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An Efficient Route to Alkyl Chlorides from Alcohols Using the Complex TCT/DMF

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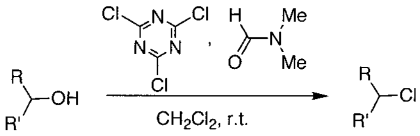
ABSTRACT



Efficient conversion of alcohols and *β*-amino alcohols to the corresponding chlorides (and bromides) can be carried out at room temperature in methylene chloride, using 2,4,6-trichloro[1,3,5]triazine and *N,N*-dimethyl formamide. This procedure can also be applied to optically active carbinols.

The transformation of alcohols into the corresponding alkyl halides is one of the most studied reactions in organic synthesis, and many reagents can be usually used. Often the conversion requires elaborate reagents and quite drastic reaction conditions. Most of the methods employed utilize reagents such as thionyl chloride,[1] phosphorus halides,[2] phenylmethyleniminium,[3] benzoxazolium,[4] Vilsmeier−Haack,[5] and Viehe salts.[6] In this context, the development of efficient reagents to use in mild conditions has interested organic chemists. The procedure based on the use of triphenylphosphine-carbon tetrahalides seems to meet these requirements but suffers the inconvenience of generating stoichiometric triphenylphosphine oxide as byproduct. To resolve these drawbacks, (chloro-phenylthiomethylene)dimethylammonium chloride was reported as a mild reagent for selective chlorination and bromination of primary alcohols.[7] However, the reagent has to be prepared through a two-step procedure that requires flash- chromatography workup. Other solutions may be the use of polymer-supported triphenyl phosphine or a filterable phosphine source such as 1,2-bis(diphenylphosphino)ethane.[8] More recently, a mild conversion of alcohols to alkyl halides using halide-based ionic liquids was reported.[9]

A search of the literature revealed that the treatment of cyanuric chloride, a very cheap reagent, with alcohols furnished the corresponding chlorides.[10] The reported procedure implied heating of the mixture to 10−20 °C below the boiling point of the alcohol and the use of excess cyanuric chloride for the complete conversion. Indeed, this method did not seem suitable for obtaining complex organic chlorides, such as those derived from amino alcohols. An accurate examination of a former report[11] showed that the treatment of the adduct formed by cyanuric chloride and dimethyl formamide with ethanol resulted in the quantitative formation of HCl and ethyl chloride.

On this basis and following our recent interest in the use of [1,3,5]triazine derivatives in organic synthesis,[12] we report

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[1] For a review, see: Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.: John Wiley & Sons: 1999; p 689.

[2] Weiss, R. G.; Snyder, E. I. *J. Chem. Soc., Chem. Commun.* **1968**, 1358; *J. Org. Chem.* **1972**, *36*, 403.

[3] Fujisawa, T.; Iida, S.; Sato, T. *Chem. Lett.* **1977**, 1173.

[4] Mukaiyama, T.; Shoda, S. I.; Watanabe, Y. *Chem. Lett.* **1977**, 383.

[5] Benazza, T.; Uzan, R.; Beaupère, D.; Demailly, G. *Tetrahedron Lett.* **1992**, *33*, 4901.

[6] Benazza, T.; Uzan, R.; Beaupère, D.; Demailly, G. *Tetrahedron Lett.* **1992**, *33*, 3129.

[7] Gomez, L.; Gellibert, F.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 6049.

[8] Pollastri, M.; Sagal, J. F.; Chang, G. *Tetrahedron Lett.* **2001**, *42*, 2459.

[9] Ren, R. X.; Xin Wu, J. *Org. Lett.* **2001**, *3*, 3027.

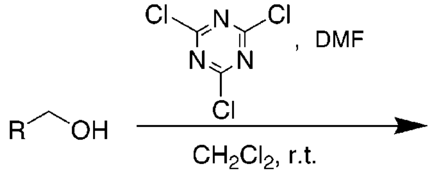
[10] Sandler, S. R. *J. Org. Chem.* **1970**, *35*, 3967.

[11] Gold, H. *Angew. Chem.* **1960**, *72*, 956.

10.1021/ol017168p CCC: $22.00

a very mild, efficient, and chemoselective procedure for the quantitative conversion of alcohols into the corresponding alkyl chlorides (Scheme 1).

