A Practical and Easy Synthesis of 2,4,6-Trisubstituted-*s*-triazines

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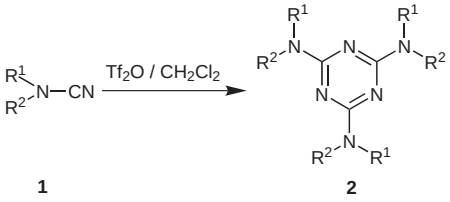
Abstract: Triflic anhydride was found to be efficient for the cyclotrimerization of dialkylcyanamides under mild conditions. The same reaction can be applied to aryl nitriles and thiocyanates.

Key words: *s*-triazines, cyanamides, triflic anhydride, cyclotrimerization, Lewis acid

Triazine derivatives are interesting compounds with biologically important properties[1–3] and are also recognized to be powerful chelating agents which can be used as liquid crystals,[4] metal complexes,[5] and as new hydrogenation catalyts.[6] However, despite a growing interest, there are some problems in the practical preparation of them. The common methods leading to *s*-triazines include oxidation of aromatic aldehydes and cyclotrimerization of nitriles. The first involves long reaction times and achieves low yields[7] while the latter needs rather harsh conditions of pressure (1000 atm) and temperature (200 ºC).[8,9] Lanthanum and yttrium triflate have been found to catalyze the reaction between ammonia and aromatic nitriles to afford 2,4,6-triaryl-*s*-triazines at lower pressure although high temperatures are necessary to carry out the process.[10] Samarium iodide catalyzes the cyclotrimerization of aryl nitriles.[11] The use of hexylamine as co-catalyst permits the use of milder reaction conditions.[12] Different Brønsted and Lewis acids and mixtures of them have been employed to promote the cyclotrimerization of nitriles and cyanamides.[9] Strong bases are also used in this reaction but the conditions would destroy other functional groups present in the system.[9] Both acidic and basic conditions require high pressure as well high temperature. On the other hand, 2,4,6-tris-(dialkylamino)-*s*-triazines are usually prepared directly by refluxing cyanuric chloride with varying excesses of the corresponding dialkylamines in an appropriate solvent.[13]

Quite recently, we have reported that the synthesis of pyrimidines from ketones and cyanamides in the presence of triflic anhydride lead to the formation of triazines instead to the expected pyrimidines.[14] Herein, we describe a facile and efficient one-pot reaction for the preparation of 2,4,6-tris-(dialkylamino)-*s*-triazines **2** which involves the cyclotrimerization of dialkylcyanamides **1** in the presence of triflic anhydride (Scheme 1).



1 **2**

Scheme 1

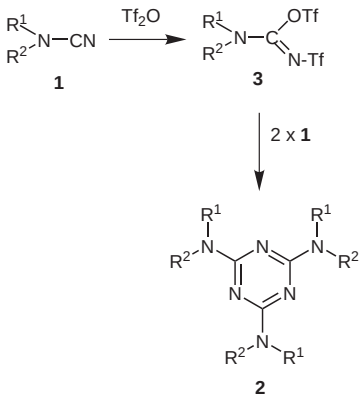
It is reported that dimethylcyanamide reacts with triflic anhydride forming an unstable isourea derivative, which undergoes a Chapman rearrangement affording a bistriflylurea **3**[15] (Scheme 2)

We have found that when dialkylcyanamides **1a**–**d** were reacted with triflic anhydride in dichloromethane at room temperature, the corresponding *s*-triazines **2a**–**d** were isolated in good yield (Table 1).

Table 1 Cyclotrimerization of Dialkylcyanamides **1**

Entry	R^1, R^2	Conditions	Product **2**	Yield (%)
1	CH_3	r.t., 12 h	**2a**	67
2	$-(CH_2)_5-$	r.t., 12 h	**2b**	81
3	$-(CH_2)_2-O(CH_2)_2-$	r.t., 12 h	**2c**	89
4	$-(CH_2)_4-$	r.t., 12 h	**2d**	73

The reaction involves the formation of the bistriflylisourea intermediate **3**,[15] which reacts quickly with two molecules of cyanamide affording the triazine **2** (Scheme 2).



1 **3** **2**

Scheme 2

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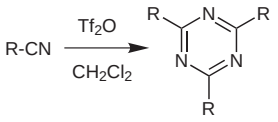
In order to extend this synthetic procedure to other classes of nitriles, we have investigated the reaction of alkyl, aryl, and thiocyanates with triflic anhydride. Thus, acetonitrile **4a**, benzonitrile **4b**, and methylthiocyanate **4c**, as model compounds, afford the corresponding *s*-triazines **5**. Reaction conditions and yields are collected in Table 2.

Table 2 Cyclotrimerization of Nitriles



4 5

Entry	R	Conditions	Product **5**	Yield [a] (%)
1	CH_3	r.t., 12 h	**5a**	89
2	C_6H_5	r.t., 12 h	**5b**	91
3	CH_3-S	r.t., 12 h	**5c**	88

In conclusion, we have disclosed a practical synthesis of trisubstituted *s*-triazines from easily available starting materials under mild conditions. In light of its operational simplicity and efficiency, this reliable method is expected to have a broad utility due to the scope of applications of the *s*-triazines.

