Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 23 Sep 2006.

To cite this article: Rita Menicagli , Corrado Malanga & Paola Peluso (1994): Selective Mono- or Dialkoxylation of 2,4,6-Trichloro-1,3,5-triazine in Solid-Liquid Phase Transfer Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:15, 2153-2158

To link to this article: http://dx.doi.org/10.1080/00397919408010229

SYNTHETIC COMMUNICATIONS, 24(15), 2153-2158 (1994)

SELECTIVE MONO- OR DIALKOXYLATION OF 2,4,6-TRICHLORO-1,3,5-TRIAZINE IN SOLID-LIQUID PHASE TRANSFER CONDITIONS

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Abstract : In solid-liquid phase transfer conditions, both the primary and the secondary alcohols react cleanly with 2,4, 6-trichloro-1,3,5-triazine to give the corresponding mono or dialkoxy derivatives depending on the reagent molar ratio.

The increasing interest in enantiomerically pure compounds has recently led to intensified efforts to develop technologies[1] for enantiomeric separation as well as methodologies[2] for increasingly efficient processes of chiral discrimination. Taking into account the key role played by chiral selectors,[2c] specially if supported on solid matrix, we recently undertook a research into the synthesis of new polyfunctional chiral selectors that could be used as they are or bonded to solid matrixes.

Such an idea suggested the use of 2,4,6-trichloro-1,3,5-triazine (cyanuryl chloride) **1** as the starting material, (Scheme 1) taking into account that the replacement, one by one, of the chlorine atoms by nucleophiles,[3] would have allowed the synthesis of both symmetric and nonsymmetric substituted 1,3,5-triazine derivatives.

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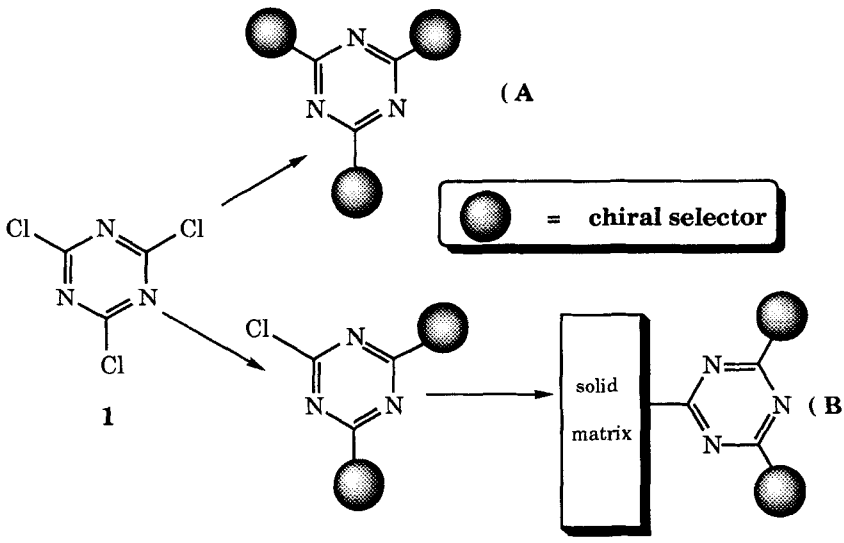
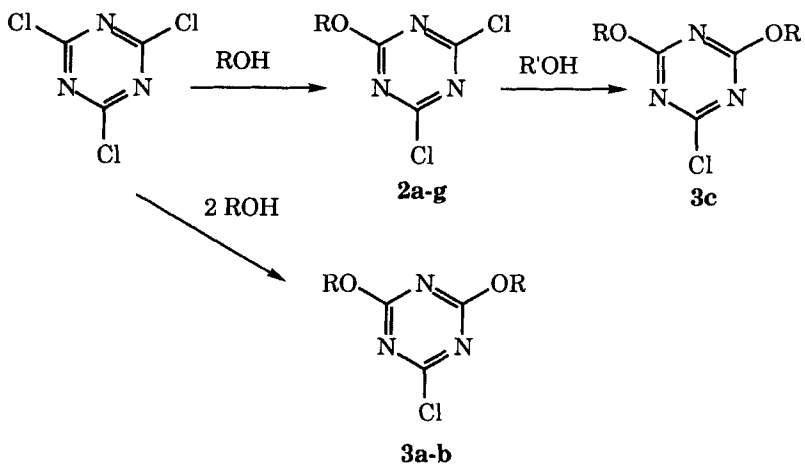