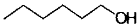
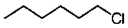
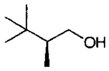
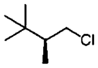
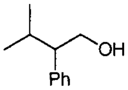
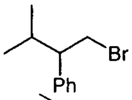
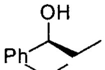
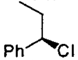
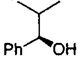
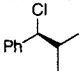
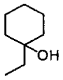
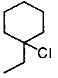
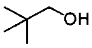
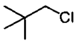
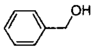
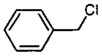
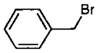
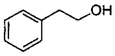
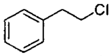
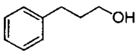
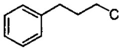
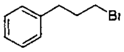
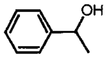
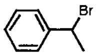
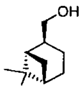
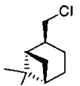
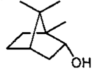
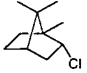
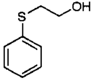
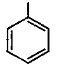
Scheme 1



The procedure is based on the reaction of 2,4,6-trichloro-[1,3,5]triazine (TCT) with DMF, followed by the addition of a CH_2Cl_2 solution of 1 mol equiv of the alcohol. At 25 °C this system effects rapidly the quantitative conversion of the alcohols to the corresponding chlorides (Table 1), which can be recovered chemically pure after a simple aqueous workup that removes the triazine byproducts. The reaction is generally fast, requiring from 10−15 min to 4 h for completion in most of the cases. Reduced rates were observed with sterically constrained alcohols, such as borneol and neopentyl alcohol. As in other cases, 2-phenylsulfanyl-1-ethanol reacts very slowly (ca. 72 h). Reaction of diols gave monochlorination using 1 mol equiv of the diol, and the conversion to dichloride is complete only using 0.5 mol equiv. At least with the optically active alcohols we have tested, the data collected show that the reaction occurs with inversion of configuration at the chiral center. In fact, a sample of (*R*)-1-phenyl-2-methyl-1-propanol, $[\alpha]^{25}_{D} + 42.1$ (*c* 2, ether), gave (S)-1-phenyl-2-methyl-1-chloropropane, $[\alpha]^{25}_{D}$ −40.8 (*c* 1, ether).[13,14] Analogously, (*S*)-1-phenyl-1-propanol, $[\alpha]^{22}_{D} - 20.2$ (neat), gave (*R*)-1-phenyl-1-chloropropane, $[\alpha]^{25}_{D} + 24.9$ (neat).

Alkyl bromides can be obtained by addition of sodium bromide and the alcohol to the TCT/DMF mixture in CH_2Cl_2. However, in this case, a noticeable amount of the alkyl chloride may be recovered as byproduct.[15] Use of sodium iodide did not lead to the formation of alkyl iodide.[16]

Table 1. Conversion of Aliphatic Alcohols into the Corresponding Alkyl Halides

entry	alcohol	product	reaction[a] time	yield (%)
1			15 min	96
2			15 min	98
3			30 min	70[b]
4			1 h	98
5			1 h	99
6			4 h	98
7			12 h	99
8			15 min	98
9			15 min	98
10			15 min	97
11			15 min	99
12			15 min	80[b]
13			30 min	70[b]
14			4 h	99
15			12 h	98
16			48 h	98

[a] For complete conversion of the alcohol. [b] The corresponding chloride is formed also.

Most interestingly, the reaction is applicable for the synthesis of *N*-protected *β*-amino chlorides. Under the usual conditions, *N*-protected *β*-amino alcohols are in fact converted to the corresponding chlorides, with slightly reduced rates (Table 2); however, the reaction is complete within 4 h. Moreover, the method is compatible with the common *N*-protecting groups, and no deprotection was noted even with *N*-Boc-protected amino acids, if working in the presence of $NaHCO_3$.

The stereochemical results indicate the occurrence of a Sn_2 reaction that may be consistent with the mechanism

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(12) (a) Falorni, M.; Porcheddu, A.; Taddei, M. *Tetrahedron Lett.* **1999**, *40*, 4395. (b) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **1999**, *64*, 8962. (c) Falchi, A.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *Synlett* **2000**, 275. (d) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534. (e) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 1519. (f) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041. (g) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, *66*, 7907.

(13) Giacomelli, G.; Lardicci, L. *J. Org. Chem.* **1981**, *46*, 3116.

(14) Kwart, H.; Givens, E. N.; Collins, C. J. *J. Am. Chem. Soc.* **1969**, *91*, 5532.

