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One-step conversion of amides and esters to acid chlorides with PCl_3

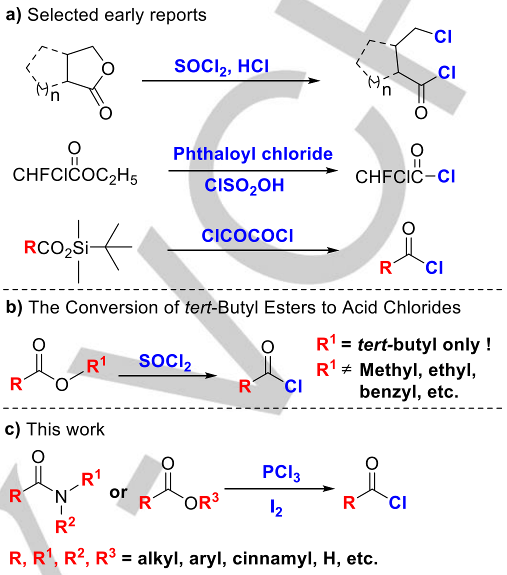
Fangshao Li, [§] Xiaofang Wu, [§] Fengzhe Guo, Zi-Long Tang and Jing Xiao*

Abstract: A general and efficient idine-promoted chlorination of amides and esters with phosphorus trichloride is described. For the first time, various inactivated amides including secondary and tertiary amides were directly converted to the corresponding acid chlorides in one-step. The substrate scope of methyl esters including aromatic and aliphatic esters was also explored under this system. This method is simple, scalable and wide in scope, which provides an approach to preparation of these acid chlorides.

Introduction

Acid chlorides are highly important intermediates in organic synthesis.[1, 2] They are generally synthesized by the reaction of carboxylic acids with chlorinating reagents such as thionyl chloride,[3] oxalyl chloride,[4] phosphorus oxychloride,[5] phosphorus pentachloride,[6] phosgene[7] and others.[1, 2] Apart from the chlorination of carboxylic acids, there are only few literatures reported for the direct conversion of other functional groups to aid chlorides. Early reports by the groups of Molander, Middleton and Wissner have shown that lactones,[8] ethyl chlorofluoroacetate[9] and *tert*-butyldimethylsilyl esters[10] could undergo this chlorination to afford acid chlorides (Scheme 1a). Recently, Sammakia group successfully demonstrated the chlorination of *tert*-butyl esters (Scheme 1b).[11] However, methyl esters are unreactive under the above systems. To the best of our knowledge, there is also no report on the direct conversion of amides to acid chlorides in one step. Thus, the development of a new, simple and practical approach for broadening the substrate scope of noncarboxylic acids is highly desirable.

Recently, we focused on the utilization of P-containing small molecules in the organic synthesis.[12] As part of our ongoing work, we are attracted by the conversion of noncarboxylic acid compounds to the acid chlorides with PCl_3 due to the potential of high chloride atom utilization in PCl_3. Herein, we report the direct conversion of various amides and esters to the corresponding acid chlorides with PCl_3 in one-step (Scheme 1c). This reaction is practical, easily scale-up and has a broad substrate scope, which provides an alternative method to synthesis of acid chlorides from noncarboxylic acid compounds.



Scheme 1. Direct conversion of esters and amides to acid chlorides.

Results and Discussion

We initiated our research on the direct chlorination of *N*, *N*-dimethylbenzamide. As demonstrated in Table 1, a mixture of *N*, *N*-dimethylbenzamide **1a** (0.3 mmol), PCl_3 (0.36 mmol) and DMF (0.6 mmol) was stirred in DCE (0.6 mL) at 100 °C for 22 h under air to afford benzoyl chloride in 57% yield (entry 1). Interestingly, when 10 mmol% molecular I_2 was added in the reaction, the product was generated in 98% yield (entry 2). Further reducing the amount of PCl_3 or I_2 did not improve the reaction efficiency (entries 3-5). A screening of solvents failed to show any improvement in the yield of **2a** (entries 6-9). We observed 93% yield of the product was generated when the reaction time was reduced to 12 hours (entry 10). Lowering the reaction temperature led to decrease the yield of **2a** (entry 11). It is known that DMF could react with PCl_3 to form the Vilsmeier−Haack reagent, which serves as the active chlorinating agent.[13a, 13b] However, it should be noted that the reaction also occurred in the absence of DMF, albeit with low yield (entry 12). A control experiment showed that, in the absence of I_2 and DMF, only trace of the product **2a** was formed (entry 13). These results indicated that molecular I_2 also plays an important role this reaction. We suspected that another active chlorinating agent adduct PCl_3I_2 was probably generated by the reaction of PCl_3 with I_2.[13c] Interestingly, control experiments showed that the proper amount of water is beneficial to the reaction (entries 14 and 15).

