Thionyl Chloride-Benzotriazole in Methylene Chloride: A Convenient Solution for Conversion of Alcohols and Carboxylic Acids Expeditiously into Alkyl Chlorides and Acid Chlorides by Simple Titration

Sachin S. Chaudhari, Krishnacharya G. Akamanchi*

Pharmaceuticals and Fine Chemicals Division, Department of Chemical Technology, University of Mumbai, Matunga, Mumbai-400 019, India

Fax (91)22 414 5614, E-mail: kga@udct.ernet.in

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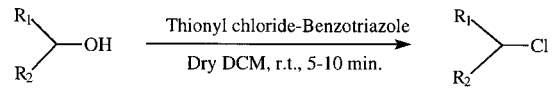
Abstract: A solution of 1:1 equivalent of thionyl chloride and benzotriazole in dry methylene chloride efficiently transforms alcohols and carboxylic acids into the corresponding alkyl chlorides and acid chlorides respectively at room temperature, with excellent yields by simple titration.

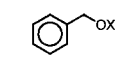
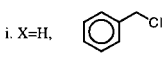
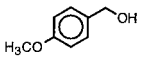
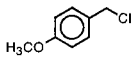
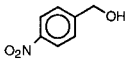
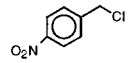
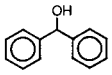
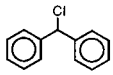
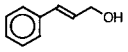
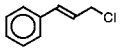
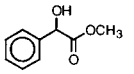
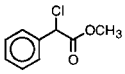
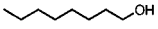
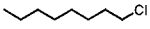
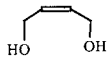
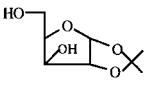
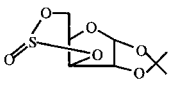
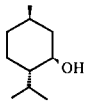
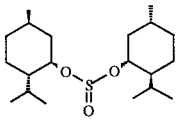
Key words: benzotriazole, thionyl chloride, chlorination, alcohols, carboxylic acids

Transformation of alcohols and carboxylic acids to the corresponding alkyl chlorides[1] and acid chlorides[2] respectively are two of the basic functional group transformations in organic synthesis. A plethora of reagents and systems with varying generality are available for these transformations. Commonly used classical reagents are thionyl chloride,[3a] phosphorous trichloride[3b] and phosphorous pentachloride.[3c] These are used as such or in combination with a base. Though these transformations are routine ones, newer systems continue to be developed as reflected by the recent reports where TMSCl / DMSO,[4a] CCl_4 / Cu / Fe / $CuBr(Phen)_2$,[4b] TMSCl / $K_2Cr_2O_4$,[4c] TPP / dichloroselenurate,[4d] trichloroisocyanuric acid / TPP[4e] were used for the conversion of alcohols to alkyl chlorides and trichloroacetonitrile / TPP[4f] was used for the conversion of carboxylic acids to acid chlorides. The present letter describes an alternative and cost effective system.

Thionyl chloride can be used alone[2e,3a] or in combination with bases such as pyridine[2f, 3d] and triethylamine.[5] However, the reactions are invariably slow and often require reflux temperature. There are some modifications to overcome these difficulties e.g. use of DMF.[2b] Recently, we have reported an efficient transformation of aldoximes to the corresponding nitriles at room temperature, in high yields using thionyl chloride-benzotriazole combination.[6] We have further explored this combination for the chlorination of alcohols and carboxylic acids. The exploitable features of benzotriazole are that it is a mild base as well as acid which leaves options to use either acid or alkali wash for its ready removal from the reaction mixture. It is a solid and water insoluble, nonodoriferous and more importantly it is a good leaving group. These are some advantages over commonly used bases like triethylamine and pyridine. Moreover, benzotriazole (1 mol) dissolves readily in thionyl chloride (1 mol) at room temperature giving a clear viscous solution, the dissolution is slightly

Table 1 Conversion of Alcohols into Alkyl Chlorides and Sulfites[a]



Entry	Alcohol	Product	Yield (%)[b,c]
1.	 X= H, SiMe3	 i. X=H, ii. X= SiMe3, ---NR[d]	95 ---
2.			100
3.			94
4.			100
5.			100
6.			90
7.			90
8.			91
9.			92
10.			88
11.			88
12.			94[e]
			100[f]
13.			96
14.			100

[a] All reactions were carried out by following general procedure. [b] Yields refer to pure isolated product. [c] Structures are confirmed by IR, ^{1}H-NMR, mp/bp. [d] NR --- No Reaction. [e] 2.5 mole of reagent was used. [f] 1.2 mole of reagent was used.

endothermic.[7] This solution can be readily diluted with dry DCM and the stock solution of known concentration can be prepared for use whenever needed.

