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One-step Conversion of Protected Alcohols into Alkyl Halides using Dimethylphosgeniminium Salt

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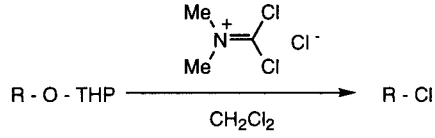
Abstract: *Efficient conversion of tetrahydro-2-pyranyl (THP)protected alcohols into the corresponding halides using dichlorophosgeniminium chloride in the presence of tetraalkylammonium halide.*

The direct conversion of protected alcohols into the corresponding halides is a useful transformation for many synthesis.[1] Various reagents are currently available for this purpose including triphenylphosphine/ carbon tetrabromide[2], triphenylphosphine dibromide[3] or 1,2-bis(triphenylphosphino)-ethane tetrabromide[4]. However, no reagent is known that allows the formation of alkyl chlorides.

Herein, we report that the reactions of tetrahydropyranylated alcohols with N,N-dimethyl-phosgeniminium chloride [5] yield the corresponding alkyl chlorides in good yields (Scheme 1, Table 1).

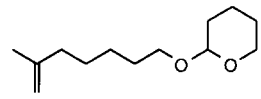
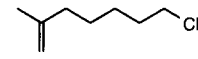
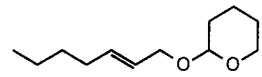
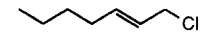
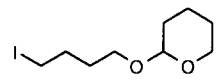
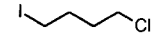
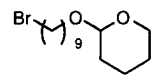
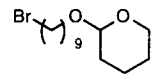
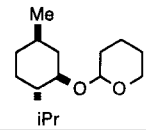
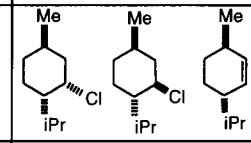
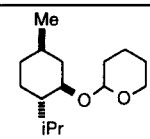
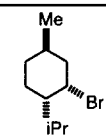
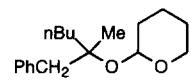
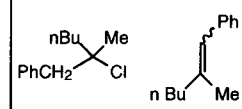


Scheme 1

This conversion is conveniently accomplished by the addition of the Viehe salt (1.05 eq.) as a solid to a solution of THP-protected alcohols (1 eq.) in anhydrous dichloromethane (0.3M) under argon at 0°C. After completion of the reaction and aqueous work-up, the crude alkyl chlorides were purified by column chromatography.

Following this procedure, excellent yields were obtained using primary protected alcohols (entries 1 to 4, table 1). Interestingly, we also observed that one could directly obtain the alkyl bromide derivative by adding the Viehe salt to a mixture of tetrabutylammonium bromide (2eq.) and tetrahydropyranylated alcohols (1 eq.) under the same conditions as described above (entry 5, table 1). Unfortunately, under the same conditions, the presence of tetraethylammonium iodide did not afford the expected alkyl iodides. The starting material remained unchanged and the Viehe salt was consumed with production of iodine.

Table 1: Preparation of alkyl halides from tetrahydro-2-pyranylated alcohols [6]

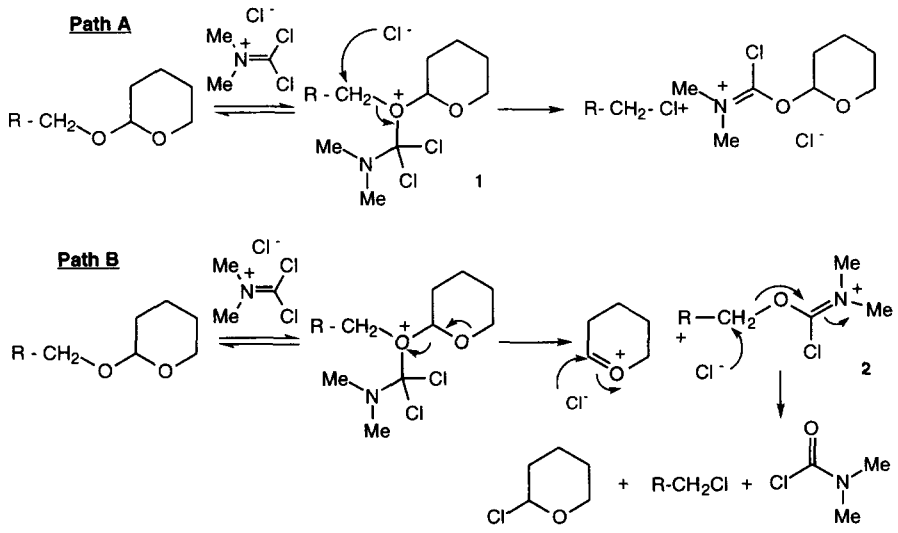
Entry	Substrates	Products	Conditions	Yield(%)
1			a	78
2			a	80
3			a	95
4			a	95
5			b	96
6			a c d e	42:18:40 [f] 60:0:40 [f] 45:50:5 [f] 86:0:14 [f]
7			b	83
8			a	30:70

