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An efficient method for chlorination of alcohols using PPh_3/Cl_3CCONH_2

Wanchai Pluempanupat and Warinthorn Chavasiri*

Natural Products Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University, Patumwan, Bangkok 10330, Thailand

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Abstract—A new and convenient method for the chlorination of alcohols utilizing PPh_3/Cl_3CCONH_2 is addressed. Various alcohols could smoothly be converted into their corresponding alkyl chlorides in high yield under mild conditions with short reaction times. A mechanism is disclosed with the evidence of inversion of configuration of the analogous alkyl chloride derived from *R*-(−)-2-octanol.

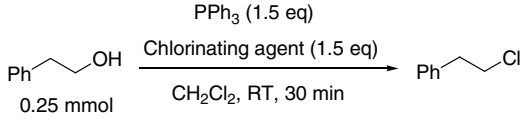
Alkyl chlorides are generally used as both synthetically useful intermediates and valuable end products.[1] Although alkyl chlorides can be prepared from various starting materials, the general and simple protocols mostly stem from the conversion of alcohols. The main reasons being due to the uncomplicated process of the conversion, the variety and good availability of alcohols.[2] Chlorodehydration has been accepted as a general and basic transformation pathway using HCl gas, $SOCl_2$, $(COCl)_2$, PCl_3 or TMSCl; nonetheless, the co-regeneration of HCl often causes undesired side reactions.[3] A new methodology with controllable selectivity is therefore still necessary and is a relevant task for organic chemists.[4]

PPh_3-halogenated reagents such as PPh_3/CCl_4, PPh_3/Cl_3CCCl_3, $PPh_3/Cl_3CCOCCl_3$ or PPh_3/Cl_3CCN systems have been reported as viable routes for the chlorination of alcohols with high efficiency.[5] These reagents are attractive since reactions can be formed under mild and acid-free conditions with good yields.

We have recently introduced Cl_3CCONH_2 as an alternative halogenated reagent for conversion of carboxylic acids to their analogous amides and esters upon its combination with PPh_3.[6] This reagent is less reactive compared with Cl_3CCN, however, its cheaper cost and the ease of work-up make this reagent more practical. We report herein, the use of PPh_3/Cl_3CCONH_2 for the conversion of alcohols into their corresponding alkyl chlorides.

Optimum conditions for the preparation of alkyl chlorides from alcohols utilizing various chlorinated reagents coupled with PPh_3 were examined (Table 1).

Table 1. Effect of chlorinating agents



Entry	Chlorinating agent	Yield[a] (%)
1	None	0
2	CCl_4	Trace
3	$CHCl_3$	0
4	Cl_3CCCl_3	Quant
5	Cl_3CCH_2OH	0
6	$CH_3CO_2CH_2CCl_3$	0
7	Cl_3CF	0
8	Cl_3CCN	Quant
9	$Cl_3CCOCCl_3$	95
10	Cl_3CCO_2H	35
11	Cl_3CCO_2Et	82
12	$Cl_3CCO_2{}^iPr$	71
13	Cl_3CCONH_2	81
14	$Cl_3CCONHPh$	80

[a] Determined by ^1H NMR.

Keywords: Chlorination; Alcohols; Triphenylphosphine; Trichloroacetamide.
* Corresponding author. Tel.: +66 2 2187625; fax: +66 2 2187598; e-mail: warintho@yahoo.com

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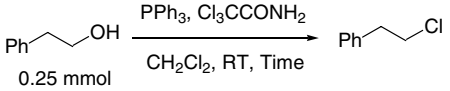
Variable parameters studied were the types of chlorinating agent, ratio of PPh_3 and chlorinating agent and reaction time.[7] 2-Phenylethanol was chosen as a model compound to avoid the benzylic effect. A typical procedure involved the reaction of alcohol (1 equiv), halogenating reagent (1.5 equiv) and PPh_3 (1.5 equiv) in CH_2Cl_2 at rt (30 °C) for 30 min.

