

## Reactivity of chlorinating agents/ $\text{PPh}_3$ for the chlorination of alcohols and carboxylic acids: a comparative study

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**Abstract**—The reactivity of chlorinating agents was examined with the aid of  $^1\text{H}$  NMR using competitive reactions between selected chlorinating agents and  $\text{CBr}_4$  towards alcohols and carboxylic acids. The reactivity was greatly dependent on the type of substituent on the chlorinating agents.  $\text{COCCl}_3$  and CN substituted trichloromethyl groups enhanced the reactivity of the chlorinating agent with  $\text{PPh}_3$  for the chlorination of alcohols and carboxylic acids.

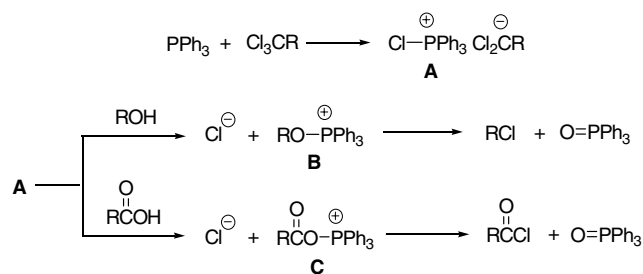
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Alkyl chlorides and acid chlorides are generally utilized as both synthetically useful intermediates and valuable end products in chemical industries and pharmaceutical science.<sup>1,2</sup> These compounds are prepared by the reaction of alcohols and carboxylic acids with common reagents such as  $\text{SOCl}_2$  and  $(\text{COCl})_2$ .<sup>3</sup> However, such protocols cannot be applied to acid-sensitive compounds due to the vigorous conditions and the formation of strong acid (HCl) during the process. One applicable method involves the use of  $\text{PPh}_3$  and a chlorinating agent ( $\text{Cl}_3\text{CR}$ ,  $\text{R} = \text{Cl}, \text{CCl}_3, \text{COCCl}_3, \text{CN}$  or  $\text{CONH}_2$ ).<sup>4–6</sup> These coupling reagents are important since the chlorination of alcohols and carboxylic acids could be performed efficiently under mild and acid-free conditions to afford the desired alkyl and acid chlorides in high to excellent yields.

The conversion of alcohols and carboxylic acids into the corresponding chlorides with various coupling reagents proceeded via a similar mechanism (Scheme 1).<sup>6,7</sup>  $\text{PPh}_3$  reacts with  $\text{Cl}_3\text{CR}$  to give an intermediate **A** which subsequently reacts with alcohols or carboxylic acids yielding an alkoxyphosphonium salt (**B** or **C**) which then transforms to the corresponding chlorides by  $\text{S}_{\text{N}}2$  displacement.

**Keywords:** Chlorinating agent;  $\text{PPh}_3$ ; Alcohol; Carboxylic acid.

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Scheme 1. General mechanism.

We have recently explored the effect of various chlorinating agents on the chlorination of alcohols and carboxylic acids and have also introduced  $\text{Cl}_3\text{CCONH}_2$  as another versatile chlorinating agent.<sup>6</sup> The difference in reactivity of these reagents under optimized conditions could be observed. For example, the chlorination of a carboxylic acid using  $\text{Cl}_3\text{CCN}/\text{PPh}_3$  smoothly proceeded at room temperature while  $\text{Cl}_3\text{CCONH}_2/\text{PPh}_3$  required reflux in  $\text{CH}_2\text{Cl}_2$ . In addition,  $\text{Cl}_3\text{CCN}$  was a more efficient reagent for the conversion of sulfonic acids to sulfonyl chlorides under the same conditions.<sup>8</sup> Presumably, the type of electron-withdrawing group on the chlorinating agents could affect the reactivity.

The reactivity of these reagents has nevertheless not yet been thoroughly examined. We report herein a relative

reactivity study of various chlorinating agents towards the chlorination of alcohols and carboxylic acids.

The reactivity of various chlorinating agents was investigated using a competitive reaction between a reference compound ( $\text{CBr}_4$ ) and various chlorinating agents towards 2-phenylethanol (Table 1). The reactivity of selected chlorinating agents was rationalized by the ratio of the yield obtained of 2-phenylethyl chloride (**1**) and 2-phenylethyl bromide (**2**).

The ratio of **1** and **2** was calculated by  $^1\text{H}$  NMR, utilizing toluene as an internal standard (Fig. 1). The

spectrum displayed two triplet signals for the halide substituted methylene protons at  $\delta_{\text{H}}$  3.62 and 3.47, respectively.

