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A practical chlorination of *tert*-butyl esters with PCl_3 generating acid chlorides

Xiaofang Wu, Lei Zhou, Ruoqi Yang, Fengzhe Guo, Zi-Long Tang and Jing Xiao

Abstract

For the first time, using PCl_3, a range of *tert*-butyl esters is chlorinated successfully, allowing access of both aromatic acid chlorides and aliphatic acid chlorides in good yields. The method features simple reaction conditions and wide substrate scope. Various *tert*-butyl esters including aryl esters, alkenyl esters, and alkyl esters were tolerated well in the reaction. A plausible mechanism is proposed.

Keywords

acid chlorides, chlorinating reagent, chlorination, phosphorus trichloride, *tert*-butyl esters

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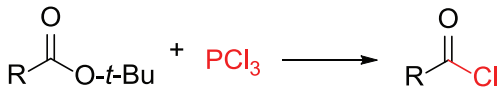


PCl_3 (0.667–1.0 equiv.) as chlorinating reagent
15 examples, up to 96% yield!

Introduction

Acid chlorides (RCOCl) are important intermediates in organic synthesis and are widely used in agricultural chemicals, medicines, dye industries, and so on.[1–4] RCOCls are commonly prepared from reactions of the corresponding carboxylic acids or anhydrides with chlorinating reagents such as oxalyl chloride,[5–7] thionyl chloride,[8–10] phosphorus oxychloride,[11] phosphorus pentachloride,[12,13] and triphosgene.[14] In addition to the above well-known methods for preparing acid chlorides from carboxylic acids, there are only a few literature reports on the conversion of other functional groups into acid chlorides directly.[15–18] Among them, a few examples of the conversion of *tert*-butyl esters into the corresponding acid chlorides were demonstrated.[19–22] However, the chlorinating reagent was limited to thionyl chloride and a large excess was required in the reaction. Therefore, the development of practical, green, and simple methods for the conversion of esters into acid chlorides is still desirable.

Phosphorus trichloride (PCl_3) is a cheap and readily available industrial chemical. Although one molecule of PCl_3 may provide three chlorine atoms for chlorination, there are few examples using PCl_3 for chlorination and most of them are limited to the conversion of carboxylic acids into acid chlorides.[23–26] We were interested in the potential of PCl_3 for the conversion of esters into the corresponding acid chlorides. Herein, we report a practical and simple method for the chlorination of *tert*-butyl esters with PCl_3, allowing access to various acid chlorides. Notably, good yields of the desired products could be obtained even when 0.667 equiv. of PCl_3 were used in gram-scale reactions.

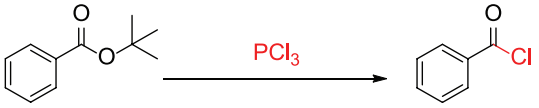
Results and discussion

We started this work with the reaction of *tert*-butyl benzoate (**1a**) with PCl_3. As shown in Table 1, an 86% yield of benzoyl chloride was generated at 80 °C under N_2 by mixing **1a** and PCl_3 for 3 h (entry 1). Delightfully, a 98% yield of **2a** was obtained when the mixture was stirred under air in a 25-mL sealed tube (entry 2). Further screening of the solvent did not improve the reaction efficiency (entries 3–5). Notably, the reaction also proceeded smoothly under

Key Laboratory of Theoretical Organic Chemistry and Functional Molecule of Ministry of Education, School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan, P.R. China

Corresponding author:
Jing Xiao, Key Laboratory of Theoretical Organic Chemistry and Functional Molecule of Ministry of Education, School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan 411201, P.R. China.
Email: XiaoJing@hnust.edu.cn