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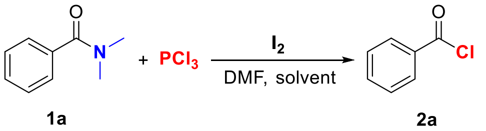
Table 1. Optimization of the reaction conditions.[a]

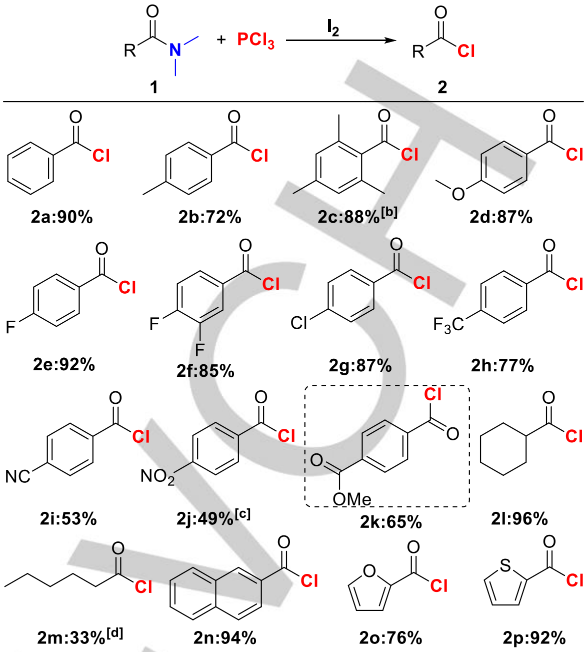


entry	PCl$_3$ (equiv.)	I$_2$ (equiv.)	Solvent (mL)	Yield[b]
1	1.2	0	DCE	57%
2	1.2	0.1	DCE	98%
3	1.0	0.1	DCE	95%
4	2/3	0.1	DCE	51%
5	1.0	0.05	DCE	81%
6	1.0	0.1	CH$_3$CN	65%
7	1.0	0.1	toluene	71%
8	1.0	0.1	hexane	47%
9	1.0	0.1	PhCl	82%
10	**1.0**	**0.1**	**DCE**	**93%**[c]
11	1.0	0.1	DCE	77%[d]
12	1.0	0.1	DCE	23%[e]
13	1.0	0	DCE	Trace[e]
14	1.0	0.1	DCE	69%[f]
15	1.0	0.1	DCE	83%[f,g]

[a] Reaction conditions: A mixture of **1a** (0.3 mmol), PCl$_3$, DMF (0.6 mmol) in solvent (0.6 mL) was stirred in a sealed tube with air at 100 °C for 22 hours; [b]GC yield based on **1a** using *n*-dodecane as an internal standard. [c]12 hours. [d]80 °C. [e]No DMF was used. [f]Dried DCE and DMF were used under N$_2$. [g] H$_2$O (0.3 mmol) was added.

With the established procedure in hand, the scope of amides was investigated. As shown in Table 2, various amides bearing whether electron-rich groups or electron-deficient groups such as methyl, methoxy, halogen, CF$_3$ and CN groups proceeded efficiently with PCl$_3$ in one-step to give the corresponding products in good to excellent yields (**2a**-**2i**). To our delight, substrate bearing a strong electron-withdrawing group NO$_2$ was also well chlorinated (**2j**). Notably, when methyl 4-(dimethylcarbamoyl)benzoate was subjected to the reaction, the ester group remained intact, affording the corresponding product in 65% yield (**2k**). This result indicated that amides are more easily chlorinated than esters by PCl$_3$ under this system. Moreover, alkyl amides such as *N*, *N*-dimethylcyclohexanecarboxamide and *N*, *N*-dimethylhexanamide were also formed the corresponding products in 96% and 33% yield, respectively (**2l** and **2m**). *N*, *N*-dimethyl-2-naphthamide proceeded readily to afford acid chloride in 94% yield (**2n**). It should be noted that heterocyclic amides such as *N*, *N*-dimethylfuran-2-carboxamide and *N*, *N*-dimethylthiophene-2-carboxamide exhibited good reactivity, furnishing the products in 76% and 92%, respectively (**2o** and **2p**).

