REACTION OF DISUBSTITUTED CYANAMIDES WITH FORMAMIDES UNDER HIGH PRESSURE

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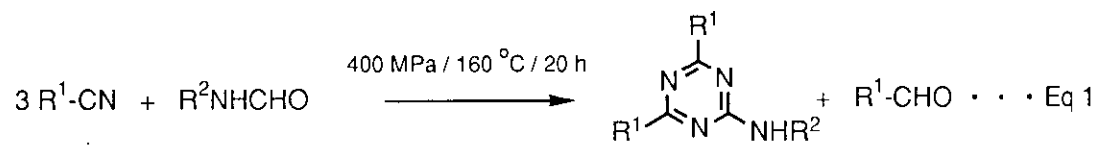
Abstract - High pressure-assisted co-cyclization of disubstituted cyanamides with formamide or monosubstituted formamides gave 2-amino- or 2-monosubstituted amino-4,6-bis(disubstituted amino)-1,3,5-triazines in one pot.

High pressure technique is an attractive method to synthesize heterocycles, and many successful works developed recently are introduced in the reviews.[1,2] We have paid much attention to the specific reactivity of disubstituted cyanamides (**1**), which are the most electron-donating and active among related cyano-compounds such as nitriles, cyanate esters, and thiocyanate esters, and have been investigating on their reaction with carbon disulfide,[3] carbonyl sulfide,[4] and phenyl isothiocyanates[5] under high pressure. As the results, we have found that **1** give various kinds of heterocycles *via* novel paths which are not known under ambient pressure, and that **1** are versatile materials for synthesizing heterocycles. Meanwhile, it was reported that there are many compounds having chemosterilizing,[6] antiflammatory[7] activity and other bioactive functions[8] among polysubstituted 2,4,6-triamino-1,3,5-triazines, and they have been prepared through tedious multiple-step aminations of cyanuric chloride. Here we report the reaction of **1** with formamide or monosubstituted formamides (**2**) under high pressure to give 2-amino- or 2-monosubstituted amino-4,6-bis(disubstituted amino)-1,3,5-triazines (**3**) directly, shown below (Eq1).



Eq 1

1a - d **2a - c** **3a - l**

1a: R^1 = piperidino **2a**: R^2 = H

1b: R^1 = morpholino **2b**: R^2 = Me

1c: R^1 = pyrrolidino **2c**: R^2 = Ph

1d: R^1 = dimethylamino

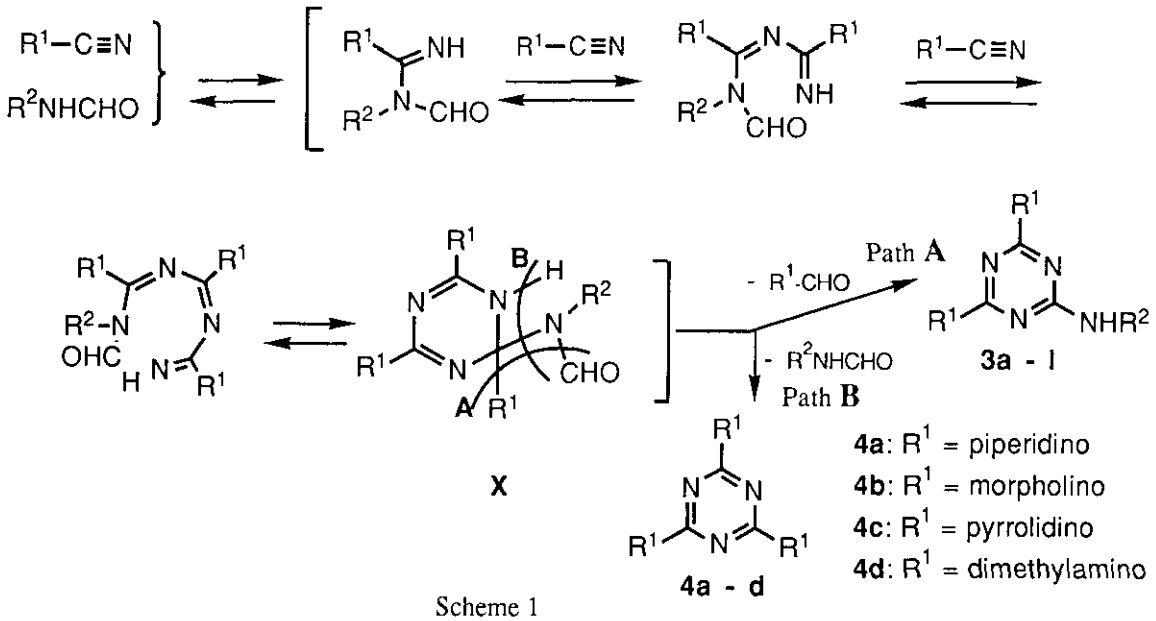
A mixture of disubstituted cyanamide (**1a - d**, 3 eq) and formamide or monosubstituted formamide (**2a -**

