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(Chloro-phenylthio-methylene)dimethylammonium chloride (CPMA) an efficient reagent for selective chlorination and bromination of primary alcohols

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Abstract

(Chloro-phenylthio-methylene)dimethylammonium chloride reacts smoothly with a variety of alcohols, to afford the corresponding alkyl chloride in good yields. In the presence of tetrabuthylammonium bromide the corresponding bromide is obtained. Selective halogenation of primary hydroxyl groups in the presence of an unprotected secondary one is described. The mild reaction conditions involved are compatible with the major alcohol protecting groups as well as with acid sensitive functions like epoxides.

Conversion of alcohols into the corresponding alkyl halides is one of the most described transformations in organic synthesis. Many reagents, from very simple to very elaborate, are commonly used to carry out this transformation.[1] For instance, reflux of alcohols in aqueous hydrochloric acid yields the corresponding alkyl chlorides.[2] This method, though very simple, is limited to robust substrates. To perform chlorination or bromination of hydroxyl groups on polyfunctionalized fragile substrates, more elaborated reagents have been developed and widely used—for instance, thionyl chloride, phosphorus halides,[3] phenylmethyleniminium,[4] benzoxazolium,[5] benzothiazolium,[6] Vilsmeier Haack,[7] and Viehe[8] salts. All these reagent, though very useful and efficient, often suffer some lack of selectivity, especially between primary and secondary alcohols or in the presence of acid-sensitive groups like epoxides.[9] Moreover, some protecting groups being sensitive to halogenating agents,[10] selective halogenation of an hydroxylated polyfunctional molecule still remains tricky.

Herein, we report the synthesis and the use of (chloro-phenylthio-methylene)dimethylammonium chloride (CPMA) for the mild and selective chlorination or bromination of primary hydroxyl groups (Scheme 1).

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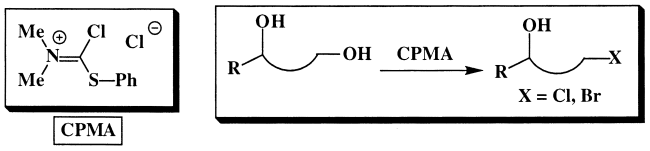
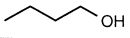
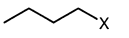
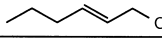
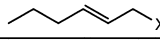
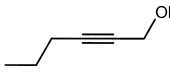
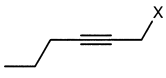
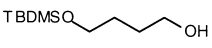
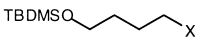
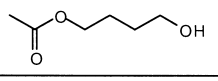
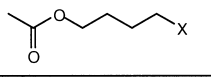
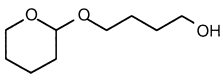
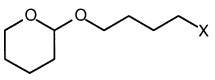
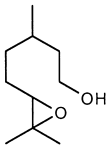
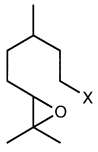
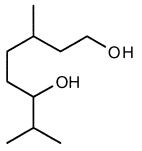
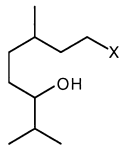
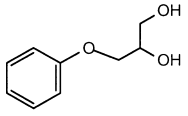
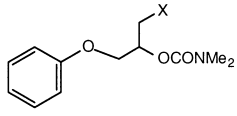


Scheme 1.

CPMA is easily prepared by a reaction of *S*-phenyl-*N*,*N*-dimethyldithiocarbamate with phosgene and is isolated as a white, stable solid.[11] Reaction with primary alcohols under very mild conditions gives the corresponding alkyl halides in high yield. The compatibility of this reagent with various functional and protecting groups was studied. The results are summarized in Table 1.

Table 1

Entry	Substrate	Product	Yield (%) X=Cl	Yield (%) X=Br
1			97[a,e]	97[b,e]
2			95[a]	96[b]
3			96[a]	96[b]
4			91[a]	90[b]
5			92[a]	92[b]
6			90[c]	90[d]
7			89[c]	87[d]
8			88[a]	85[b]
9			89[a]	87[b]

a) CPMA, CH_2Cl_2; b) CPMA, $nBu_4N^+Br^-$, CH_2Cl_2; c) CPMA, NEt_3 CH_2Cl_2; d) CPMA, $nBu_4N^+Br^-$, NEt_3 CH_2Cl_2; e) Yield determined by NMR on the crude mixture. The product being volatile, the isolated yield is about 20 % lower than the indicated value.

