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Chlorination of Aliphatic Primary Alcohols via Triphosgene–Triethylamine Activation

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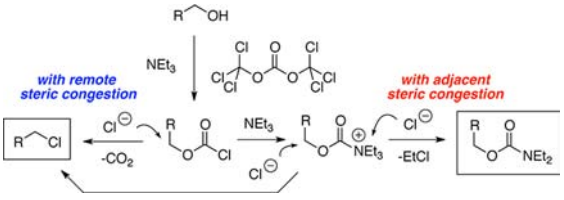
ABSTRACT



Activation of primary aliphatic alcohols with triphosgene and triethylamine mixtures afforded either alkyl chloride or diethylcarbamate products, and the switch in selectivity appeared to be driven by sterics. The reaction conditions to achieve this highly useful transformation were unexceptionally mild and readily tolerated by a wide range of sensitive functionalities.

Alkyl chlorides are ubiquitous in organic chemistry. More than 2000 chlorine-containing natural products have been identified; many of which display potent biological activity of various kinds.[1] There are numerous synthetic, chlorine-containing small-molecule examples with industrial, agricultural, and pharmaceutical applications.[2] In addition, alkyl chlorides are important synthons in synthetic chemistry and have been used to achieve innumerable synthetic transformations.[3] As a result of this widespread interest and utility, research in synthetic method development for installation of C–Cl bonds remains an important topic.[4]

Driven by our synthetic interests in chlorine-containing natural products, we recently explored a mild method for chemoselective chlorination of primary aliphatic alcohols in the presence of nearby ionizable functionalities, such as 1,3-diol **1a**. As shown in Table 1, preliminary studies involving treatment of this diol with classical chlorination reagents, such as $SOCl_2$ and PCl_5, only produced complex mixtures. Further attempts using PPh_3-CCl_4 or PPh_3-triphosgene activation indeed led to chlorination at the primary alcohol and afforded chloroalcohol **2a** in modest yield; however, these reactions were hampered by tedious removal of the triphenylphosphine-derived byproducts. Surprisingly, exposure of **1a** with triphosgene in the presence of triethylamine led to the *rapid and clean* production of the target product **2a** in quantitative yield (entry 5). Similarly, treatment of **1a** with commercially purchased phosgene solution and triethylamine also produced **2a** in an excellent yield (entry 6). In both cases, chlorination was selective for the primary position, leaving the nearby tertiary alcohol intact. Interestingly, chlorination did not

[†] X-ray crystallography graduate student participant.

(1) (a) Shibuya, G. M.; Kanady, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514–12518. (b) Gribble., G. W. *Prog. Chem. Org. Nat. Prod.* **2010**, *91*, 1–613.

(2) (a) Rossberg, M.; Lendle, W.; Pfleiderer, G.; Tögel, A.; Dreher, E.-L.; Langer, E.; Rassaerts, H.; Kleinschmidt, P.; Strack, H.; Cook, R.; Beck, U.; Lipper, K.-A.; Torkelson, T. R.; Löser, E.; Beutel, K. K.; Mann, T. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2006. (b) Naumann, K. "How Chlorine in Molecules Affects Biological Activity." Science Dossier, November 2003. www.eurochlor.org (accessed on April 24, 2012).

(3) (a) Jana, R.; Pathak, T. P.; Sigman., M. S. *Chem. Rev.* **2011**, *111*, 1417–1492. (b) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745–777.

(4) Examples of recent efforts in diastereoselective chlorination en route to chlorosulfolipid natural product syntheses: (a) Bedke, D. K.; Vanderwal, C. D. *Nat. Prod. Rep.* **2011**, *28*, 15–25. (b) Yoshimitsu, T.; Fukumoto, N.; Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696–702. (c) Yoshimitsu, T.; Fujumoto, N.; Nakatani, R.; Kojima, N.; Tanaka, T. *J. Org. Chem.* **2010**, *75*, 5425–5437. (d) Nilewski, C.; Geisser, R. W.; Carreira, E. M. *Nature* **2009**, *457*, 573–576. (e) Bedke, D. K.; Shibuya, G. M.; Pereira, A.; Gerwick, W. H.; Haines, T. H.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 7570–7572. (f) Bedke, D. K.; Shibuya, G. M.; Pereira, A. R.; Gerwick, W. H.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2010**, *132*, 2542–2543.