c, 1 eq) was pressurerized to 400 MPa, and heated at 160°C for 20 h, to afford 2-amino- or 2-monosubstituted amino-4,6-bis(disubstituted amino)-1,3,5-triazines (**3a - l**) in moderate to good yields in one pot. Their yields and mps are summarized in Table 1. In these reactions, 2,4,6-tris(disubstituted amino)-1,3,5-triazines (**4a - d**) were also afforded as by-products around 20 % yields as summarized in Table 1. From these results, a plausible pathway for this reaction was estimated as shown in Scheme 1.

Table1

2-Amino- or 2-monosubstituted amino-4,6-bis(disubstituted amino)-1,3,5-triazines (**3a - l**) and 2,4,6-tris(disubstituted amino)-1,3,5-triazines (**4a - d**).

1a - d	2a - c	3a - l	Yield/%	mp/°C (Reported)	4a - d	Yield/ %	mp/°C (Reported)
1a	2a	3a	60	202 -204 (201 - 203)[8]			
1a	2b	3b	50	118 -119 (110 - 118)[9]			
1a	2c	3c	37	136 -137 (137.5 - 138)[10]	4a	14	217 - 220 (219 - 221)[11]
1b	2a	3d	52	171 -172 (170 - 172)[12]	4b	20	286 - 288 (284 - 289)[11]
1b	2b	3e	66	116 -118			
1b	2c	3f	58	168 -169			
1c	2a	3g	72	231 -233 (232 - 233)[8]			
1c	2b	3h	64	107 -109	4c	23	186 -188 (186.6 - 189.5)[11]
1c	2c	3i	66	155 -156			
1d	2a	3j	65	229 -231 (230)[13]			
1d	2b	3k	35	102 -104 (98 - 103)[6]	4d	24	170 - 172 (171 - 172)[14]
1d	2c	3l	61	151 -152 (151.3 -153)[15]			



Scheme 1

Three molecules of disubstituted cyanamide react to one molecule of a formamide consecutively through a proton migration to form a 3:1 adduct, dihydro-1,3,5-triazine derivative (**X**), and then **X** converts to **3**

with eliminating disubstituted formamide (Path **A**) or affords **4** by liberation of the original formamide (Path **B**). When these reactions were carried out under the condition of 200 MPa - 160°C or 800 MPa - 100°C, **3** or **4** was not obtained, but the starting materials (**1** and **2**) were recovered. Therefore, it is clear that these reactions need both higher pressure and higher temperature. No reaction occurred by the use of dimethyl formamide instead of **2**, and acetamide instead of **2** gave only a trace amount of **3**. These facts show that both the amino proton and formyl group play important roles, and both are essential to these reactions.

Hence, it is proved that disubstituted cyanamides react with formamide or monosubstituted formamides under high pressure to give numerous 2-amino- or 2-monosubstituted amino-4,6-bis(disubstituted amino)-1,3,5- triazines directly *via* an unique pathway, and it is believed that this high pressure synthesis, thus developed, contributes to researching such bioactive functionalities.

EXPERIMENTAL

All melting points were measured on a Mettler FP90 microscope plate, and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 300BB spectrometer in the solution of $CDCl_3$ using TMS as an internal standard. IR spectra were measured on a JASCO (FT-5300) spectrophotometer using KBr disks.

