Studies in the synthesis of 2,4,6-trichloro-1,3,5-triazine derivatives

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Manuscript received 25 February 2002, revised 7 August 2002, accepted 6 September 2002

2,4,6-Trichloro-1,3,5-triazine derivatives are reacted selectively (one or more at a time) with nucleophilic reagents (*p*-fluoroaniline, *p*-toluidine and different substituted amines); even the deactivated mono- and disubstituted and sometimes trisubstituted products of 2,4,6-trichloro-1,3,5-triazine show high reactivity towards substitution. The mechanism of this reaction has been discussed.

s-Triazine derivatives possess various biological activities¹. In order to obtain some new compounds having biological activities, three chlorine atoms of 2,4,6-trichloro-1,3,5-triazine have been replaced by *p*-fluoroaniline, *p*-toluidine and different substituted amines. 2,4-Dichloro-6-(4-fluoroanilino)-1,3,5-triazine (**2**) has been prepared by treating cyanuric chloride with *p*-fluoroaniline (**1**). The mixture was kept alkaline during the reaction with sodium hydroxide and the contents were poured on ice and acidified with dil. HCl to furnish the product **2** in quantitative yield.

The second chlorine atom of **2** has been replaced by *p*-toluidine to give 2-chloro-4-(4-fluoroanilino)-6-(4-methylanilino)-1,3,5-triazine (**3**) as the sole product. The third chlorine atom of **3** has been replaced by different aromatic amines to produce 2-alkyl/aryl-amino-4-(fluoroanilino)-6-(4-methylanilino)-1,3,5-triazines (**4**).

Results and discussion

2,4,6-Trichloro-1,3,5-triazine derivatives (cyanuric chloride) reacts selectively with nucleophilic reagents^{2,3}. Cyanuric chloride is a weak base. If one of its chlorines is re-placed by NHR, OR or SR, the basicity is increased because of the electron-releasing effect of these groups substituted at α -positions of the ring nitrogen atoms. The substitution is catalyzed by acid⁴. To prevent possible acid catalysis in the substitution of the chlorine atom of 2,4,6-trichloro-1,3,5-triazine by OH, OCH₃ or OC₂H₅ to give a hydroxy, methoxy or ethoxy dichloro-*s*-triazine, the reaction is best carried out in the presence of an acid binding medium preferably sodium bicarbonate. Substitution by the electron-donating group adjacent to ring nitrogen atom is in the following decreasing sequence : OC₆H₅ > OCH₃ > OCH₂H₅ > NH₂ > NHCH₃ > NHC₂H₅ > NC(CH₃)₂ > OH. The reactivity of the chlorine atom in the 2,4-disubstituted-6-chloro-1,3,5-triazines behave similarly for the substitution reaction.

Experimental

Purity of all the compounds was checked by TLC (silica gel G) using iodine vapor as the detecting agent. M.ps. were determined in open capillary tubes using a Gallen - Kamp apparatus and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 577 spectrophotometer, mass spectra on Kratos MS-30 and MS-50 spectrometers operat-

Scheme 1

ing at an ionization potential of 70 eV and PMR spectra on a Jeol FX 90Q apparatus (89.99 MHz) with TMS as the internal standard.

2,4-Dichloro-6-(4-fluoroanilino)-1,3,5-triazine (2) : To 2,4,6-trichloro-1,3,5-triazine (18.4 g, 0.1 mol) dissolved in acetone (100 ml) cooled at 0°, *p*-fluoroaniline (11.1 g, 0.1 mol) dissolved in acetone (100 ml) was added with stirring at 0–5°, followed by dropwise addition of NaOH (4.0 g, 0.1 mol) in water (50 ml). Contents were stirred for 3 h, then poured into ice-water and acidified with dil. HCl. The resulting solid was washed with acetone, dried and crystallized from ethanol, (79%), m.p. 186° (Found : C, 41.55; H, 1.88; N, 21.56. $C_9H_5Cl_2FN_4$ requires : C, 41.69; H, 1.93; N, 21.62%; $\nu_{\max}$ 3130 cm^{-1} (NH); δ 9.85 (1H, s, NH), 8.5–8.1 (4H, m, ArH); m/z M^+ , 259.

2-Chloro-4-(4-fluoroanilino)-6-(4-methylanilino)-1,3,5-triazine (3) : A solution of **2** (25.9 g, 0.1 mol) dissolved in acetone (100 ml) was added to *p*-toluidine (10.7 g, 0.1 mol) in acetone (100 ml) slowly with stirring followed by the addition of NaOH (4.0 g, 0.1 mol) in water (50 ml). The reaction mixture was stirred for 3 h at 30–40°, then poured in ice-water and acidified with dil. HCl. The resulting solid was washed with acetone, dried and crystallized from ethanol, (75%), m.p. 254° (Found : C, 58.31; H, 4.01; N, 21.28. $C_{16}H_{13}ClFN_5$ requires : C, 58.27; H, 3.94; N,

21.24%; $\nu_{\max}$ 3120 cm^{-1} (NH); δ 8.7 (2H, s, NH), 8.4–7.8 (8H, m, ArH), 2.21 (3H, s, CH_3); m/z M^+ , 329.5.

2-(4'-Chlorophenyl)amino-4-(4-fluoroanilino)-6-(4-methylanilino)-1,3,5-triazine (4a) : To a solution of **3** (0.01 mol) in dioxane (50 ml) were added *p*-chloroaniline (0.01 ml) and NaOH (0.01 mol) in water (10 ml) and the mixture was refluxed at 85–90° for 2 h. It was poured onto ice and the resulting solid was dried and crystallized from ethanol, (68%), m.p. 205° (Found : C, 62.82; H, 4.24; N, 19.92. $C_{22}H_{18}ClFN_6$ requires : C, 62.78; H, 4.28; N, 19.97%; $\nu_{\max}$ 3100 cm^{-1} (NH); δ 8.1 (3H, s, NH), 8.0–7.5 (12 H, m, ArH), 2.0 (3H, s, CH_3); m/z M^+ , 420.5. Compounds (**4b–m**) were similarly prepared (yields 53–66%) : **4b**, m.p. 300°d; **c**, 196°; **d**, 182°; **e**, 292°; **f**, 234°; **g**, 262; **h**, 250°; **i**, 300°; **j**, 266°; **k**, 277°; **l**, 172°; **m**, 284°.

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