(15) The bromide can be recovered by accurate distillation or flash chromatography.

(16) No result was obtained even with the addition of tetrabutylamonium iodide. The presence of tetrabutylammonium bromide causes the formation of the alkyl bromide in low yields.

(17) **Representative Procedure. Chlorination of (*S*)-(1-Hydroxymethyl-3-methylbutyl)-carbamic Acid Benzyl Ester.** 2,4,6-Trichloro-[1,3,5]triazine (1.83 g, 10.0 mmol) was added to DMF (2 mL), maintained at 25 °C. After the formation of a white solid, the reaction was monitored (TLC) until complete disappearance of TCT, and CH_2Cl_2 (25 mL) was added, followed by the alcohol (2.39 g, 9.5 mmol). After the addition, the mixture was stirred at room temperature and monitored (TLC) until completion (4 h). Water (20 mL) was added, and then the organic phase was washed with 15 mL of a saturated solution of Na_2CO_3, followed by 1 N HCl and brine. The organic layers were dried (Na_2SO_4), and the solvent evaporated to yield (*S*)-(1-chloromethyl-3-methylbutyl)-carbamic acid benzyl ester, which was isolated without other purifications (2.28 g, 89%).

Table 2. Conversion of Diols and Unsaturated and β-amino Alcohols into the Corresponding Alkyl Halides

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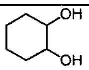
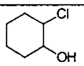
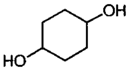
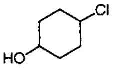
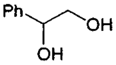
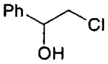
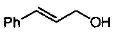
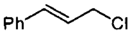
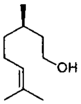
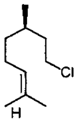
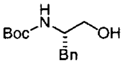
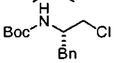
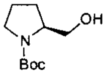
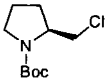
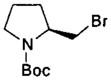
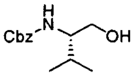
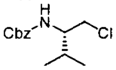
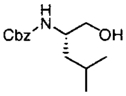
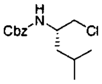
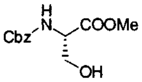
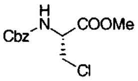
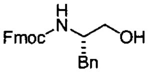
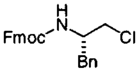
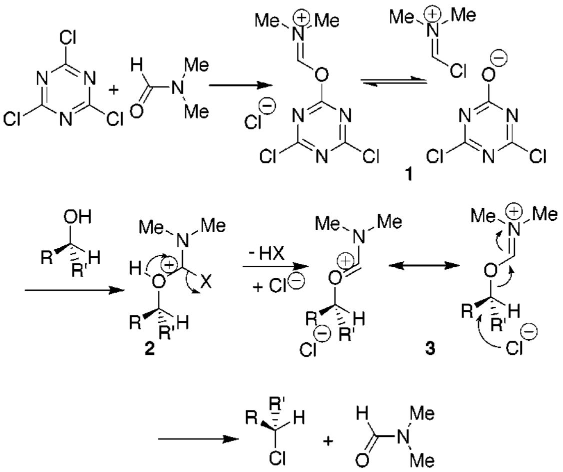
1			15 min	98
2			15 min	95
3			15 min	98
4			15 min	92
5			15 min	98
6			30 min	93
7			40 min	94
8			40 min	70[b]
9			4 h	83
10			4 h	89
11			4 h	94
12			4 h	97

[a] For complete conversion of the alcohol. [b] The corresponding chloride is formed also.

depicted in Scheme 2. The Vilsmeier–Haack-type complex should add the hydroxyl group of the alcohol to form the cationic species **3**; subsequent nucleophilic attack of halide ion should produce the corresponding halide.[17]

Scheme 2



In conclusion, the procedure reported here is operationally simple and allows a rapid and high-yielding conversion of alcohols to the corresponding chlorides and bromides under very mild conditions. The method seems to be more convenient with respect to other reports and can be used as a valid alternative to other methods, so avoiding tedious purifications or the use of more toxic reagents.

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Note Added after ASAP: There was a nitrogen omitted from the second reagent above the arrow in the abstract in the version posted ASAP on 1/17/02. The print and final Web version was posted (1/23/02).

Supporting Information Available: Physical and spectroscopic data for all unknown compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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