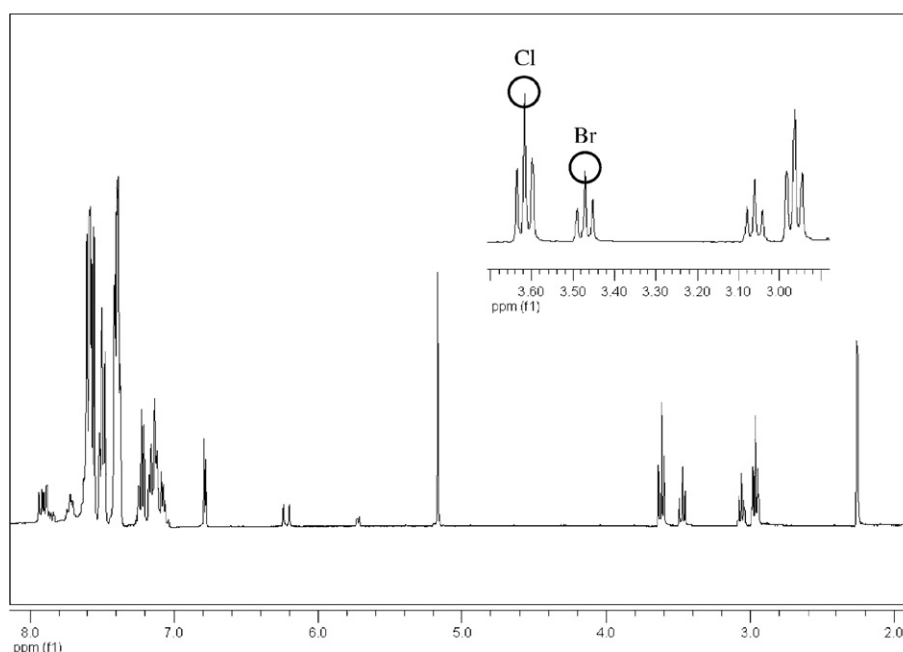
In the absence of chlorinating agent, **2** was obtained as the sole product in high yield (entry 1). No reactivity was observed when using chlorinating agents containing an alkyl group or another Cl atom ( $\text{CCl}_4$ ) on the  $\text{Cl}_3\text{C}$ -group under the specified conditions (entries 2–4). The reactivity of  $\text{Cl}_3\text{CCONH}_2$  was comparatively similar to those of  $\text{Cl}_3\text{CCCl}_3$ ,  $\text{Cl}_3\text{CCO}_2\text{Et}$ ,  $\text{Cl}_3\text{CCO}_2^i\text{Pr}$  and  $\text{Cl}_3\text{CCONHPh}$  (entries 5–9). On the other hand, both  $\text{Cl}_3\text{CCOCCl}_3$  and  $\text{Cl}_3\text{CCN}$ , bearing a strong electron-

**Table 1.** Reactivity comparison of chlorinating agents on the chlorination of 2-phenylethanol

Entry	Chlorinating agent	Yield <sup>a</sup> (%)		Ratio of 1/2	Reactivity <sup>b</sup>
		<b>1</b>	<b>2</b>		
1	None	0	69	—	—
2	$\text{CCl}_4$	0	70	—	—
3	$\text{Cl}_3\text{CCH}_2\text{OH}$	0	57	—	—
4	$\text{CH}_3\text{CO}_2\text{CH}_2\text{CCl}_3$	0	62	—	—
5	$\text{Cl}_3\text{CCCl}_3$	23	76	0.30	1.07
6	$\text{Cl}_3\text{CCO}_2\text{Et}$	26	73	0.36	1.29
7	$\text{Cl}_3\text{CCO}_2^i\text{Pr}$	27	73	0.37	1.32
8	$\text{Cl}_3\text{CCONH}_2$	21	76	0.28	1
9	$\text{Cl}_3\text{CCONHPh}$	14	70	0.20	0.71
10	$\text{Cl}_3\text{CCOCCl}_3$	70	24	2.92	10.43
11	$\text{Cl}_3\text{CCN}$	65	32	2.03	7.25

<sup>a</sup> The yield was determined based on  $^1\text{H}$  NMR integration.

<sup>b</sup> Based on  $\text{Cl}_3\text{CCONH}_2$ .



**Figure 1.**  $^1\text{H}$  NMR spectrum of **1** and **2** in the crude mixture from the competitive reaction between  $\text{Cl}_3\text{CCN}$  and  $\text{CBr}_4$ .

withdrawing group, showed significantly higher reactivity, 10.43- and 7.25-fold, over  $\text{Cl}_3\text{CCONH}_2$  (entries 10 and 11).