Reaction of Cyanamides and Nitriles with Triflic Anhydride; General Procedure

Tf_2O[16] (0.5 g, 1.7 mmol) was added to a solution of the corresponding cyanamide **1a–d** (5.1 mmol) or nitrile **4a–c** (5.1 mmol) in CH_2Cl_2 (20 mL) and stirred for 12 h at r.t. The reaction mixture was carefully neutralized with aq sat. soln of $NaHCO_3$. After extraction with CH_2Cl_2 (3 × 50 mL), the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent provided a solid, which was recrystallized twice from the appropriate solvent.

***N*,*N*′,*N*′,*N*′′,*N*′′-Hexamethyl-1,3,5-triazine-2,4,6-triamine (2a)**

White powder; yield: 67%; mp 174–175 ºC (EtOH).

IR (KBr): 2885, 1370 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.25 (s, CH_3N).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 40.0 (CH_3N), 159.6 (C arom.).

MS (EI): *m*/*z* (%) = 210 (M^+·,100), 195 (M – CH_3, 63).

Anal. Calcd for $C_9H_{18}N_6$: C, 51.41; H, 8.63; N, 39.97. Found: C, 51.22; H, 8.77; N, 39.58.

2,4,6-Tripiperidin-1-yl-1,3,5-triazine (2b)

White needles; yield: 81%; mp 215–216 ºC (EtOH).

IR (KBr): 2931, 2848, 1533, 1481 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.65 (m, 18 H, CH_2), 3.65–3.75 (m, 12 H, CH_2N).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.1, 25.8 (CH_2), 44.1 (CH_2N), 165.3 (C arom).

MS (EI): *m*/*z* (%) = 330 (M^+·, 100), 301 (M – C_2H_5, 91), 247 (M – C_5H_9N, 75).

Anal. Calcd for $C_{18}H_{30}N_6$: C, 65.42; H, 9.15; N, 25.43. Found: C, 65.28; H, 8.99; N, 24.83.

2,4,6-Trimorpholin-4-yl-1,3,5-triazine (2c)

White powder; yield: 89%; mp 263–264 ºC (EtOH).

IR (KBr): 2960, 2858, 1544, 1479 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.10–3.17 (m, 12 H, CH_2N), 3.58–3.66 (m, 12 H, CH_2O).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 48.7 (CH_2N), 65.5 (CH_2O), 165.2 (C arom).

MS (EI): *m*/*z* (%) = 336 (M^+·,100), 306 (M – CH_2O, 78), 279 (54).

Anal. Calcd for $C_{15}H_{24}N_6O_3$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.19; H, 7.25; N, 24.24.

2,4,6-Tripyrrolidin-1-yl-1,3,5-triazine (2d)

White needles; yield: 73%; mp 178–179 (EtOH).

IR(KBr): 2930, 2850, 1535, 1480 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.83–1.91 (m, 12 H, CH_2), 3.48–3.56 (m, 12 H, CH_2N).

^{13}C NMR(75.47 MHz, $CDCl_3$): δ = 25.3 (CH_2), 45.8 (CH_2N), 163.2 (C arom).

MS (EI): *m*/*z* (%) = 288 (M^+·,100), 260 (M – C_2H_4, 85), 232 (42), 219 (M – C_4H_7N, 25).

Anal. Calcd for $C_{15}H_{24}N_6$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.88; H, 7.99; N, 28.93.

2,4,6-Trimethyl-1,3,5-triazine (5a)

White needles; yield: 89%; mp 54–55 ºC (purified by vacuum sublimation).[10]

IR (KBr): 1548, 1436 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s)

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.4 (CH_3), 175.9 (C arom).

MS (EI): *m*/*z* (%) = 123 (M^+·,100), 108 (M – CH_3, 85).

2,4,6-Triphenyl-1,3,5-triazine (5b)

White powder; yield: 91%; mp 230–231 ºC ($CHCl_3$–EtOH).[10]

IR (KBr): 1522, 1367, 743, 683 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.64 (m, 9 H), 8.77–8.82 (m, 6 H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 128.6, 129.0, 132.5 (CH arom), 136.2, 171.6 (C arom).

MS(EI): *m*/*z* (%) = 309 (M^+·,57), 103 (C_7H_5N, 100).

2,4,6-Tris(methylthio)-1,3,5-triazine (5c)

Pale yellow powder; yield: 88%; mp 175–176 ºC (EtOH).

IR (KBr): 1481, 1244 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.52 (s, SCH_3).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 13.3 (SCH_3), 179.7 (C arom).

MS (EI): *m*/*z* (%) = 219 (M^+·,100), 204 (M – CH_3, 12), 158 (54).

Anal. Calcd for $C_6H_9N_3S_3$: C, 32.85; H, 4.14; N, 19.16; S, 43.86. Found: C, 32.33; H, 3.88; N, 18.88; S, 43.11.

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