SCHEME 1

The reactivity of **1** with amines, alcohols, thiols and phenols has been widely put to use in the synthesis of dyes,[4] herbicides,[5] insecticides,[3] fungicides,[6] pesticides,[3] drugs[3,7] and more recently in the preparation of immobilized enzymes,[8] a new class of polypode ligands[9] and chiral stationary phases for GLC[10] and HPLC.[11]

While the reaction conditions necessary to perform the symmetric nucleophilic substitution of **1** (Scheme 1, path A) are well known,[12] no efficient methods for the preparation of selectively disubstituted-1,3,5-triazines (Scheme 1, path B) have so far been described.[12] The lack of a convenient synthetic approach to these last compounds prompted us to establish whether, in phase-transfer conditions, **1** undergoes substitution by alcohols. We found that, in suitable solid-liquid phase transfer conditions, **1** reacts with alcohols, and produces selectively 2-alkoxy-4,6-dichloro- **2a-g**, or 2,4-dialkoxy-6-chloro-1,3,5-triazines **3a-c**, in nearly quantitative yields (Scheme 2). In particular, compounds **2a-g** (Table, runs 1-7) were prepared by adding a benzene or toluene solution of a suitable alcohol to a mixture of cyanuryl chloride, K_2CO_3 and a catalytic amount of 18-crown-6 in the same solvent (ROH : **1** : K_2CO_3 = 1 : 1 : 1 molar ratio).



SCHEME 2

The one-step preparation of symmetric 2,4-dialkoxy-6-chloro-1,3,5-triazines **3a-b** (Table, runs 10, 11) was carried out in the same reaction conditions by reacting **1** with two molar equivalents of alcohol; finally **3c** (Table, run 12) was prepared, step by step, according to the same synthetic strategy.

To conclude we wish to emphasize that in the reaction conditions described here sterically hindered and tertiary alcohols do not react at all (Table, runs 8-9).

Studies are in progress to establish whether, in comparable phase-transfer conditions, *i)* **1** undergoes substitution by other heteroatom (N, S) nucleophiles and *ii)* optically active polyfunctional triazine derivatives can be successfully prepared.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer (200 MHz and 50.3 MHz respectively) in $CDCl_3$ if not otherwise stated. Chemical shifts (δ) are reported in ppm downfield from internal TMS. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. MS spectra were recorded on a VG-Analytical 7070 mass spectrometer. All the compounds prepared showed a satisfactory elemental analysis.

Table: Reaction conditions for the preparation of **2a-g** and **3a-c**

Run	R	R'	Compounds	Solvnt.,°C, hr	Yield% [a]
1	Et		**2a**	PhH,80,25	98
2	*i*-Pr		**2b**	PhH,80,32	98 (32) [b]
3	*n*-Pentyl		**2c**	PhMe,25,24	86 (56) [b]
4	*n*-Octyl		**2d**	PhH,25,24	97 (61) [b]
5	But-2-enyl		**2e**	PhMe,25,24	75
6	Bn		**2f**	PhH,80,90	84
7	*p*-MeO-Ph		**2g**	PhMe[c]	73
8	*t*-Bu			PhH,80,48	---
9	Bornyl			PhH,80,48	---
10	Et	Et	**3a**	PhMe,110,24	75 (14) [d]
11	*p*-MeO-Ph	*p*-MeO-Ph	**3b**	PhH[c]	96
12	Allyl	*n*-Pentyl	**3c**	PhMe,110,48	76

[a] Isolated yields, the number in brackets are reported yields. [b] See ref. 4. [c] Reaction carried out at 0°C (2h) and then at 25°C (22h). [d] See ref. 13.

General Procedure. In a typical run, both compounds **2** and **3c** were prepared by dropping the solution of the suitable alcohol (20 mmol) to a mixture of **1** or **2b** respectively (20 mmol), K_2CO_3 (20 mmol) and 18-crown-6 (0.6 mmol) in the same solvent (Table). After the required time at the suitable temperature (Table), the reaction mixture was filtered from Celite. The removal of the solvent yielded > 95% chemically pure products. Compounds **3a-b** were prepared likewise by reacting **1** with two molar equivalent of the nucleophile.

The ^1H NMR, ^{13}C NMR and MS spectra of the compounds obtained are shown below.

2a: ^1H NMR, 4.58 (q, 2H, J=7.1 Hz, -CH_2-), 1.47 (t, 3H, J=7.1 Hz, CH_3-) ppm; ^{13}C NMR, 172.44, 170.90, 66.54, 13.88 ppm; MS m/z (I%), 193 (M^+,2), 149 (100).