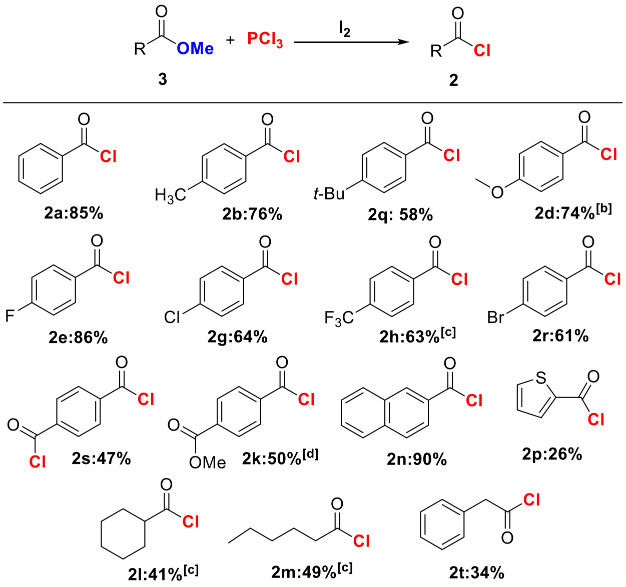
Table 2. Substrate scope of chlorination of amides.[a]



[a] Reaction conditions: A mixture of **1** (1.3 mmol), PCl$_3$ (1.3 mmol), I$_2$ (0.13 mmol), DMF (2.6 mmol) in DCE (2.0 mL) was stirred at 100 °C for 12 hours under air; Isolated yields were based on three parallel reactions. [b]DMF (1.3 mmol), 160 °C for 36 h. [c]I$_2$ (0.26 mmol) was used. [d]No DMF was used and PCl$_3$ (1.0 mmol) were used.

Encouraged by the above results, we explored the possibility of chlorination of methyl esters. As demonstrated in Table 3, the use of methyl benzoate afforded the corresponding acid chloride in 85% yield (**2a**). Various methyl esters bearing whether electron-donating or electron-withdrawing substituents such as methyl, *tert*-butyl, methoxy, fluorine, chlorine, trifluoromethyl, bromine and formyl chloride groups were chlorinated smoothly to give the desired products in good yields (**2b**, **2d**-**2h** and **2q**-**2s**). Delightfully, when dimethyl terephthalate was subjected to the reaction, monochlorination could be achieved selectively under the slightly modified conditions (**2k**). Moreover, methyl 2-naphthoate was also well tolerated in this system (**2n**). Notably,

Table 3. Substrate scope of chlorination of methyl esters.[a]

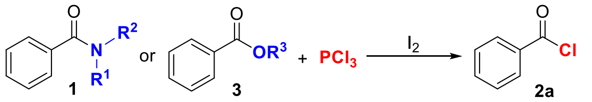


[a] Reaction conditions: A mixture of **3** (1.3 mmol), PCl$_3$ (1.3 mmol) and I$_2$ (0.26 mmol) was stirred in a sealed tube at 160 °C for 48 hours. [b]PhCl (0.6 mL). [c]I$_2$ (0.52 mmol) were used. [d]PCl$_3$ (2.6 mmol) were used.

thiophene-derived ester could also be introduced, albeit in lower yield (**2p**). Employing different alkyl esters such as methyl cyclohexanecarboxylate, methyl hexanoate and methyl 2-phenylacetate in the reaction all gave modest yields (**2l, 2m** and **2t**). With respect to the low yields of these aliphatic clusters, we attributed to the remaining starting materials (14%-50%) in the reaction and the decomposition in high temperature due to the less table of aliphatic acid chlorides.

