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Pivaloyl chloride/DMF: a new reagent for conversion of alcohols to chlorides

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ABSTRACT

An efficient procedure for conversion of alcohols into the corresponding chlorides is described. Pivaloyl chloride/DMF complex is employed as a mild and inexpensive reagent. A possible reaction mechanism is proposed.

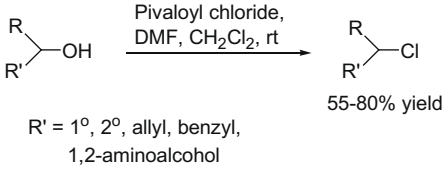
Conversion of alcohols into the corresponding chlorides is one of the most important and commonly used transformation in organic synthesis and development of such a procedure is still desirable in academia as well as in industrial research. A number of reagents have been employed to carry out this transformation. Some of the methods developed for this purpose utilize reagents such as thionyl chloride,[1] PCl_5,[2] *N,N*-diphenylchlorophenylmethyleniminiumchloride,[3] 2-chlorobenzoxazolium salts,[4] benzothiazolium salts,[5] Vilsmeier–Haack salt,[6] Vieche salts,[7] (chloro-phenylthiomethylene)dimethylammoniumchloride,[8] polymer-supported triphenyl phosphine or a filterable phosphine source such as 1,2-bis(diphenylphosphino)ethane.[9] More recently, halide based ionic liquids[10] and complex of TCT–DMF[11] have been reported to effect this transformation.

During our recent endeavor with HKR (hydrolytic kinetic resolution) mediated synthesis of biologically active compounds, we required to convert a diol into the required epoxide through pivalate via a three step-sequence reaction. Interestingly, we observed an efficient chlorination of alcohol instead of its protection as pivalate when reaction was performed in DMF. This could probably be attributed to the generation of a new reactive species responsible for chlorination and this observation prompted us to initiate a systematic investigation of pivaloyl chloride/DMF reagent system for chlorination of alcohol. Herein we wish to disclose our results for a very mild and efficient conversion of alcohol to chloride.

In a typical experimental procedure,[12] when alcohols were treated with a pre-formed complex of DMF and pivaloyl chloride in dichloromethane, it gave the corresponding chloro compounds in moderate to good yields (Scheme 1).

The present procedure is quite general as a wide range of structurally varied alcohols such as primary, secondary, allylic, homoallylic, and benzylic ones underwent smooth conversion with pivaloyl chloride/DMF into their corresponding chlorides under mild reaction conditions in moderate to good yields of the corresponding chloride (Table 1). It should be mentioned here that in some cases small amount (5–15% yield) of the pivaloyl ester of the corresponding alcohol was also obtained as a side product.[13] The superiority of this procedure can be clearly visualized in chlorination of β-amino alcohol leading to the corresponding chloro compound in good yield without formation of any side product (Table 1, entry 10). The cleavage of acetonide group under the reaction conditions employed was not observed. It should be mentioned here that the amino acid based azide thus prepared could serve as a useful building block to synthesise a new class of unnatural *C*-glycosyl amino acid featuring a triazole moiety between the sugar and amino acid entities.[15] PMBCl, an important protecting group in organic synthesis was also synthesized from the corresponding alcohol (Table 1, entry 1). Our method yielded the product free from any acidic impurities while the conventional method of its synthesis using hydrochloric acid generally affords the product contaminated with acidic impurities.

In order to examine the stereospecificity of the present method, we employed (*R*)-octane-2-ol (Table 1, entry 12) and subjected this to reaction with pivaloyl chloride/DMF reagent to give (*S*)-2-chlorooctane, $[\alpha]_D^{20}$ +36.0 (*c* 0.8, ether), lit.[4] $[\alpha]_D^{20}$ +33.0 (*c* 0.8, ether); lit.[3] $[\alpha]_D^{20}$ +36.02. The measurement of optical rotation and its comparison with literature values indicated that the reaction occurs with inversion of configuration via S_N2 displacement leading to the corresponding chloro product in enantiomerically pure form. A possible explanation for reaction mechanism is depicted in Scheme 2. The involvement of Vilsmeier–Haack type complex as a possible reactive intermediate is invoked which adds on the hydroxyl group of the alcohol to form the cationic species followed by



Scheme 1.