General procedure of synthesizing 2-amino- or 2-mono-substituted amino-4,6-bis(disubstituted amino)-1,3,5-triazines (3a - l).

A mixture of piperidinecarbonitrile (660 mg, 6 mmol) and *N*-formylaniline (242 mg, 2 mmol) was placed in a sealed Teflon tube. The tube was compressed to 400 MPa in a high-pressure equipment,[16] and maintained for 20 h at 160°C. After being cooled to rt, the reaction mixture was depressurized, passed through on a silica gel column (Wako gel 200, AcOEt : hexane = 1 : 1). The crude products fractionated were purified by recrystallization to afford 2-anilino-4,6-dipiperidino-1,3,5-triazine (**3c**) and 2,4,6-tris(piperidino)-1,3,5-triazine (**4a**), respectively . According to the above-mentioned method, the mixture of a disubstituted cyanamide (**1a - d**) and formamide or a monosubstituted formamide (**2a - c**) was pressurerized, worked up on a silica gel column, and the crude products fractionated were purified by recrystallization from water (**3d, g, j**), methanol (**3e, h, k**), or ethanol (**3a, b, c, f, i, l**; **4a - d**) to give the corresponding 2-amino- or 2-monosubstituted amino-4,6-bis(disubstituted amino)-1,3,5-triazines (**3a - l**) and 2,4,6-tris(disubstituted amino)-1,3,5-triazines (**4a - d**). Their yields, based on **1**, and their mps are summarized in Table 1. The IR, ^{1}H NMR spectral data and the analytical results for novel products (**3e, f, h, i**) are shown below.

2-Methylamino-4,6-dimorpholino-1,3,5-triazine (3e).

^{1}H NMR δ = 2.92 (*d*, 3H, *J*=5.0 Hz, CH_3), 3.68 - 3.77 (*m*, 16H), 4.73 (*br s*, 1H, NH); IR ν 3450, 2962, 2854, 1537, 1485, 1439, 1259, 1111. Anal. Calcd for $C_{12}H_{20}N_6O_2$: C, 51.42; H, 7.19; N, 29.98. Found: C, 51.32; H, 7.17; N, 30.02.

2-Anilino-4,6-dimorpholino-1,3,5-triazine (3f).

^{1}H NMR δ = 3.71 - 3.79 (*m*, 16H), 6.77 (*br s*, 1H, NH), 6.96 - 7.55 (*m*, 5H, Arom H); IR ν 3364, 2845, 1612, 1543, 1510, 1257, 1111. Anal. Calcd for $C_{17}H_{22}N_6O_2$: C, 59.63; H, 6.48; N, 24.54. Found: C, 59.68; H, 6.49; N, 24.61.

2-Methylamino-4,6-dipyrrolidino-1,3,5-triazine (3h).

^{1}H NMR δ = 1.86 - 1.91 (*m*, 8H), 2.93 (*d*, 3H, *J*=5.0 Hz, CH_3), 3.50 - 3.55 (*m*, 8H), 4.62 (*br s*, 1H, NH); IR ν 3267, 2970, 2868, 1514, 1450, 1379, 1332, 808. Anal. Calcd for $C_{12}H_{20}N_6$: C, 58.04; H, 8.12; N, 33.84. Found: C, 58.32; H, 8.20; N, 33.85.

2-Anilino-4,6-dipyrrolidino-1,3,5-triazine (3i).

^{1}H NMR δ = 1.87 - 1.95 (*m*, 8H), 3.50 - 3.59 (*m*, 8H), 6.87 (*br s*, 1H, NH), 6.93 - 6.98 (*m*, 1H), 7.24 - 7.30 (*m*, 2H), 7.66 - 7.69(*m*, 2H) ; IR ν 3269, 2968, 2870, 1514, 1475, 1390, 1342, 804. Anal. Calcd for $C_{17}H_{22}N_6$: C, 65.78; H, 7.14; N, 27.07. Found: C, 65.47; H, 7.18; N, 27.20.

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