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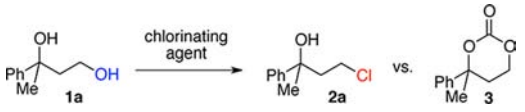
take place when pyridine or Hünig's base was used as a substitute for triethylamine. Instead, the reaction produced cyclic carbonate **3**.[5]

Table 1. Optimization Study



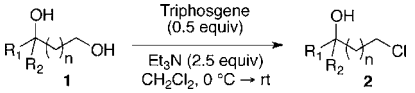
entry	chlorinating agents	yield in **2**[a]	yield in **3**[a]
1	$SOCl_2$	complex mixture	--
2	PCl_5	complex mixture	--
3	CCl_4, PPh_3	30%	--
4	Triphosgene, PPh_3	78%	--
5	Triphosgene, TEA	98%	--
6	Phosgene, TEA	89%	--
7	Triphosgene, Py	--	86%
8	Triphosgene, DIPEA	--	45%

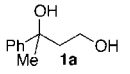
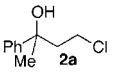
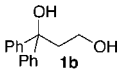
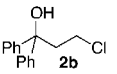
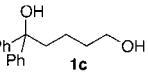
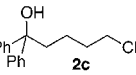
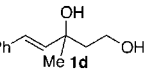
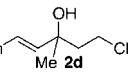
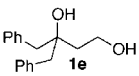
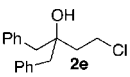
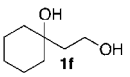
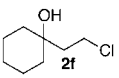
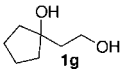
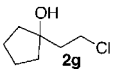
[a] Yield based on product isolated by flash chromatography.

Triphosgene, $(Cl_3CO)_2C{=}O$, is a relatively safe substitute for notoriously toxic phosgene gas. It exists as a stable nonhygrosopic crystalline material at rt, and its handling and storage do not demand meticulously anhydrous conditions, thus making it very convenient for typical laboratory scale operations.[6] This reagent has been used to achieve various functional group interconversions, particularly the insertion of the carbonyl moiety.[7] The use of triphosgene in chlorination reactions is also known. There is ample precedent for the conversion of reactive (i.e., benzylic, propargylic, and allylic) alcohols to the corresponding chlorides via triphosgene activation in pyridine-buffered organic media.[8] Chlorination of simple aliphatic alcohols, however, requires stronger activation, most notably through the use of a nucleophilic promoter, such as triphenylphosphine that facilitates triphosgene decomposition and promotes the ensuing chlorination.[9] Due to the unexpected propensity of triphosgene and triethylamine mixtures to chlorinate diol **1a**, we believed this unexplored reaction warranted further investigation on its scope and limitations.

As shown in Table 2, exposure of a number of diols (**1a**–**1g**), each bearing a primary and a tertiary alcohol, to triphosgene–triethylamine resulted in chemoselective chlorination at the primary alcohol, and the chloroalcohol products **2a**–**2g** were obtained in excellent yields. Our typical chlorination reaction employed 0.5 equiv of triphosgene and 2.5 equiv of triethylamine per equivalent of

Table 2. Chemoselective Chlorination of Aliphatic Primary Alcohol vs Tertiary Alcohol



entry	starting material[a]	product	yield[b]
1			98% 98%[c]
2			92%
3			89%
4			85%
5			97%
6			93%
7			96%

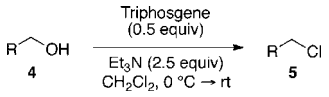
[a] Diols **1a** and **1d** are racemic. [b] Yield based on product isolated by flash chromatography. [c] Performed under nonanhydrous conditions.

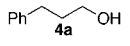
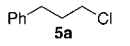
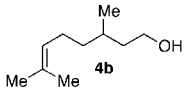
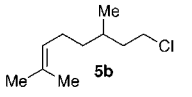
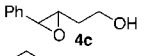
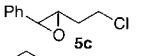
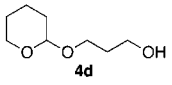
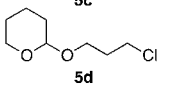
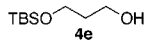
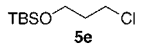
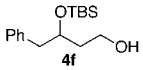
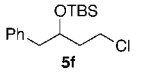
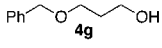
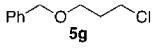
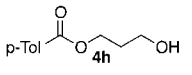
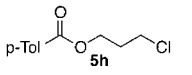
the participating hydroxy group. The activation was performed in dichloromethane at 0 °C, and the mixture was subsequently warmed to ambient temperature.[10] While these reactions were performed under anhydrous conditions, we found that chlorination under less rigorous conditions was equally effective (entry 1). As indicated in entries 2 and 3, the distance between the two hydroxy groups appeared to have no effect on the chlorination reaction, and the structural identity of the resulting chloroalcohols **2b** and **2c** was unambiguously confirmed through X-ray crystallography.[11] Entries 1–4 further demonstrate that highly ionizable tertiary alcohols (**1a**–**1d**) are stable, thus underscoring the mild nature of the reaction conditions.