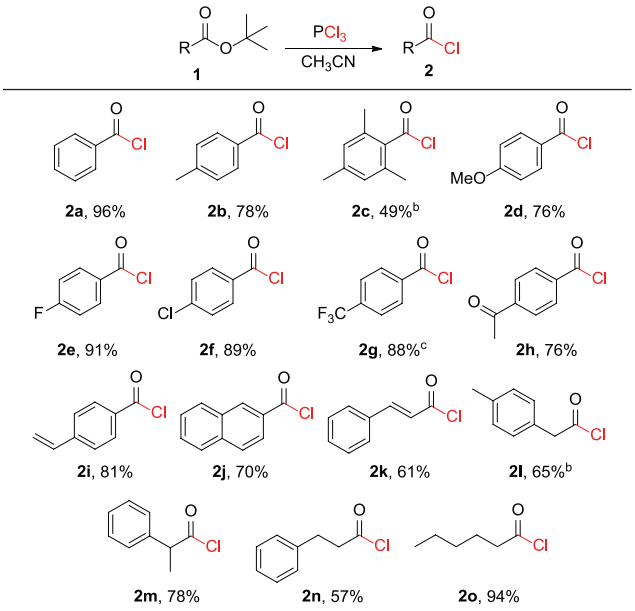
Table 1. Optimization of the reaction conditions.[a]



Entry	Conditions	Solvent	Yield[b]
1	N_2	CH_3CN	86%
2	**Air**	**CH_3CN**	**98%**
3	Air	THF	35%
4	Air	Toluene	75%
5	Air	$CHCl_3$	74%
6	Air	None	89%[c]
7	Air	CH_3CN	81%[d]
8	Air	CH_3CN	83%[e]

[a]Conditions: a mixture of **1a** (0.3 mmol) and PCl_3 (0.3 mmol) in solvent (0.6 mL) was stirred at 80 °C for 3 h.
[b]GC yield based on **1a** using dodecane as an internal standard.
[c]No solvent.
[d]0.667 equiv. of PCl_3 were used.
[e]10 mmol scale, 0.667 equiv. of PCl_3, CH_3CN (20 mL).
Bold: means the conditions listed in entry 2 is the optimum conditions.

Table 2. Reactions of *tert*-butyl esters with PCl_3.[a]

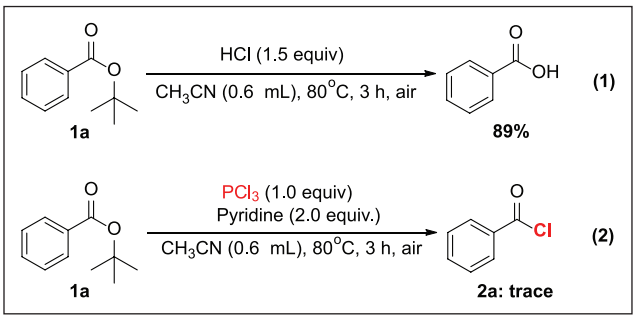


[a]Conditions: 1 (1.3 mmol), PCl_3 (1.3 mmol), CH_3CN (2.0 mL), 80 °C, 3 h. Isolated yields of the product were based on three parallel reactions.
[b]60 °C, 6 h.
[c]100 °C.

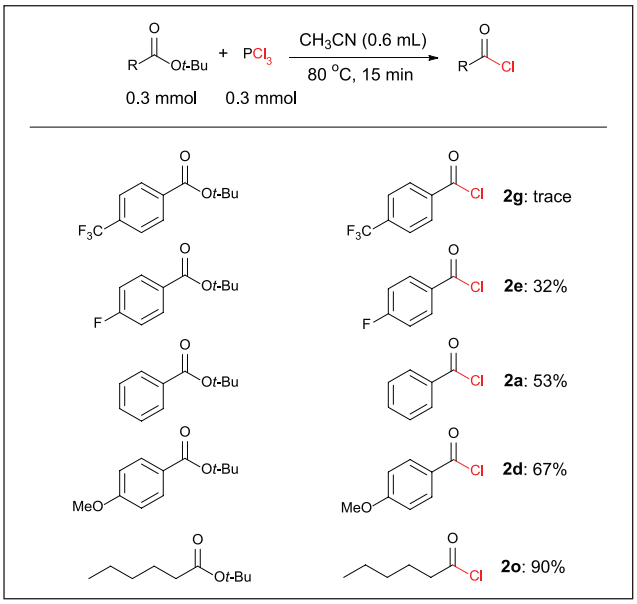
solvent-free conditions, albeit with a decreased yield (entry 6). Using 0.667 equiv. of PCl_3, the product was generated in 81% yield (entry 7), indicating that more than two Cl atoms from PCl_3 were utilized for the chlorination. In particular, when the reaction was scaled up to 10 mmol, an 83% yield of product was obtained even when 0.667 equiv. of PCl_3 was used in the reaction (entry 8).