The efficiency of the chlorinating agent greatly depended on the type of substituent on the chlorinating agents. The reagents in entries 2–4 have been previously utilized for conversion of alcohols into alkyl chlorides.[5] Under the specified conditions, the desired product was obtained in low yield except in the case of Cl_3CCCl_3, which gave a quantitative yield. No reaction occurred with a chlorinating agent containing an alkyl group or F atom on the trichloromethyl group (Cl_3C–) (entries 5–7). Cl_3CCN and $Cl_3CCOCCl_3$ (entries 8–9), reagents bearing electron-withdrawing groups, gave the desired products in quantitative yields, while Cl_3CCO_2H (entry 10) gave only a poor yield of the desired product. This was probably because of its acidity, which may cause the reaction medium to become acidic and thus incompatible for further reaction to take place. Other electron-withdrawing group-containing reagents (entries 11–14) were chosen to prove this assumption. For example, Cl_3CCO_2Et, Cl_3CCONH_2 and $Cl_3CCONHPh$ (entries 11, 13 and 14) furnished the target product in high yields. Based on the results obtained, Cl_3CCONH_2 was considered as the most suitable chlorinating agent for further investigation because it has not been studied previously, and it is commercially available, cheap and leads to a simple work-up procedure.

The quantities of PPh_3 and Cl_3CCONH_2 were varied to find a suitable ratio to provide the maximum yield of alkyl chloride (Table 2). The use of PPh_3 and Cl_3CCONH_2 in a 1:1 ratio (based on alcohol) furnished the corresponding alkyl chloride in moderate yield (entry 2). Increasing the amount of PPh_3 and Cl_3CCONH_2 over 1 equiv significantly elevated the yield of the target product (entries 3–7). A short reaction time (15 min) was also possible with the production of alkyl chloride in quantitative yield (entry 6).

These optimized reaction conditions were extended to investigate the conversion of various alcohols including primary, secondary and tertiary into their corresponding alkyl chlorides (Table 3).

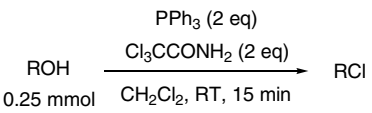
Table 2. Effect of PPh_3 and Cl_3CCONH_2 ratio



Entry	PPh_3 (equiv)	Cl_3CCONH_2 (equiv)	Time (min)	Yield[a] (%)
1	0.5	0.5	15	15
2	1.0	1.0	15	53
3	1.2	1.2	15	73
4	1.5	1.5	15	75
5	1.5	1.5	30	81
6	2.0	2.0	15	Quant
7	2.0	2.0	30	Quant

[a] Determined by ^1H NMR.

Table 3. Chlorination of alcohols with PPh_3/Cl_3CCONH_2

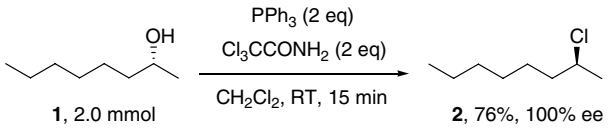


Entry	ROH	RCl[a] (%)
1	1-Octanol	96, 95[b,c]
2	1-Dodecanol	98
3	1-Octadecanol	96
4	2-Phenylethanol	Quant, 99[b,c]
5	3-Phenyl-1-propanol	92
6	(±)-2-Octanol	Quant
7	Cyclooctanol	56*[,d]
8	Cyclododecanol	62*[,e]
9	(±)-2-*tert*-Butylcyclohexanol	26*[,f]
10	(±)-4-*tert*-Butylcyclohexanol	76*[,g]
11	2-Adamantanol	Quant
12	1-Adamantanol	68
13	2-Phenyl-2-propanol	72*[,h]
14	1,1-Diphenylethanol	11*[,i]

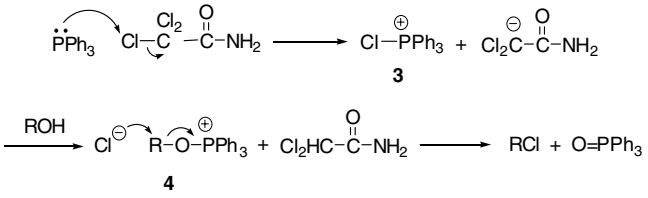
[a] Determined by ^1H NMR.
[b] Isolated pure product.
[c] 1 mmol of ROH was used.
[d] 1.40:1.
[e] 1.44:1.
[f] 0.33:1.
[g] 2.71:1.
[h] 4.50:1.
[i] 0.12:1.
* RCl:olefin ratio.