a: dimethylphosgeniminium chloride, CH_2Cl_2; b: dimethylphosgeniminium chloride, $nBu_4N^+Br^-$, CH_2Cl_2;
c: dimethylphosgeniminium chloride, $nEt_4N^+Cl^-$, CH_2Cl_2; d: dimethylphosgeniminium chloride, acetonitrile;
e: dimethylphosgeniminium chloride, acetonitrile, $nEt_4N^+Cl^-$, 0°C; f: ratio determined by ^1H NMR spectroscopy, 100% conversion of the starting material

We studied the reactivity of protected menthol as a model of secondary substrate in order to investigate the product outcome as well as the stereochemistry of the reaction . When the reaction was carried out in acetonitrile and in the presence of tetraethylammonium chloride (entry 6, condition e, table 1), only one diastereomer was formed, possessing a *cis*-relationship between the isopropyl group and the chlorine. Under these conditions, the alkene of β-elimination was the minor product (14%). Interestingly, when the reaction was performed under the standard conditions (entry 6, condition a, table 1), 40 % of alkene was formed and this is consistent with the lower nucleophilicity of the chloride anion in a less polar solvent. A lower diastereoselectivity was also observed for the substitution process. When tetraethylammonium chloride was added to the reaction mixture (entry 7, condition c, table 1), diastereoselectivity of the reaction was controlled but competitive elimination could not be avoided. Menthyl bromide was directly prepared from tetrahydropyranylated menthol using dichlorophosgeniminium chloride in the presence of two equivalents of anhydrous N-tetrabutylammonium bromide (entry 7, table 1). In that particular case, the substitution occurred with complete inversion of configuration and no competitive elimination was observed.

The attempts to optimize this protocol to protected tertiary alcohols were unsuccessful as the reaction gave the alkene of β-elimination as the major product (entry 8, table 1). Under the standard conditions, only 30% of tertiary alkyl chloride was formed.

Although we did not study in detail the mechanism of this reaction, two mechanistic pathways (Path A or B) could be considered for that transformation, as illustrated for a primary protected alcohol (scheme 2).



Scheme 2

In both cases, the phosgeneniminium salt activates the acetal towards nucleophilic substitution with the chloride anion. The addition of the chloride anion could occur either on intermediate **1** (Path A) or **2** (Path B). For protected menthol (entry 6, table 1), SN_1/SN_2 mechanisms and elimination processes operate simultaneously. For a tetrahydropyranylated tertiary alcohol (entry 8), the elimination process is highly predominant and the expected tertiary alkyl chloride is the minor product (30%).

The presently developed method provides a convenient means to obtain directly alkyl bromides or chlorides from tetrahydro-2-pyranyl protected alcohols in a one-step reaction. Complete inversion of configuration was achieved for chiral secondary alcohols. The combined use of commercial dichlorophosgeniminium chloride with the appropriate ammonium halide controls the product outcome of the reaction into the desired halide. However, the reaction could not be applied to the preparation of iodoalkanes. The reagent reported herein complements those already described in the literature as this is the first reagent which allows a direct preparation of alkyl chlorides from protected alcohols.

Acknowledgment

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References and notes

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(6) All new compounds have been fully characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy.

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