With the optimum conditions identified, we next investigated the generality of this reaction. As shown in Table 2, various *tert*-butyl esters were efficiently chlorinated by PCl_3. Electron-rich aryl esters such as *tert*-butyl 4-methylbenzoate, *tert*-butyl 2,4,6-trimethylbenzoate, and *tert*-butyl 4-methoxybenzoate were compatible under the present reaction conditions, affording the corresponding acid chlorides (**2b–d**) in good-to-high yields. Esters with electron-withdrawing groups such as F, Cl, CF_3, and Ac on the benzene ring also reacted smoothly with PCl_3, giving the expected products **2e–h** in good yields. A substrate bearing a vinyl group was also applicable in this chlorination reaction, furnishing the desired product **2i** in 81% yield. The substrate scope was also extended to *tert*-butyl 2-naphthoate, and the expected product, 2-naphthoyl chloride (**2j**), was obtained in 70% yield under similar conditions. Moreover, *tert*-butyl cinnamate was tolerated well in this system to give product **2k**. Another remarkable feature of this reaction is the successful chlorination of alkyl esters. For example, *tert*-butyl benzylic esters **1l** and **1m** and simple alkyl *tert*-butyl esters **1n** and **1o** reacted with PCl_3 readily to afford the desired products in good-to-excellent yields. However, when methyl, isopropyl, phenyl, and benzyl benzoate were subjected to the reaction, only trace amounts of the desired products were detected by gas chromatography–mass spectrometry (GC-MS).

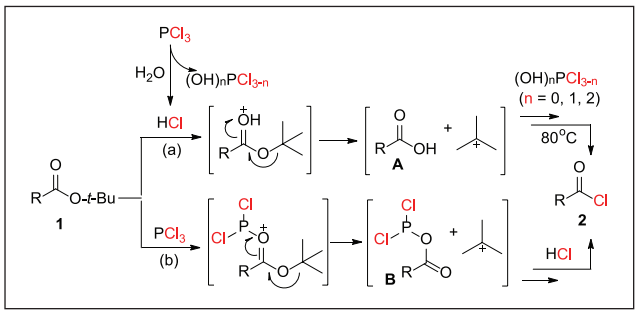
To evaluate the difference in reactivity between different *tert*-butyl esters, the reactions of alkyl and aryl esters bearing different substituents (CF_3, F, H, and MeO) with PCl_3 were conducted. As shown in Scheme 1, only a trace amount of product was detected when electron-deficient *tert*-butyl 4-(trifluoromethyl)benzoate and PCl_3 were stirred in CH_3CN (0.6 mL) at 80 °C for 15 min. *Tert*-butyl 4-fluorobenzoate reacted with PCl_3; however, the yield was low (32%) compared to that obtained using *tert*-butyl benzoate (53% yield). In contrast, compared with *tert*-butyl benzoate, electron-rich *tert*-butyl 4-methoxybenzoate gave the product **2d** in a higher yield (67%). Furthermore, *tert*-butyl hexanoate was chlorinated by PCl_3 successfully, furnishing the desired product in 90% yield. Thus, the reactivity of the benzoic esters follows an increasing order of $CF_3 < F < H < OMe$, that is, an electron-rich ester was more rapidly chlorinated by PCl_3 than an electron-deficient ester. In addition, it appears that alkyl esters have higher reactivity than aryl esters under this system.



To gain some insights into the reaction, two control experiments were performed. HCl (1.5 equiv.) was used instead of PCl_3 in the reaction and an 89% yield of PhCOOH was generated (equation 1). According to the literature,[27,28] an acid can react with PCl_3 to give the corresponding chloride. To confirm the critical role of HCl in the reaction, 2.0 equiv. of pyridine were added, with only a trace amount of product detected (equation 2). These results revealed that the



Scheme 1. Reactions of different *tert*-butyl esters with PCl_3.



Scheme 2. Plausible mechanism.

corresponding acid generated from the acidolysis of the ester with HCl was probably the intermediate in the reaction.

Based on the above results and previous literature reports,[19,27,28] we speculated that there are two paths for the reaction. As shown in Scheme 2, one pathway involves the protonation of **1** by HCl generated from the reaction of PCl_3 with H_2O present in air or solvent (path a). The other is the complexation of **1** with PCl_3 followed by elimination of a *tert*-butyl cation (path b). The intermediates **A** and **B** which are produced during these two processes can react with $(OH)_nPCl_{3-n}$ (n = 0, 1, 2) or HCl to afford acid chlorides **2**.