Chlorination of primary alcohols is conveniently performed by addition of CPMA (1.2 equiv.) to a solution of alcohol (1 equiv.) in anhydrous dichloromethane (0.3 M) under argon at 0°C. The resulting mixture is stirred at room temperature for 3 h. The reaction is then quenched by addition of a saturated solution of potassium carbonate. The aqueous layer is extracted with methylene chloride and the combined organic phases are dried over magnesium sulfate and concentrated under vacuum. The residue is purified by column chromatography. Interestingly, except for 1,2-diol (entry 9), the thiocarbamate is recovered quantitatively at the end of the reaction and no unpleasant smell arising from thiophenol release was noticed.

Alkylchlorides were consistently obtained in high yields ranging from 89 to 97%. Functionality such as alkene, alkyne, TBS-ether and acetate proved to be stable under these reaction conditions (entries 2–5). THP-protected alcohols, which give the corresponding chlorides in the presence of other methyleniminium salts[5] were shown to be stable upon treatment with CPMA (entry 6). Similarly, epoxides, which are known to give the corresponding dichlorides with other iminium reagents, remained untouched under our conditions (entry 7).

The selectivity of CPMA was demonstrated by the chlorination in high yield of a primary hydroxyl group in the presence of an unprotected secondary one (entry 8). In the presence of 5 equiv. of reagent and after 5 days of reaction, no chlorination of the secondary alcohol was observed. Additional proof of the selectivity was given by reacting menthol in the presence of 5 equiv. of CPMA. After 2 days no chlorinated product could be detected.

Noteworthy, other reagents like tetramethyl-α-halogenoenamine, although efficient for chlorination of secondary alcohols—i.e. menthol—may show some selectivity between primary and secondary alcohols when using an equimolar amount of the reagent and the primary alcohol.[12] In contrast, CPMA is totally unreactive toward secondary alcohols—i.e. menthol—even in the presence of an excess of CPMA.

Reaction of 1,2 diols gave selective chlorination of the primary hydroxyl group (entry 9). However, the neighboring secondary hydroxyl group was converted into the corresponding *N*,*N*-dimethylcarbamate by an intramolecular substitution on the activated alkoxyiminium intermediate. A similar reaction had already been observed when treating an unprotected pentitol with Viehe's salt.[8b]

Alkyl bromide derivatives were obtained by the addition of CPMA (1.2 equiv.) to a mixture of tetrabutylammonium bromide (2 equiv.) and the alcohol (1 equiv.) under the above-described conditions. Table 1 shows that the yields of bromination are almost identical to those obtained for the chlorination reaction. Addition in the reaction mixture of tetrabutylammonium iodide, fluoride, or cyanide did not lead to the formation of the corresponding substitution product.

The mildness and the selectivity of CPMA compared to previously described methyleniminium salts might be explained by both the stabilization of the positive charge of the iminium center by the sulfur atom and the steric hindrance due to the phenyl residue. Both effects resulted in a decrease of electrophilicity of the central carbon atom and thus, in the increase of selectivity.

In summary, we describe in this paper an original reagent (CPMA) for the selective chlorination or bromination of primary hydroxyl groups. This reagent prepared on a multigram scale is isolated as a non-hygroscopic white powder that can be stored for months without special precaution. Noteworthy, during the reaction and work-up no formation of thiophenol side product was detected. CPMA has proven to be compatible with sensitive functionalities and allows the selective chlorination and bromination of a primary alcohol in the presence of an unprotected secondary one.

Acknowledgements

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11. (a) Original conditions for the preparation of **1**: Copeland, C.; Stick, R. V. *Aust. J. Chem*. **1984**, *37*, 1483–1487. (b) New method for the preparation of CPMA: To dimethylthiocarbamoyl chloride (1 g, 8.1 mmol) in dichloromethane (20 mL) under nitrogen was added thiophenol (0.67 mL, 6.5 mmol), triethylamine (1.1 mL, 8.1 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol). The mixture was heating at reflux for 12 h. Basic work-up (CH_2Cl_2/$NaHCO_3$ aq.) gave an oil and subsequent flash chromatography (hexane:AcOEt, 3:1) gave the corresponding dithiocarbamate (1.42 g, 89%). Treatment with phosgene (3.3 mL, 1.93 M in toluene) in toluene (10 mL) for 2 h at 60°C followed by concentration gave CPMA as a white solid which was washed with toluene. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.07 (s, 6H), 7.37–7.66 (m, 3H), 7.79–7.82 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 178.7, 136.9, 133.6, 131.2, 124.7, 50.0, 47.8. IR (film CsI) ν (cm^{-1}) 1667, 1596, 1476, 1441, 1406, 1365, 1259, 1235, 1103, 1088, 990, 752, 688. Elemental analysis calcd for ($C_9H_{11}Cl_2NS$): C, 45.8%; H, 4.7%; Cl, 30.0%; S, 13.6%. Found: C, 45.6%; H, 5.0%; Cl, 29.7%; S, 13.4%. Mp decomposes above 60°C.
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