The reactions were performed by following the general procedure.[8] The required amount of reagent (1.25 mmol equivalent) was added directly from the burette to a solution of substrate (1 mmol) in dry DCM with stirring. The reaction was fast and before the addition was complete benzotriazole hydrochloride started separating out as a solid indicating the progress of the reaction.

Under the reaction conditions primary, (Table 1, entries 1 and 10) secondary, (Table 1, entries 4 and 9) and tertiary alcohols (Table 1, entry 11) were converted into their corresponding alkyl chlorides efficiently. Substrates carrying electron donating (Table 1, entry 2) and electron withdrawing groups (Table 1, entry 3) had practically no effect on the overall transformation. Sensitive alcohols such as furfuryl alcohol, (Table 1, entry 7) tetrahydrofurfuryl alcohol (Table 1, entry 8) and α,β-unsaturated alcohol (Table 1, entry 5) were transformed into the corresponding chlorides without any difficulties. It is noteworthy that acid sensitive methoxy group, (Table 1, entry 2) and acetonide group (Table 1, entry 13) were compatible under the reaction conditions employed. As expected, alcohols protected as trimethyl silyl ether (Table 1, entry 1-ii) were recovered completely unaffected.

In the case of butene-1,4-diol a 2.5 mole equivalent of the reagent gave 1,4-dichlorobutane and 1.2 mole equivalent gave cyclic sulfite. Cyclic sulfite was formed while attempting selective chlorination in 1,2-isopropylidene xylofuranoside (Table 1, entry 13). Reaction with (-)-menthol ended in formation of dimenthyl sulfite[9] instead of menthyl chloride (Table 1, entry 14).

Varieties of carboxylic acids like aromatic, aliphatic, and α,β-unsaturated such as cinnamic acid were transformed into acid chlorides rapidly without any difficulties (Table 2). The crude products obtained were sufficiently pure and can be directly used in the next step without further purifications. Amides can also be converted into the corresponding nitriles using this combination, but the yields are poor even after the use of 5 equivalent of the reagent combination.

In conclusion, the new reaction system described here offers a quick, convenient, and inexpensive alternative to other methods for the synthesis of alkyl chlorides and acid chlorides. In addition, the transformation using reactive thionyl chloride-benzotriazole combination in methylene chloride can be carried out simply by titration at room temperature in high yields, which may have wide synthetic applicabilty.

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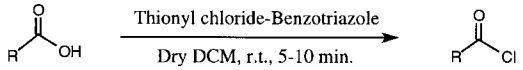
Table 2 Conversion of Carboxylic Acids into Acid Chlorides[a]



Entry	R	Yields (%)[b,c]
1.	C_6H_5	100
2.	p-$NO_2C_6H_4$	94
3.	p-ClC_6H_4	95
4.	o-IC_6H_4	92
5.	p-$OCH_3C_6H_4$	94
6.	p-$CH_3C_6H_4$	92
7.	C_6H_5-CH=CH-	90
8.	C_6H_5-CH_2-	90
9.	C_6H_5-CO-$(CH_2)_2$-	91
10.	C_6H_5-CO-	90
11.	CH_3-$(CH_2)_6$-	92

[a] All reactions were carried out by following general procedure. [b] Yields refer to the isolated product. [c] Structures are confirmed by IR, ^{1}H-NMR and mp/bp.

References and Notes

(1) a) Lee, J. B.; Nolan, T. J. *Can. J. Chem*. **1966**, *44*, 1331; b) Yoshihara, M.; Eda, T.; Sakaki, K.; Maeshima, T. *Synthesis* **1980**, 746; c) Itoh, H.; Saito, T.; Oshima, K.; Nozaki, J. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 1456; d) Hwang, C. K.; Li, W. S.; Nicolaou, K. C. *Tetrahedron Lett.* **1984**, *25*, 2295; e) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc*. **1985**, *107*, 3285; f) Blame, G.; Gore, J.; Fournet, G. *Tetrahedron Lett*. **1986**, *27*, 1907; g) Camps, F.; Gasol, V.; Guerrero, A. *Synthesis* **1987**, 511; h) Lee, J. G.; Kang, K. K. *J. Org. Chem*. **1988**, *53*, 3634; i) Ioe, E. M.; Jones, C. J. *Polyhedron* **1992**, *11*, 3123.