Conclusion

In summary, the conversion of various *tert*-butyl esters into acid chlorides was achieved using PCl_3 as the chlorinating reagent, providing a variety of acid chlorides in good-to-excellent yields. Unlike other methods using a large excess of the chlorinating reagent in the reaction, this approach features simple reaction conditions and no more than 1 equiv. of PCl_3 is used.

Experimental

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All reactions were performed in 25-mL glass Schlenk tubes carried out under an air atmosphere. Visualization on thin layer chromatography (TLC) was achieved using UV light (254 nm). ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AV-II 500-MHz NMR spectrometer (^{1}H: 500 MHz, ^{13}C: 125.76 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in ppm and referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$: 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). The coupling constants (*J*) are given in Hz. GC-MS was conducted on a Shimadzu GCMS-QP2010 plus equipped with an EI ion source. A FULI GC9790II instrument equipped with flame ionization detector (FID) was used to analysis the reaction mixture.

Typical procedure for the reaction of *tert*-butyl esters with PCl_3 (yield based on three parallel reactions): under air, the esters (1.3 mmol) and PCl_3 (1.3 mmol) were added to a 25-mL dried Schlenk tube, followed by CH_3CN (2.0 mL). The sealed tube was heated at 80 °C for 3 h. After the reaction mixture had been cooled to room temperature, evaporation of the solvent under vacuum and distillation of the residue under reduced pressure gave the analytically pure acid chloride.

Note that the yields listed below are based on three parallel reactions and each reaction was performed on 1.3 mmol scale. The mass of the product is the total mass for three parallel reactions.

Benzoyl chloride (2a): Colorless oil, yield 96% (3.74 mmol, 526 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 7.5 Hz, 2H), 7.73–7.70 (m, 1H), 7.56–7.53 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 168.5, 135.4, 133.2, 131.5, 129.0. GC-MS (EI, 70 eV): *m*/*z* = 140 (M^+).[29]

4-Methylbenzoyl chloride (2b): Light yellow oil, yield 78% (3.04 mmol, 470 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 168.0, 146.9, 131.6, 130.5, 129.7, 21.8. GC-MS (EI, 70 eV): *m*/*z* = 154 (M^+).[30]

2,4,6-Trimethylbenzoyl chloride (2c): Colorless oil, yield 49% (1.91 mmol, 349 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (s, 2H), 2.42 (s, 6H), 2.34 (s, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 170.7, 140.7, 136.3, 133.0, 128.6, 21.2, 19.4. GC-MS (EI, 70 eV): *m*/*z* = 182 (M^+).[31]

4-Methoxybenzoyl chloride (2d): White solid, yield 76% (2.96 mmol, 506 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10–8.08 (m, 2H), 6.99–6.97 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 167.2, 165.4, 134.0, 125.4, 114.3, 55.8. GC-MS (EI, 70 eV): *m*/*z* = 170 (M^+).[30]

4-Fluorobenzoyl chloride (2e): Colorless oil, yield 91% (3.55 mmol, 563 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19–8.16 (m, 2H), 7.24–7.20 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 167.1 (d, $J_{C\text{-}F}$ = 258.9 Hz), 167.1, 134.3 (d, $J_{C\text{-}F}$ = 9.9 Hz), 129.5, 116.3 (d, $J_{C\text{-}F}$ = 22.1 Hz). GC-MS (EI, 70 eV): *m*/*z* = 158 (M^+).[30]

4-Chlorobenzoyl chloride (2f): Colorless oil, yield 89% (3.47 mmol, 607 mg); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08–8.06 (m, 2H), 7.51–7.50 (m, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 167.4, 142.3, 132.6, 131.6, 129.4. GC-MS (EI, 70 eV): *m*/*z* = 175 (M^+).[30]

4-(Trifluoromethyl)benzoyl chloride (2g): Colorless oil, yield 88% (3.43 mmol, 716 mg); ^{1}H NMR (500 MHz,

