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A CONVENIENT METHOD FOR THE PREPARATION OF SOME NEW DERIVATIVES OF 1,3,5-*s*-TRIAZINE UNDER SOLVENT FREE CONDITION

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Abstract- Nucleophilic reactions on cyanuric chloride were carried out under solvent free conditions to give 1,3,5-*s*-triazine derivatives with excellent yields.

A search through literature revealed that cyanuric chloride (**1**) is a well-known and very important accessible compound which has been extensively used in 1,3,5-*s*-triazine synthesis.[1] It has been also employed as a chlorinating agent for conversion of alcohols into alkyl halides.[2,3]

Many 1,3,5-*s*-triazine derivatives have been widely studied due to their interesting biological activities, of which some are of pharmaceutical importance as antitumor[4] and antiviral[5] medicines. In addition, these compounds are of potentially considerable therapeutic importance in the treatment of, e.g., cancer[6] and depression.[7] They are also valuable as bridging agent to synthesize reactive dyes,[8,9] herbicides,[10] bases for dendrimers[11,12] and estrogen receptor modulators.[13]

Pd-catalyzed amination of different heteroaryl halides with aliphatic and aromatic substrates has been described by several groups.[14-19] However, no catalyzed C-N bond formation has been reported on 1,3,5-*s*-triazine derivatives.

Reported procedure for nucleophilic reactions of cyanuric chloride employed solid phase strategy to yield mixed products,[20] or the solution phase procedures involving a high level of instrumentation and relatively vigorous reaction conditions such as long reaction times.[21,22] In a different investigation,[23] an easy technique for the positionally addressable and parallel to chemical synthesis on a membrane support called SPOT-synthesis,[24] was developed to synthesis some 1,3,5-*s*-triazine derivatives. However, this procedure requires planar polymeric supports and a linker system.

As mentioned above, due to the importance and appliance of cyanuric chloride and its derivatives, we wish to report a rapid, solvent free and single product procedure for the preparation of some new products from substitution reactions between nucleophiles and cyanuric chloride.

Different kinds of nucleophiles such as imidazole, pyrazole, piperidine, morpholine and 4-piperidinol were reacted with cyanuric chloride (Figure 1). Reactions were completed after a short time and spectroscopic

data show that all chlorine atoms were replaced by nucleophiles to afford the corresponding 1,3,5-s-triazine derivatives.

The interesting feature of our approach is that, the presence of any bases such as sodium alkoxide, pyridine, or triethylamine is not necessary for the successful course of reaction. This conveniently eliminates any possible interference of such bases as nucleophiles in these reactions. Additionally, it was noted that the reaction with some nucleophiles such as imidazole and pyrazole was initiated upon melting of the reaction mixture and completed in few minutes. In the cases of pyridine and morpholine, the reaction occurs vigorously which nessititates the prior cooling of the reaction mixture.

Determination of the difference between the masses of the initial materials and products indicated that, in some cases, **(2,3)**, HCl gas was absorbed by substrate whereas in other cases, **(4-6)**, HCl gas was evolved out of the reaction medium.