To further probe the compatibility of our chlorination conditions with common functional and protecting groups, we strategically chose the substrates in Table 3. Aliphatic alcohols **4a** and **4b** gave the corresponding alkyl chlorides in good yields,[12] demonstrating tolerance for alkene and aromatic functionality (entries 1–2). Likewise, the highly ionizable epoxide **4c** was a suitable substrate.

(5) Burk, R. M.; Roof, M. B. *Tetrahedron Lett.* **1993**, *34*, 395–398.
(6) (a) Eckert, H.; Foster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894–895. (b) Damle, S. B. *Chem. Eng. News* **1993**, *71*, 4. (c) Cotarca, L. *Org. Process Res. Dev.* **1999**, *3*, 377.
(7) Roestamadji, J.; Mobashery, S.; Banerjee, A. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: 2006, and references therein.
(8) Goren, Z.; Heeg, M. J.; Mobashery, S. *J. Org. Chem.* **1991**, *56*, 7186–7188.
(9) (a) Avdagic, A.; Gelo-Pujic, M.; Sunjic, V. *Synthesis* **1995**, *11*, 1427–1431. (b) Portada, T.; Roje, M.; Raza, Z.; Caplar, V.; Zinic, M.; Sunjic, V. *Eur. J. Org. Chem.* **2007**, *5*, 838–856. (c) Wells, A. *Synth. Commun.* **1994**, *24*, 1715–1719.
(10) In typical cases, the starting material was fully consumed within minutes; however, for generality, our protocol called for an additional 3 h of stirring to ensure completion prior to aqueous workup. See Supporting Information (SI) for a detailed experimental protocol.
(11) CCDC 879959 (compound **2b**) and 879960 (compound **2c**) contain the supplementary crystallographic data for this paper, which can be obtained free of charge via www.ccdc.cam.ac.uk/ data_request/ cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033. See SI.
(12) The relatively lower yield was attributed to the high volatility of the resulting alkyl chloride product.

Table 3. Functional Group Compatibility



entry	starting material[a]	product	yield[b,c,d]
1	 **4a**	 **5a**	82%
2	 **4b**	 **5b**	67%
3	 **4c**	 **5c**	87%
4	 **4d**	 **5d**	65%
5	 **4e**	 **5e**	78%
6	 **4f**	 **5f**	81%
7	 **4g**	 **5g**	84%
8	 **4h**	 **5h**	98%

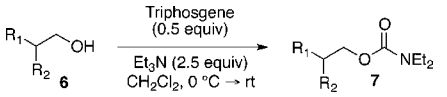
[a] Alcohols **4b**, **4c**, **4d**, and **4f** are racemic. [b] Yield based on product isolated by flash chromatography. [c] Lower yields attributed to the volatility of the alkyl chloride. [d] Minor (< 10%) diethylcarbamate byproduct was detected by GC-MS or crude NMR in some cases.

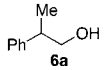
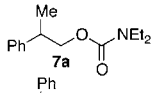
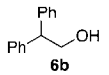
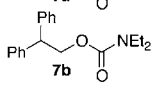
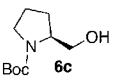
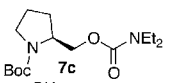
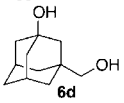
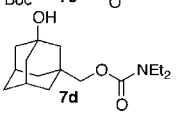
Substrates containing acid sensitive protecting groups such as THP and TBS ethers (**4d**–**4f**) were readily converted to chlorides **5d**–**5f** without complications (entries 4–6).[12] As expected, benzyl ether **4g** and aryl ester **4h** were also found to be compatible functionalities (entries 7–8). When attempts were made to activate substrates containing branching at the α-carbon, in relation to the primary alcohol, the reaction surprisingly produced diethylcarbamate adducts (Table 4),[13,14] and chlorination did not occur. For example, 2-phenyl-propanol **6a** and 2,2-diphenylethanol **6b** yielded diethylcarbamates **7a** and **7b** respectively in good yield. *N*-Boc-prolinol **6c** and adamantyl diol **6d** also provided their corresponding **7c** and **7d**.

(13) Dealkylation of tertiary benzylamines with triphosgene has been previously observed: (a) Lemoucheux, L.; Rouden, J.; Ibazizene, M.; Sobrio, F.; Lasne, M.-C. *J. Org. Chem.* **2003**, *68*, 7289–7297 and references therein. (b) Banwell, M. G.; Coster, M. J.; Harvey, M. J.; Moraes, J. *J. Org. Chem.* **2003**, *68*, 613–616. (c) Igarashi, J.; Kobayashi, Y. *Tetrahedron Lett.* **2005**, *46*, 6381–6384.