The prominent reactivity of  $\text{Cl}_3\text{CCOCCl}_3$  and  $\text{Cl}_3\text{CCN}$  was confirmed using another experiment (Table 2). Selected chlorinating agents coupled with  $\text{PPh}_3$  were allowed to react with 2-phenylethanol to produce **1** within 5 min. The mixture was then treated with  $\text{CBr}_4$  to transform the remaining alcohol into **2**. If the chlorinating agent selected was reactive, it would afford **1** in high yields before addition of  $\text{CBr}_4$  to yield **2**. Interestingly,  $\text{Cl}_3\text{CCOCCl}_3$  and  $\text{Cl}_3\text{CCN}$  could still produce **1** in high yields compared with  $\text{Cl}_3\text{CCONH}_2$  (entries 2–4). This clearly indicated that these reagents possessed high reactivity which was in good agreement with prior observations.

Furthermore, the reagents bearing electron-withdrawing groups were also investigated in a competitive reaction with diphenylacetic acid under the same conditions (Table 3). Similar levels of reactivity were observed in the cases of  $\text{Cl}_3\text{CCONH}_2$ ,  $\text{Cl}_3\text{CCCl}_3$  and  $\text{Cl}_3\text{CCO}_2\text{Et}$  being 1, 0.73 and 0.69, respectively (entries 2–4).

$\text{Cl}_3\text{CCOCCl}_3$  and  $\text{Cl}_3\text{CCN}$  still exhibited the highest levels of reactivity (entries 5 and 6).

It should be pointed out here that  $\text{Cl}_3\text{CCN}$  displayed higher reactivity than  $\text{Cl}_3\text{CCOCCl}_3$  in the case of diphenylacetic acid. On the other hand, in the case of 2-phenylethanol,  $\text{Cl}_3\text{CCOCCl}_3$  showed higher reactivity than  $\text{Cl}_3\text{CCN}$ .

Considering the reactivity of the chlorinating agents on the formation of alkyl chlorides and acid chlorides, chlorinating agents possessing strong electron-withdrawing groups such as  $\text{COCCl}_3$  and  $\text{CN}$  showed the highest reactivity. This postulation can be used as a fundamental concept for the development of new efficient chlorinating agents or as a guideline to optimize suitable conditions.

A typical experimental procedure is as follows: To a stirred solution of 2-phenylethanol or diphenylacetic acid (0.25 mmol) and a mixture of chlorinating agent (0.188 mmol) and  $\text{CBr}_4$  (0.188 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (0.5 mL) was added  $\text{PPh}_3$  (0.375 mmol) at rt under an  $\text{N}_2$  atmosphere. After 15 min, the amount of the

**Table 2.** Reactivity comparison of chlorinating agents on the chlorination of 2-phenylethanol

Entry	Chlorinating agent	Yield <sup>a</sup> (%)		Ratio of 1/2	Reactivity <sup>b</sup>
		1	2		
1	None	0	75	—	—
2	$\text{Cl}_3\text{CCONH}_2$	21	67	0.31	1
3	$\text{Cl}_3\text{CCOCCl}_3$	97	0	—	—
4	$\text{Cl}_3\text{CCN}$	76	22	3.45	11.13

<sup>a</sup> The yield was determined based on  $^1\text{H}$  NMR integration.

<sup>b</sup> Based on  $\text{Cl}_3\text{CCONH}_2$ .

**Table 3.** Reactivity comparison of chlorinating agents on the chlorination of diphenylacetic acid

Entry	Chlorinating agent	Yield <sup>a</sup> (%)		Ratio of 3/4	Reactivity <sup>b</sup>
		3	4		
1	None	0	82	—	—
2	$\text{Cl}_3\text{CCCl}_3$	50	49	1.02	0.73
3	$\text{Cl}_3\text{CCO}_2\text{Et}$	49	51	0.96	0.69
4	$\text{Cl}_3\text{CCONH}_2$	49	35	1.40	1
5	$\text{Cl}_3\text{CCOCCl}_3$	80	14	5.71	4.08
6	$\text{Cl}_3\text{CCN}$	Quant	0	—	—

<sup>a</sup> The yield was determined based on  $^1\text{H}$  NMR integration.

<sup>b</sup> Based on  $\text{Cl}_3\text{CCONH}_2$ .

corresponding products in the crude mixture was determined by  $^1\text{H}$  NMR using toluene as an internal standard.

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