have been fully characterized by spectroscopic data and microanalyses.



1 **2** **3**

a) ortho
b) metha
c) para



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Scheme. A. $[(CH_3)_2NC(=NH)NH_2]_2 \cdot H_2SO_4$, NaH, DMF.
B. 1. NaN_3, NH_4Cl, DMF,
2. HCl.

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Experimental

Melting points were recorded in a Thomas Hoover (Uni-melt) capillary melting point apparatus and are uncorrected . ^{1}H- and ^{13}C-NMR spectra were obtained in DMSO-d_6/TMS using a Jeol JNM-GX 270 MHz spectrometer. Elemental analyses were obtained from Atlantic Microlab Inc. (Norcross, GA). IR spectra (KBr pellets) were recorded on a Bruker JFS 113 v FT-IR spectrometer (Karlsruhe, FRG). Mass spectra were recorded on a VG Instruments 70-SE spectrometer (Georgia Institute of Technology, Atlanta, GA). All chemicals were purchased from Aldrich Chemical or Fisher Scientific Co. Compound **2c** was prepared according to the literature[7]. All reactions were conveniently monitored by TLC (silica-gel plates) in several solvent systems ($CHCl_3$, $CHCl_3$: CH_3OH: 28% NH_3 in water = 7:5:2 or 11:4:1, v/v/v). The final samples were dried overnight in a vacuum oven at 60 °C.

Syntheses of 4,6-bis(cyanophenyl)-2-dimethylamino-1,3,5-triazines (**2a-b**)

A mixture of 1,2- or 1,3-dicyanobenzene (25.6 g, 0.2 mol), 1,1-dimethylguanidine sulfate (13.6 g, 0.05 mol), and sodium hydride (8.0 g of 60% oil dispersion, 0.2 mol) was placed in a 500-ml one-necked flask. The flask was fitted with a magnetic stirrer, and a reflux condenser, and cooled in an ice bath. N,N-Dimethylformamide (200 ml) was added in slowly through a pressure equalising dropping funnel top--connected to the condenser which was flushed with dry nitrogen. The reaction mixture was brought to 75 °C, held at this temperature with stirring for 6 h, and then decomposed by careful addition of ice-water (200). The resulting solid was filtered, washed with water, dried, subjected to silica-gel column chromatography,

and eluted with chloroform. The bisnitriles were recrystallized from methanol to afford chromatographically pure **2a** (3.97g, 12%), or **2b** (3.11g, 10%), respectively.

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4,6-Bis(2-cyanophenyl)-2-dimethylamino-1,3,5-triazine (**2a**)

M. p. 221-2 °C.

Anal. for $C_{19}H_{14}N_6$, calc. C, 69.92; H, 4.32; N, 25.76. Found C, 70.00; H, 4.31; N, 25.69.

^{1}H-NMR, δ 3.39 (s, 6H), 7.70-7.95 (m, 4H), 8.01 (d, 2H, J=7.33 Hz), 8.69 (d, 2H, J=7.33 Hz).

^{13}C-NMR, δ 36.5, 111.0, 118.8, 130.7, 132.2, 133.0, 135.4, 138.1, 164.6, 168.4.

IR, ν 2936, 2214, 1603, 1548, 1505, 1447, 1426, 1366, 1222, 1005.

MS, m/z (rel. int.), 326 (66), 325 (100), 311 (16), 300 (25), 255 (9).

4,6-Bis(3-cyanophenyl)-2-dimethylamino-1,3,5-triazine (**2b**)

M. p. 224-5 °C.

Anal. for $C_{19}H_{14}N_6$, calc. C, 69.92; H, 4.32; N, 25.76. Found C, 69.80; H, 4.35; N, 25.68.

^{1}H-NMR, δ 3.35 (s, 6H), 7.78 (t, 2H, J=7.81 Hz), 8.06 (d, 2H, J=7.32 Hz), 8.82 (d, 2H, J=8.30 Hz), 8.86 (s, 2H).

^{13}C-NMR, δ 36.1, 112.0, 118.4, 129.9, 131.6, 132.7, 135.4, 137.3, 164.8, 168.4.

IR, ν 3068, 2921, 2230, 1593, 1562, 1510, 1376, 1238, 1187, 1099.

MS, m/z (rel. int.), 326 (100), 311 (83), 297 (79), 283 (19), 154 (37).