To examine the generality of this reaction, we subjected different amides and esters to this system. As shown in Table 4, secondary or tertiary amides could be directly converted to the corresponding acid chlorides in good to excellent yields (entries 1-4). However, only trace of product was generated when *N*, *N*-diphenylbenzamide was used (entry 5). On the other hand, in addition to methyl esters, phenyl, benzyl, *n*-hexyl, cinnamyl, *n*-hexyl and cyclohexyl esters all provided the desired product **2a** in good to excellent yields under the similar conditions (entries 6-10). These results indicated that this method could be a useful approach for the conversion of amides and esters to the corresponding acid chlorides.

Table 4. Substrate scope with different amides and esters.[a]



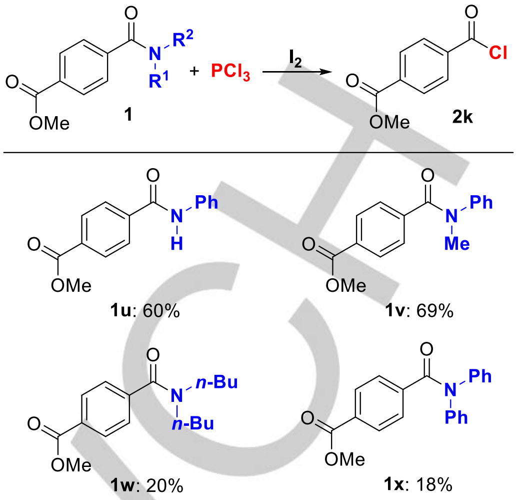
Entry	R^1 =	R^2 =	Yield	Entry	R^3 =	Yield[b]
1	H	Ph	91%	6	Ph	94%
2	Me	Ph	85%	7	Bn	83%
3	Me	Cy	79%	8	Cinnamyl	62%
4	*n*-Bu	*n*-Bu	67%	9	*n*-hexyl	30%
5	Ph	Ph	trace	10	Cy	52%[c]

[a] Reaction conditions: A mixture of **1** (1.3 mmol), PCl_3 (1.3 mmol), I_2 (0.13 mmol), DMF (2.6 mmol) in DCE (2.0 mL) was stirred at 100 °C for 12 hours under air. [b]A mixture of **3** (1.3 mmol), PCl_3 (1.3 mmol) and I_2 (0.26 mmol) was stirred at 160 °C for 48 hours under air. [c]130 °C.

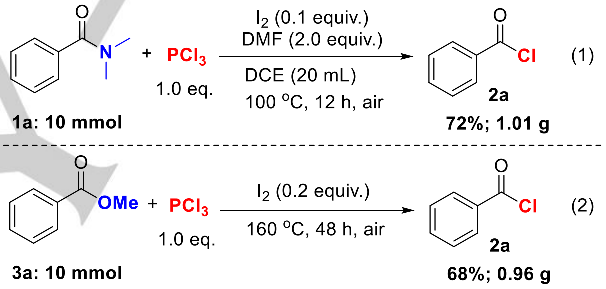
To further explore the difference in reactivity between amides and esters, four different amides bearing methyl ester group were examined under this system. As shown in Table 5, good yields of **2k** were obtained when methyl 4-(phenylcarbamoyl)benzoate (**1u**) and methyl 4-(methyl(phenyl)carbamoyl)benzoate (**1v**) were used in this system. However, more sterically hindered methyl 4-(dibutylcarbamoyl)benzoate (**1w)** and methyl 4-(diphenylcarbamoyl)benzoate (**1x)** gave the corresponding products in 20% and 18% yields, respectively. Interestingly, a large number of starting materials were recovered, and the methyl ester group remained intact in these reactions. Therefore, it is reasonable to conclude that amides are more reactive than esters under this system. It appears that the steric effect of amides affects this chlorination reaction.

To probe the scaling possibilities, we conducted two gram-scale reactions. As shown in Scheme 2, a mixture of *N*, *N*-dimethylbenzamide **1a** (10.0 mmol), PCl_3 (10.0 mmol), I_2 (1.0 mmol) and DMF (20.0 mmol) was stirred in CH_3CN (20 mL) at 100 °C for 12 hours under air in a 100 mL sealed Schlenk tube. As anticipated, 72% (1.01 g) yield of product **2a** was generated (equation 1). Under the solvent-free condition, the chlorination of methyl benzoate **3a** underwent smoothly to afford the product in 68% yield (equation 2).