2b: ^1H NMR, 5.42 (septet, 1H, J=6.2 Hz, >CHO-), 1.44 (d, 6H, J=6.2 Hz, $C\underline{H}_3(C\underline{H}_3)$CHO-) ppm; ^{13}C NMR, 172.41, 170.44, 74.90, 21.40 ppm; MS m/z (I%), 207 (M^+,1), 55 (100).

2c: ^1H NMR, 4.46 (t, 2H, J=6.6 Hz, -CH_2O-), 1.88-1.74 (m, 2H, -CH_2CH_2O-), 1.49-1.32 (m, 4H, $CH_3(C\underline{H}_2)_2$), 0.92 (t, 3H, J=7.1 Hz, CH_3-) ppm;^{13}C NMR, 172.32, 170.94, 69.98, 27.77, 27.58, 22.14, 13.64 ppm; MS m/z (I%), 192 (M^+-44,5), 166 (100).

2d: ^{1}H NMR (C_6D_6), 3.96 (t, 2H, J=6.6 Hz, -CH_2O-), 1.50-1.10 (m, 12H, $CH_3(C\underline{H}_2)_6$-), 0.90 (t, 3H, J=6.6 Hz, CH_3-) ppm;^{13}C NMR (C_6D_6), 172.77, 171.42, 70.14, 31.88, 29.23, 28.21, 25.63, 22.76, 14.02 ppm; MS m/z (I%), 142 (M^+-35,8), 166 (100).

2e: ^{1}H NMR (C_6D_6), 5.60-5.25 (m, 2H, CH=CH), 4.37 (d, 2H, J=5.8 Hz, $CH_2$0-), 1.42 (dd, 3H, J=6.0 Hz, J= 1.0 Hz, CH_3-) ppm;^{13}C NMR (C_6D_6), 172.61, 171.02, 133.09, 123.76, 70.16, 17.33 ppm; MS m/z (I%), 204 (M^+-15,4), 55 (100).

2f: ^{1}H NMR (C_6D_6), 7.30-7.00 (m, 5H, Ar), 4.90 (s, 2H, -CH_2-) ppm;^{13}C NMR (C_6D_6), 172.51, 133.84, 129.01, 128.68, 128.35, 71.66 ppm; MS m/z (I%), 255 (M^+,11), 91 (100).

2g: ^{1}H NMR, 7.12-6.92 (m, 4H, Ar), 3.82 (s, 3H, CH_3) ppm; ^{13}C NMR, 172.97, 171.37, 157.96, 144.57, 121.69, 114.77, 55.54 ppm; MS m/z (I%), 271 (M^+, 34), 236 (100).

3a: ^{1}H NMR, 4.50 (q, 4H, J=7.1 Hz, -CH_2-), 1.43 (t, 6H, J=7.1 Hz, CH_3-) ppm;^{13}C NMR, 172.76, 171.76, 65.04, 13.86 ppm; MS m/z (I%), 203 (M^+,3), 131 (100).

3b: ^{1}H NMR, 7.08-6.86 (m, 8H, Ar), 3.79 (s, 6H, CH_3) ppm;^{13}C NMR, 173.55, 172.65, 157.64, 144.89, 121.91, 114.5, 55.52 ppm; MS m/z (I%), 359 (M^+, 10), 45 (100).

3c: ^{1}H NMR, 6.04 (ddt, 1H, J=17.2 Hz, J=10.4 Hz, J=5.7 Hz, C$\underline{H}$=CH_2), 5.49-5.39 (m, 1H, CH=CH$\underline{H}$), 5.36-5.29 (m, 1H, CH=C$\underline{H}$H), 4.95 (dt, 2H, J=5.7 Hz, J=1.3 Hz, 0C$\underline{H}_2$CH=), 4.43 (t, 2H, J=6.6 Hz, 0C$\underline{H}_2$$CH_2$), 1.88-1.74 (m, 2H, 0$CH_2C\underline{H}_2$), 1.50-1.19 (m, 4H, $CH_3(C\underline{H}_2)_2$-), 0.92 (t, 3H, J=7.1 Hz, CH_3) ppm;^{13}C NMR, 172.53, 172.06, 171.74, 130.91, 119.33, 63.40, 28.04, 27.72, 22.19, 13.79 ppm; MS m/z (I%), 257 (M^+,1), 41 (100).

Acknowledgement - The present work was supported by the Consiglio Nazionale delle Ricerche (CNR, Roma), Progetto Finalizzato "Chimica Fine II".

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(Received in the UK 26 January 1994)