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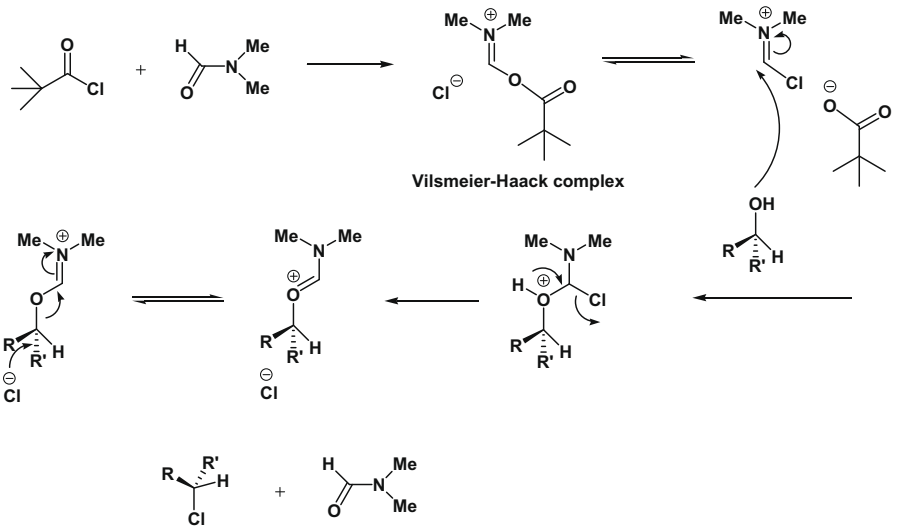
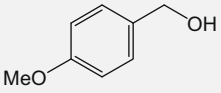
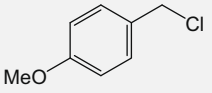
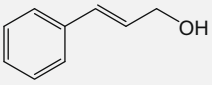
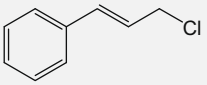
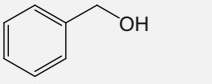
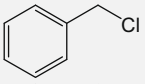
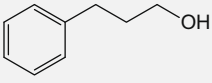
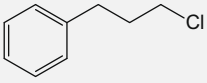
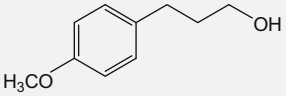
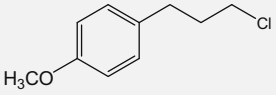
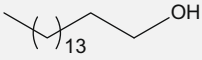
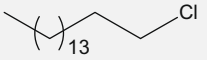
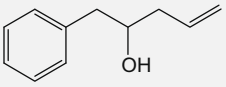
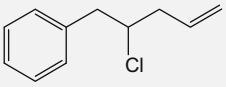
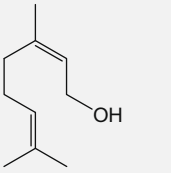
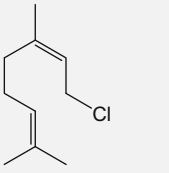
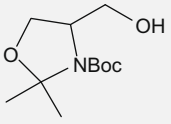
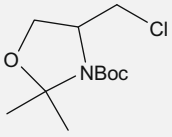


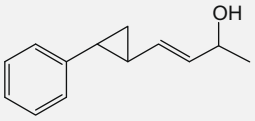
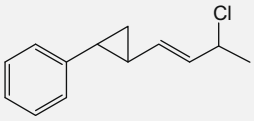
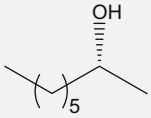
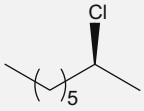
Scheme 2. Proposed mechanism for chlorination of alcohol.

Table 1
Dimethylformamide/pivaloyl chloride mediated conversion of alcohols to chlorides

Entry	Alcohol	Product	Reaction time	Yield[a] (%)
1			20 min	80
2			30 min	70
3			30 min	80
4			20 min	80
5			2 h	70
6			2 h	70
7			1 h	75
8			5 h	60
9			1 h	65
10			4 h	55

(*continued on next page*)

Table 1 (*continued*)

Entry	Alcohol	Product	Reaction time	Yield[a] (%)
11			4 h	60
12			1 h	60

[a] Crude yield of the chloro products.

subsequent nucleophilic attack of chloride ion in S_N2 fashion to produce the corresponding chloride.