Table 5. Reactions of different amides with PCl_3.[a]

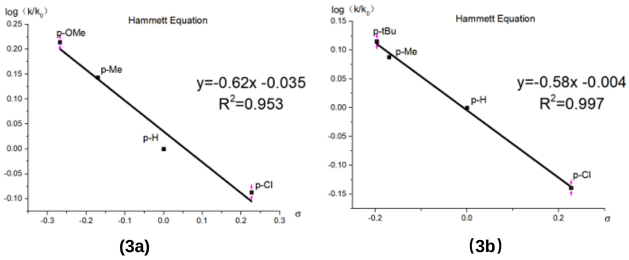


[a] Reaction conditions: A mixture of **1** (0.3 mmol), PCl_3 (0.3 mmol), I_2 (0.03 mmol), DMF (0.6 mmol) in DCE (0.6 mL) was stirred at 100 °C for 12 hours under air.



Scheme 2. Scale-up reactions.

For further understanding of this reaction, we established two Hammett equations by using different amides and esters. Pleasingly, two linear relationships between different electron-rich and electron-deficient groups were found independently in the chlorination of *p*-substituted *N*, *N*-dimethylbenzamide (Scheme **3a**) and methyl benzoate derivatives (Scheme **3b**). Both Hammett equations are linear with negative slope, which suggested that the electron-rich groups accelerated the process. The reason for this phenomenon may be attributed to the high reactivity of forming the corresponding carboxylic acid from electron-rich amides and esters.



(3a) (3b)

Scheme 3. Hammett equations.

Conclusions

In conclusion, we have successfully developed an iodine-promoted direct conversion of inactivated amides and esters to valuable acid chlorides in one-step. By using PCl_3/I_2 system, a variety of substrates including aliphatic and aromatic amides and esters could react with PCl_3 to afford the corresponding products in good yields. This protocol features of practical, simple and easily scaled-up, providing not only a direct way for the preparation of acid chlorides, but also insights for transformation of amides and esters under metal-free conditions.

Experimental Section

Typical procedure for the chlorination of amides: Under air, a mixture of amides **1** (1.3 mmol), PCl_3, I_2 and DMF in DCE (2.0 mL) was stirred in a 25 mL closed sealed tube in oil bath at indicated temperature for indicated time. After the mixture was cooled down to the room temperature, the solvent was evaporated under vacuum and distillation of the residue under reduced pressure gave analytically pure acid chlorides **2**.

Typical procedure for the chlorination of esters: Under air, a mixture of esters **3** (1.3 mmol), PCl_3 and I_2 was stirred in a 25 mL closed sealed tube in oil bath at indicated temperature for indicated time. After the mixture was cooled down to the room temperature, the solvent was evaporated under vacuum and distillation of the residue under reduced pressure gave analytically pure acid chlorides **2**.

Acknowledgments ((optional))

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Keywords: phosphorus trichloride • chlorination• acid chlorides • esters • amides

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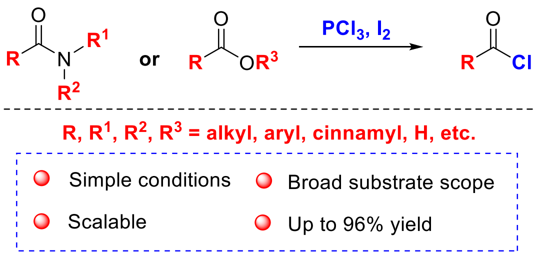

Key Topic*

*Fangshao Li, § Xiaofang Wu, § Fengzhe Guo, Zi-Long Tang and Jing Xiao**

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One-step conversion of amides and esters to acid chlorides with PCl_3

A general and efficient iodine-promoted chlorination of amides and esters with phosphorus trichloride is described. For the first time, various inactivated amides including secondary and tertiary amides were directly converted to the corresponding acid chlorides in one-step. The substrate scope of methyl esters including aromatic and aliphatic esters was also explored under this system. This method is simple, scalable and wide in scope, which provides an approach to preparation of these acid chlorides.