Various primary alcohols could be completely converted into the corresponding alkyl chlorides in high to quantitative yields (entries 1–5).[8] The carbon chain length, perhaps relating to steric hindrance, did not affect this reaction (entries 1–3). Similarly, secondary alkyl chlorides could also be obtained in high yield (entry 6). Cyclic compounds, on the other hand, were converted into cyclic chlorides upon treatment with PPh_3/Cl_3CCONH_2 in low to moderate yields (entries 7–10) except for 2-adamantanol (entry 11). The olefinic product was detected in this reaction with an almost equivalent amount of the alkyl chloride present. This implied that the reaction may competitively proceed via two pathways, that is, substitution versus elimination. The conversion of a tertiary alcohol into its corresponding alkyl chloride could also be accomplished in high yield (entry 13). In the case of tertiary alcohols with more phenyl substituents at the tertiary carbon atom, the chloride product was detected in low yield. Peradventure, this alcohol, which was considered to react via an E_2 reaction, also gave an olefin as the main product (entry 14).

Further examination of this method was performed using an optically active substrate, *R*-(−)-2-octanol (**1**) (Scheme 1). Under the standard protocol, chiral alcohol **1** ($[\alpha]_D^{25}$ −9.6, *c* 0.97, $CHCl_3$) (lit. $[\alpha]_D^{17}$ −9.9)[9] was successfully transformed into the alkyl chloride **2** ($[\alpha]_D^{25}$ +26.9, *c* 0.58, $CHCl_3$) (lit. $[\alpha]_D$ +26.1)[4d,9] in good isolated yield with complete inversion of configuration.[8,10]



Scheme 1. Chlorination of *R*-(−)-2-octanol.



Scheme 2. Proposed mechanism.

The mechanism for the conversion of alcohols into their corresponding alkyl chlorides using PPh_3/CCl_4 has been addressed.[5a,11] We considered that the reaction using PPh_3/Cl_3CCONH_2 should proceed similarly (Scheme 2). PPh_3 reacts with Cl_3CCONH_2 to give intermediate **3**, which then reacts with the alcohol to give alkoxyphosphonium salt **4**, which decomposes to give the alkyl chloride and triphenylphosphine oxide.

The effect of external nucleophiles such as NaCl, trimethylsilyl azide ($TMSN_3$) was also carefully examined.[12] Surprisingly, external chloride did not increase the % yield of the corresponding alkyl chloride. Similarly, the alkyl chloride was still the predominant product without concomitant formation of an alkyl azide when external azide was added. This strongly implies that the ion pair formed (**4**) is tightly bound such that it does not react with added nucleophiles.[5a,13]

In summary, we have described a very efficient and convenient method for the preparation of alkyl chlorides from alcohols using a combination of PPh_3 and Cl_3CCONH_2 as the reagent system.

A typical experimental procedure is as follows: to a stirred solution of alcohol (0.25 mmol) and PPh_3 (0.5 mmol) in dry CH_2Cl_2 (0.5 mL) was added Cl_3CCONH_2 (0.5 mmol) at rt (30 °C) under an N_2 atmosphere. After 15 min, the reaction was quenched with cold water and the presence of the corresponding product in the crude mixture was determined by ^1H NMR utilizing toluene as an internal standard or alternatively was isolated by purification through silica gel column chromatography.

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7. Only alkyl chloride and recovered alcohol were obtained from varying the halogenated reagent, PPh_3/Cl_3CCONH_2 ratio and reaction time.
8. (a) 2-Phenethyl chloride: ^1H NMR ($CDCl_3$): δ 7.20–7.25 (m, 5H), 3.63 (t, $J = 7.4$ Hz, 2H), 2.98 (t, $J = 7.4$ Hz, 2H). (b) 1-Octyl chloride: ^1H NMR ($CDCl_3$): δ 3.53 (t, $J = 6.7$ Hz, 2H), 1.77 (m, 2H), 1.20–1.48 (m, 10H), 0.89 (t, $J = 6.7$ Hz, 3H). (c) *S*-(+)-2-octyl chloride: ^1H NMR ($CDCl_3$): δ 4.01 (sex, $J = 6.5$ Hz, 1H), 1.69 (m, 2H), 1.28–1.50 (m, 11H), 0.89 (t, $J = 6.7$ Hz, 3H).
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10. The stereochemistry was determined by comparison with *S*-(+)-2-octyl chloride by HPLC using commercially available chiral columns (column cyclobond I 2000).
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12. Conditions: (a) alcohol (1 equiv), PPh_3 (1 equiv), Cl_3CCONH_2 (1 equiv) and NaCl (5 equiv) at rt (30 °C) or 40 °C, 1 h; (b) Alcohol (1 equiv), PPh_3 (2 equiv), Cl_3CCONH_2 (2 equiv) and $TMSN_3$ (1.5 equiv) at rt (30 °C) or 40 °C, 1 h.
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