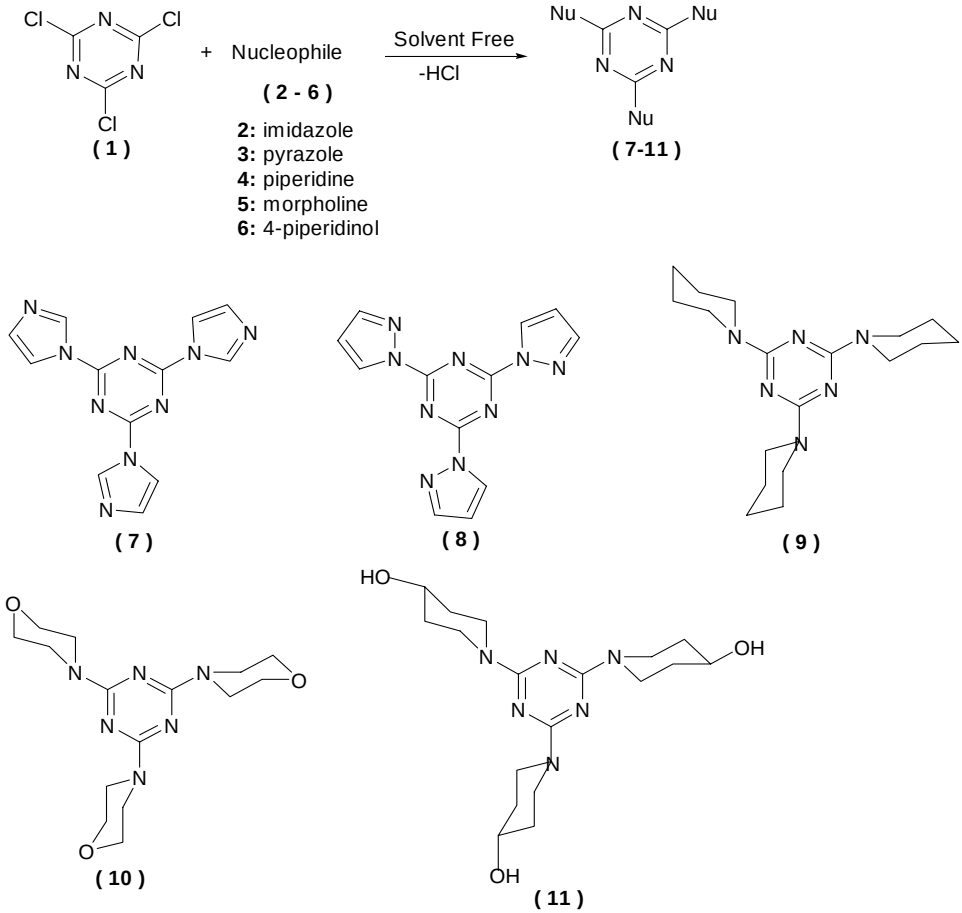

Figure 1

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies and purified prior to use. Melting points were recorded uncorrected. Yields refer to isolated pure products. IR spectra were recorded on a Shimadzu IR-470 apparatus. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL FX 90Q and Bruker AC 300 apparatus.

2,4,6-Tris(imidazol-1-yl)-1,3,5-*s*-triazine (7).

Cyanuric chloride (**1**) (1.84 g, 10 mmol) and imidazole (4.08 g, 60 mmol) were reacted by mixing in the absence of solvent for 2 min at about 70 ºC. Then, the reaction mixture was extracted with a mixture of chloroform (100 mL) and distilled water (100 mL). The organic layer was separated and the aqueous layer extracted with chloroform (3×100 mL). The combined organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated to yield a solid residue which was recrystallized from ethyl acetate to give pure product (**7**), 2.4 g (85%): mp 180 ºC (decomp); IR (KBr): υ 3110 (C−H), 1568, 1540 (C═N triazine), 1466, 1444 (C−N), 1333 (═C−N), 1242 (C−N) (cm^{-1}); ^{1}H-NMR (300 MHz): δ 7.26 (1H, q, J=0.5 Hz, C_5−H), 7.91 (1H, q, J=0.8 Hz, C_4−H), 8.69 (1H, t, J=0.5 Hz, C_2−H); ^{13}C-NMR (300 MHz): δ 116.43 (C_5), 132.26 (C_4), 136.62 (C_2), 162.56 (C triazine); MS (EI): m/z M^+ 279. Anal. Calcd for $C_{12}H_9N_9$: C, 51.64; H 3.22; N 45.14. Found: C, 51.43; H 3.28; N 45.05.

2,4,6-Tris(pyrazol-1-yl)-1,3,5-*s*-triazine (8).

Cyanuric chloride (**1**) (1.84 g, 10 mmol) and pyrazole (4.08 g, 60 mmol) were reacted by mixing in the absence of solvent for 2 min at about 60 ºC. Then, the reaction mixture was extracted with a mixture of chloroform (100 mL) and distilled water (100 mL). The organic layer was separated and the aqueous layer extracted with chloroform (3×100 mL). The combined organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated to yield a solid residue which was recrystallized from ethyl acetate to give pure product **(8)**, 2.45 g (88%); mp 238-239 ºC; IR (KBr): υ 3100 (C−H), 1583, 1525 (C═N triazine), 1442, 1392 (C═N), 1365 (═C−N), 1266 (C−N) (cm^{-1}); ^{1}H-NMR (300 MHz): δ 6.48 (1H, q, J=1.5 Hz, C_4), 7.84 (1H, q, J=0.9Hz, C_5), 8.67 (1H, q, J=2.7 Hz, C_3); ^{13}C-NMR (300 MHz): δ 110.11 (C_5), 130.39 (C_4), 145.75 (C_3), 163.31 (C triazine); MS (EI): m/z M^+ 279. Anal. Calcd for $C_{12}H_9N_9$: C, 51.64; H 3.22; N 45.14. Found: C, 51.37; H 3.31; N 45.29.