$CDCl_3$): δ 8.27 (d, J=8.5 Hz, 2H), 7.82 (d, J=8.0 Hz, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 167.6, 136.5 (q, J_{C-F}=32.7 Hz), 136.2, 131.6, 126.1 (d, J_{C-F}=3.8 Hz), 123.2 (q, J_{C-F}=272.7 Hz). GC-MS (EI, 70 eV): m/z=208 (M^+).[32]

4-Acetylbenzoyl chloride (2h): White solid, yield 76% (2.96 mmol, 541 mg); ^1H NMR (500 MHz, $CDCl_3$): δ 8.15–8.13 (m, 2H), 8.00–7.99 (m, 2H), 2.60 (s, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 197.0, 167.9, 141.8, 136.5, 131.5, 128.6, 27.0. GC-MS (EI, 70 eV): m/z=182 (M^+).[30]

4-Vinylbenzoyl chloride (2i): Light yellow oil, yield 81% (3.16 mmol, 526 mg); ^1H NMR (500 MHz, $CDCl_3$): δ 8.02–8.01 (m, 2H), 7.47–7.46 (m, 2H), 6.77–6.71 (m, 1H), 5.93 (d, J=17.5 Hz, 1H), 5.49 (d, J=11.0 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 167.8, 144.4, 135.4, 131.9, 131.9, 126.6, 118.6. GC-MS (EI, 70 eV): m/z=166 (M^+).[33]

2-Naphthoyl chloride (2j): White solid, yield 70% (2.73 mmol, 520 mg); ^1H NMR (500 MHz, $CDCl_3$): δ 8.76 (s, 1H), 8.08–8.02 (m, 2H), 7.93 (d, J=8.5 Hz, 2H), 7.73–7.69 (m, 1H), 7.65–7.62 (m, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 168.5, 136.4, 134.8, 132.3, 130.4, 130.1, 129.9, 128.9, 127.9, 127.5, 125.3. GC-MS (EI, 70 eV): m/z=190 (M^+).[34]

Cinnamoyl chloride (2k): White solid, yield 61% (2.38 mmol, 396 mg); ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J=15.5 Hz, 1H), 7.61–7.59 (m, 2H), 7.53–7.45 (m, 3H), 6.68 (d, 16.0 Hz, 1H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 166.2, 150.8, 133.0, 132.1, 129.3, 129.1, 122.3. GC-MS (EI, 70 eV): m/z=166 (M^+).[35]

2-(p-Tolyl)acetyl chloride (2l): White oil, yield 65% (2.54 mmol, 427 mg); ^1H NMR (500 MHz, $CDCl_3$): δ 7.06–7.01 (m, 4H), 3.95 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 172.2, 138.1, 129.8, 129.5, 128.3, 52.8, 21.3. GC-MS (EI, 70 eV): m/z=168 (M^+).[36]

2-Phenylpropanoyl chloride (2m): Light yellow oil, yield 78% (3.04 mmol, 513 mg); ^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.42 (m, 2H), 7.40–7.37 (m, 1H), 7.35–7.33 (m, 2H), 4.17 (q, J=7.0 Hz, 1H), 1.64 (d, J=7.0 Hz, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 175.7, 137.5, 129.2, 128.3, 128.0, 57.5, 18.8. GC-MS (EI, 70 eV): m/z=168 (M^+).[37]

3-Phenylpropanoyl chloride (2n): Colorless oil, yield 57% (2.23 mmol, 375 mg); ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.35 (m, 2H), 7.31–7.28 (m, 1H), 7.26–7.24 (m, 2H), 3.26 (t, J=8.0 Hz, 2H), 3.06 (t, J=7.5 Hz, 2H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 173.1, 138.7, 128.8, 128.4, 126.9, 48.6, 31.0. GC-MS (EI, 70 eV): m/z=168 (M^+).[19]

Hexanoyl chloride (2o): Colorless oil, yield 94% (3.67 mmol, 493 mg); ^1H NMR (500 MHz, $CDCl_3$): δ 2.90 (t, J=7.5 Hz, 2H), 1.76–1.71 (m, 2H), 1.37–1.34 (m, 4H), 0.94–0.91 (m, 3H); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 173.9, 47.1, 30.5, 24.8, 22.2, 13.8. GC-MS (EI, 70 eV): m/z=134 (M^+).[38]

Declaration of conflicting interests

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ORCID iD

Jing Xiao https://orcid.org/0000-0002-7523-2303

Supplemental material

Supplemental material for this article is available online.

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