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Syntheses of 2-dimethylamino-4,6-bis[(5-tetrazolyl)phenyl]-1,3,5-triazines (**3**)

A stirred mixture of the above bis-nitrile **2** (1g, 3.1 mmol), sodium azide (0.44g, 6.8 mmol), ammonium chloride (0.36g, 6.8 mmol), and N,N-dimethylformamide (10 ml) was heated overnight (15 h) in an oil bath at 100 °C. Evaporation of the solvent left a salt which was converted into the title compound **3** by means of 1N hydrochloric acid (10 ml). The precipitate was filtered, washed with water, and $CHCl_3$, and dried to give analytically pure **3b** (1.27g, 96%), **3c** (1.26g, 95%), or the monocyano intermediate **4** (0.31g, 27%), respectively. The di-substituted product **3a** (1.13g, 90%) was obtained after a prolonged-two day- heating of 4,6--bis(2-cyanophenyl)-2-dimethylamino-1,3,5-triazine (**2a**).

2-Dimethylamino-4,6-bis[2-(5-tetrazolyl)phenyl]-1,3,5-triazine (**3a**)

M. p. 265-6 °C,

Anal. for $C_{19}H_{16}N_{12}$ calc. C, 55.33; H, 3.91; N, 40.76. Found C, 55,35; H, 3.87; N, 40.72.

^{1}H-NMR, δ 2.64 (s, 6H), 7.60-7.70 (m, 2H), 7.70-7.80 (m, 4H), 7.95-8.00 (m, 2H).

^{13}C-NMR, δ 36.9, 126.5, 132.2 132.5, 132.8, 132.9, 138.3, 157.1, 165.1, 172.0.

IR, ν 3054, 2983, 2901, 1596, 1503, 1421, 1207, 1163, 1060, 1049.

MS, m/z (rel. int.), 369 (53), 340 (18), 325 (66), 313 (100), 300 (45).

FAB (thioglycerol), $[M+H]^+$, 413 (100).

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2-Dimethylamino-4,6-bis[3-(5-tetrazolyl)phenyl]-1,3,5-triazine monohydrate (**3b**)

M. p.> 360 °C.

Anal. for $C_{19}H_{16}N_{12}\cdot H_2O$ calc. C, 53.01; H, 4.21; N, 39.05. Found C, 53.50; H, 4.25; N, 39.22.

^{1}H-NMR, δ 3.39 (s, 6H), 7.80 (t, 2H, J=7.81Hz), 8.27 (d, 2H, J=7.81Hz), 8.74 (d, 2H, J=7.81Hz), 9.17 (s, 2H).

13C-NMR, δ 35.9, 124.6, 126.4, 129.6, 130.2, 130.7, 137.2, 155.2, 164.7, 168.9.

IR, ν 3352, 3067, 2876, 2750, 1602, 1546, 1410, 1369, 1064, 801.

MS, m/z (rel. int.), 326 (56), 311 (26), 297 (28), 185 (18), 55 (100).

2- Dimethylamino-4,6-bis[4-(5-tetrazolyl)phenyl]-1,3,5-triazine monohydrate (**3c**)

M. p.> 360 °C.

Anal. for $C_{19}H_{16}N_{12}\cdot H_2O$ calc. C, 53.01; H, 4.21; N, 39.05. Found C, 52.94; H, 4.17; N, 38.96.

^{1}H-NMR, δ 3.35 (s, 6H), 8.24 (d, 4H, J=8.30 Hz), 8.71 (d, 4H, J=8.30 Hz).

^{13}C-NMR, δ 36.1, 127.1, 127.5, 129.1, 138.6, 155.5, 165.0, 169.2.

IR, ν 3113, 2899, 1545, 1384, 1238, 1178, 907, 848, 815, 760.

MS, m/z (rel. int.), 369 (4), 326 (100), 311 (38), 297 (33), 128 (56).

6-(2-Cyanophenyl)-2-dimethylamino-4-[2-(5-tetrazolyl)phenyl-1,3,5-triazine (**4**)

M. p. 254-5 °C.

Anal. for $C_{19}H_{15}N_9$ calc. C, 61.78; H,4.09; N, 34.13. Found C, 61.86; H, 4.08; N, 34.02.

^{1}H-NMR, δ 2.79 (s, 6H), 7.65-7.90 (m, 5H), 7.99 (d, 1H, J=7.33 Hz), 8.22 (d, 1H, J=7.93 Hz), 8.47 (m, 1H).

^{13}C-NMR, δ 35.4, 36.2, 110.8, 118.7, 125.0, 130.2, 130.8, 130.9, 131.2 (double intensity), 132.0, 132.9, 135.4, 136.7, 138.1, 155.5, 164.0, 167.9, 170.9.

IR, ν 2907, 2875, 2216, 1508, 1419, 1394, 1236, 1216, 1152, 1057.

MS, m/z (rel. int.), 369 (53), 340 (18), 325 (66), 313 (100), 300 (45).

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