2,4,6-Tris(piperidin-1-yl)-1,3,5-*s*-triazine (9).

Cyanuric chloride (**1**) (1.84 g, 10 mmol) was added slowly to piperidine (5.10 g, 60 mmol) that was kept at 0-5 ºC. The reaction mixture was extracted with a mixture of chloroform (100 mL) and distilled water (100 mL). The organic layer was separated and the aqueous layer extracted with chloroform (3×100 mL). The combined organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated to yield a solid residue which was recrystallized from ethanol to give pure product **(9)**, 3.1 g (94%); mp 215-216 ºC; IR (KBr): υ 2925, 2845 (C−H), 1531, 1474 (C═N triazine), 1454, 1367 (═C−N), 1224 (C−N) (cm^{-1}); ^{1}H-NMR (90 MHz): δ 1.53 (6H, s, $(CH_2)_3$), 3.65 (4H, s, $(CH_2)_2N$); ^{13}C-NMR (90 MHz): δ 22.60 (C_4), 23.35 (C_3), 41.56 (C_2), 163.03 (C triazine); MS (EI): m/z M^+ 330. Anal. Calcd for $C_{18}H_{30}N_6$: C, 65.47; H 9.08; N 25.44. Found: C, 65.16; H 8.89; N 25.63.

2,4,6-Tris(1-morpholino)-1,3,5-*s*-triazine (10).

Cyanuric chloride (**1**) (1.84 g, 10 mmol) was added slowly to morpholine (5.22 g, 60 mmol) that was kept at 0-5 ºC. The reaction mixture was extracted with a mixture of chloroform (100 mL) and distilled water (100 mL). The organic layer was separated and the aqueous layer extracted with chloroform (3×100 mL). The combined organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated to yield a solid residue which was recrystallized from ethanol to give pure product (**10**), 3.1 g (92%): mp 284-285 ºC (decomp); IR (KBr): υ 2940, 2850 (C−H), 1540, 1473 (C═N triazine), 1445, 1359 (═C−N), 1247 (C−N), 1107 (C−O) (cm^{-1}); ^{1}H-NMR (300 MHz): δ 3.71 (4H, m, $(CH_2)_2N$), 3.75 (4H, m, $(CH_2)_2N$); ^{13}C-NMR (300 MHz): δ 43.63 (C−N), 66.86 (C−O), 165.38 (C triazine); MS (EI): m/z M^+ 336. Anal. Calcd for $C_{15}H_{24}N_6O_3$: C, 53.60; H 7.14; N 24.99. Found: C, 53.41; H 7.27; N 25.18.

2,4,6-Tris(4-piperidinol-1-yl)-1,3,5-*s*-triazine (11).

Cyanuric chloride (**1**) (1.84 g, 10 mmol) and 4-piperidinol (6.10 g, 60 mmol) were mixed and kept at about 180 ºC in an oil bath for 1 h. The reaction mixture was extracted with a mixture of ether (100 mL) and distilled water (100 mL). The organic layer was separated and the aqueous layer extracted with ether (2×100 mL). The combined organic layer was then dried over anhydrous Na_2SO_4, filtered and evaporated to yield a solid residue which was recrystallized from ethanol to give pure product (**11**), 2.98 g (92%): mp 235 ºC (decomp); IR (KBr): υ 3365 (O−H), 2925, 2845 (C−H), 1534, 1479 (C═N triazine), 1445, 1365 (═C−N), 1232 (C−N), 1053 (C−O) (cm^{-1}); ^{1}H-NMR (300 MHz): δ 3.09 (4H, m, $(CH_2)_2C$), 3.80 (4H, m, $(CH_2)_2N$), 4.35 (1H, m, OH); ^{13}C-NMR (300 MHz): δ 33.93 (C_2), 40.73 (C_3), 68.10 (C_1), 165.23 (C triazine); MS (EI): m/z M^+ 378. Anal. Calcd for $C_{18}H_{30}N_6O_3$: C, 55.85; H 7.75; N 21.70. Found: C, 55.54; H 7.80; N 21.82.

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