(2) a) Ottenheijm, H. C. J.; DE Man, J. H. M. *Synthesis* **1975**, 163; b) Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta*. **1959**, *42*, 1653; c) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett*. **1979**, *32*, 3037; d) Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L.; Panunzio, M. *Synthesis* **1983**, 306 and references cited therein; e) Hwang, Y. C.; Fowler, F. W. *J. Org. Chem*. **1985**, *50*, 2719; f) Wolfe, S.; Godfrey, J. C.; Holdrege, C. T.; Perron, Y. G. *Can. J. Chem*. **1968**, *46*, 2549; g) Masuhika, F.; Hitoshi, N. JP 92,117,344, 1992; *Chem. Abstr*. **1992**, *117*, 150719q.

(3) a) Brown, G. W., In *The Chemistry of the Hydroxyl Group*, Patai, S., Ed.; Interscience; London, **1971**, Part 1, pp. 592-622; b) Newkome, G. R.; Theriot, K. J.; Majestic, V. K.; Spruell, P. A.; Baker, G. R. *J. Org. Chem*. **1990**, *55*, 2838; c) Ansell, M. F., In *The Chemistry of Acyl Halides*, Patai, S.; Ed.; Interscience; London, **1972**, Chapter 2, pp. 35-68; d) Ward, A. M. *OSC*, **1943**, *2*, 159.

(4) a) Snyder, D. C. *J. Org. Chem.* **1995**, *60*, 2638; b) Leonel, E.; Paugam, J. P.; Nedelec, J. Y. *J. Org. Chem*. **1997**, *62*, 7061; c) Dong Soo, H.; Hyeung Ae, K. *Bull. Korean Chem. Soc.* **1998**, *19*, 1303; d) Drabowicz, J.; Luczak, J.; Mikolajczyk, M. *J. Org. Chem*. **1998**, *63*, 9565; e) Hiegel, G. A.; Ramirez, J.; Barr, R. K. *Synth. Commun*. **1999**, *29*, 1415; f) Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323.

(5) a) See reference 1a; b) Darzenes, G. *Compt. Rend*. **1911**, *152*, 1601.

(6) Chaudhari, S. S.; Akamanchi, K. G. *Synth. Commun*. **1999,** *29*, 1741.
(7) Bases such as pyridine, triethylamine, and imidazole react exothermically / violently with thionyl chloride at room temperature unlike benzotriazole, where dissolution is slightly endothermic
(8) **General procedure:** A stock solution (1.5 M) was prepared by making up volume of a viscous clear solution of thionyl chloride (5.46 mL, 0.075 mol) and benzotriazole (8.93 g, 0.075 mol) with dry DCM up to 50 mL and transferred to 50 mL graduated burette. Reaction was carried out by adding the stock solution (1.25 mmol equivalent) intermittantly from the burette to a stirred solution of alcohol (1 mmol) or carboxylic acid (1 mmol) in dry DCM (20 mL). Before the addition is complete, benzotriazole hydrochloride started separating out as a solid. Reaction mixture was swirled or stirred further for 5-10 min. At the end solid was filtered off.[10] In case of alkyl chlorides, the filtrate was washed with water (25 mL) followed by 2% NaOH solution (25 mL). The organic layer was separated and passed through anhydrous sodium sulfate. Removal of solvent gave crude product that can be directly used. It was further purified by column chromatography (15% EA/Hexane). In case of acid chlorides, the filtrate was stirred with $MgSO_4.7H_2O$ (~ 0.5 g) to destroy excess reagent. The solids were filtered off. The filtrate can be used as such or the acid chloride can be recovered by removal of solvent.
(9) a) Rebiere, F.; Samual, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991.
b) Dimenthyl sulfite, White crystalline solid, mp: 49-50°C (Lit.[9a] m.p.: 49°C), $[\alpha]_D$: -59 (c = 1, $CHCl_3$) (Lit.[9a] $[\alpha]_D$: -60), ^1H NMR (60 MHz, $CDCl_3$): δ 0.8-2.1 (m, 36H), 4.3 (m, 2H, -OCH=).
(10) Benzotriazole was recovered as follows: To a cooled solution of benzotriazole hydrochloride salt in water was added gradually a cold solution of 2% NaOH till pH was just neutral and precipitated benzotriazole was filtered off and dried. It was sufficiently pure (mp. 98°C) and can be reused.

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