Some of the crude chloro compounds which were found to be volatile and unstable were subsequently treated with sodium azide in DMF at 60 °C to afford the corresponding azide in good yield.[14]

In conclusion, a mild, general and efficient conversion of alcohols into chlorides has been developed. The noteworthy feature of the present method is the use of pivaloyl chloride/DMF as a mild, non-toxic and inexpensive reagent coupled with simple operation and ease of work-up. We believe this will present a better and more practical alternative to the existing methodologies.

Acknowledgments

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12. *Representative procedure. Chlorination of p-methoxybenzyl alcohol*: A mixture of pivaloyl chloride (1.30 g, 10.86 mmol) and DMF (5 mL) was stirred at room temperature for 1 h. To the mixture was first added CH_2Cl_2 (25 mL) followed by alcohol (1 g, 7.24 mmol). The reaction was monitored (TLC) until the complete disappearance of starting material. 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 over Na_2SO_4, and the solvent evaporated to yield *p*-methoxybenzyl chloride (0.91 g, 80%).
13. *Heptadecyl pivalate (entry 7)*: ^{1}H NMR ($CDCl_3$, 200 MHz): 0.88 (t, 3H, J = 6.0 Hz), 1.2 (s, 9H), 1.26 (br s, 26H), 1.51–1.65 (m, 2H), 4.04 (t, 2H, J = 6.8 Hz); δ_C ^{13}C NMR ($CDCl_3$, 50 MHz): 14, 22.6, 25.9, 27.1, 28.6, 29.2, 29.7, 31.9, 38.6, 64.3, 178.4.
14. (a) *1-(Azidomethyl)-2-octylcyclopropane (entry 3)*: ^{1}H NMR ($CDCl_3$, 200 MHz): 0.34–0.48 (m, 2H), 0.62–0.74 (m, 1H), 0.77–0.98 (m, 4H), 1.21–1.44 (m, 14 H), 2.99–3.18 (2H, m); δ_C ^{13}C NMR ($CDCl_3$, 50 MHz): 10.6, 14.1, 17.3, 17.8, 22.7, 29.3, 29.4, 29.5, 31.9, 33.52, 55.5. Anal. Calcd for $C_{12}H_{23}N_3$ (209.33): C, 68.85; H, 11.07; N, 20.07. Found: C, 68.55; H, 11.38; N, 20.0.
(b) *(2-Azidopent-4-enyl)benzene (entry 8)*: ^{1}H NMR ($CDCl_3$, 200 MHz): 2.85–3.05 (m, 2H), 3.26–3.55 (m, 3H), 5.21–5.33 (m, 2H), 6.82–6.92 (m, 1H), 7.17–7.35 (m, 5H); δ_C ^{13}C NMR ($CDCl_3$, 50 MHz): 33.1, 37.4, 52.3, 113.71, 127.1, 128.7, 129.3, 135.7, 160.1. Anal. Calcd for $C_{11}H_{13}N_3$ (187.24): C, 70.56; H, 7.00; N, 22.44. Found: C, 70.32; H, 6.95; N, 22.60.
(c) *(E)-(2-(3-Azidobut-1-enyl)cyclopropyl)benzene (entry 11)*: ^{1}H NMR ($CDCl_3$, 200 MHz): 0.85–0.94 (m, 2H), 1.19–1.33 (m, 5H), 2.51–2.60 (m, 1H), 5.38–5.72 (m, 1H), 5.94–6.05 (m, 1H), 7.17–7.43 (m, 5H); δ_C ^{13}C NMR ($CDCl_3$, 50 MHz): 11.1, 11.4, 21, 21.4, 64.6, 122, 122.6, 125.3, 128.4, 128.7, 131.2. Anal. Calcd for $C_{13}H_{15}N_3$ (213.28): C, 73.21; H, 7.09; N, 19.70. Found: C, 73.01; H, 7.16; N, 19.65.
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