(14) Ajaykumar, A. S.; Puranik, V. G.; Deshmukh, A. R. A. S. *Synthesis* **2007**, *8*, 1159–1164. Deshmukh and co-workers attempted similar triphosgene-TEA chlorination in THF at −20°C using α-branched a diaminoalcohol as a crude dihydrochloride salt (en route to their formal synthesis of (+)-biotin) to give the corresponding chloride in modest yield. Interestingly, when pure **6c** was treated under these conditions, the reaction predominantly produced diethylcarbamate **7c** and the chlorination product was not observed. We hypothesized that perhaps the rate of chloride substitution in Deshmukh's chemistry was tremendously amplified by the excess residual chloride ions obtained upon evaporation of the 20% HCl/MeOH deprotection solution which was employed to remove the *N*-Boc precursor.

Table 4. Reactivity Patterns with α-Branched Alcohols



entry	starting material[a]	product	yield[b]
1	 **6a**	 **7a**	62%
2	 **6b**	 **7b**	85%
3	 **6c**	 **7c**	73%
4	 **6d**	 **7d**	62%

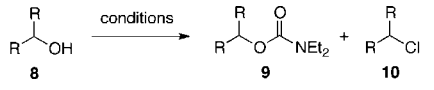
[a] Alcohol **6a** is racemic. [b] Yield based on product isolated by flash chromatography.

Having established the relative reactivity of primary and tertiary alcohols, we inevitably examined the reactivity patterns of secondary alcohols. As a starting point, 1,3-diphenylpropan-2-ol **8a** was exposed to the standard reaction conditions, resulting in a mixture of diethylcarbamate **9a** (40%) and secondary chloride **10a** (50%) (Table 5). Treatment of diol **8b** also produced a mixture of chlorodiethylcarbamate **9b** and alkyl dichloride **10b**. The product ratio interestingly favored the latter. We suspected that a higher concentration of chloride ion, a result of doubling the equivalent of triphosgene–triethylamine, might have played a role in favoring chloride substitution at the secondary alcohol position.[15a] Not surprisingly, diol-containing reactive benzylic secondary alcohol **8c** exclusively afforded dichloride **10c**. In contrast, secondary alcohols containing α-branching, such as **8d**, proved rather deviant. We initially assumed that this diol would favor formation of diethylcarbamate at the secondary alcohol, following a reactivity pattern observed in Table 4 due to the somewhat sterically congested center. Instead, a mixture of products, predominantly **9d** and **10d**, were obtained in a ratio that similarly favored the dichloride product. As shown in entry 5, chlorination of enantiomerically pure alcohol **8e** resulted in a mixture of optically active diethylcarbamate **9e** and secondary chloride **10e** with a complete inversion of the parent stereogenic center.[15b] This result strongly suggested stereospecificity of this chloride substitution reaction, which most likely proceeded via an S_N2 pathway.

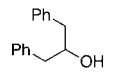
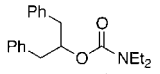
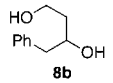
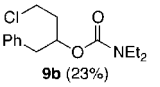
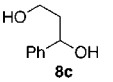
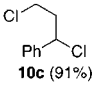
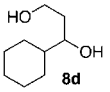
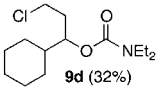
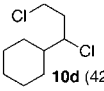
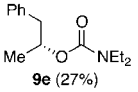
A mechanistic explanation for our experimental observations is proposed in Scheme 1.[16,17] Activation of a

(15) (a) A further mechanistic investigation concerning chlorination of secondary alcohols is currently ongoing and will be reported in due course. (b) $[\alpha]_{25}^{D}$ of **10e** = +23.05 (*c* = 8.5 in $CHCl_3$); literature: $[\alpha]_{25}^{D}$ = +23.19 (*c* = 5 in $CHCl_3$) for enantiomerically pure (*S*)-(2-chloropropyl)benzene. Masuda, S.; Nakajima, T.; Suga, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1086.

Table 5. Reactivity Patterns with Secondary Alcohol



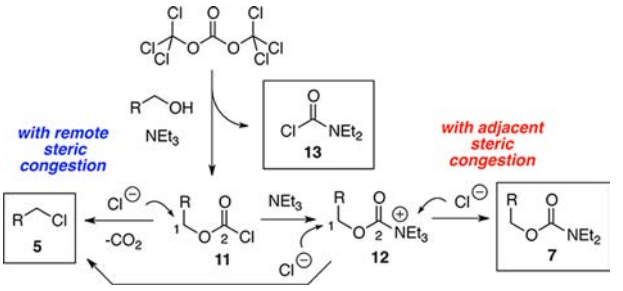
Cond. A: triphosgene (0.5 equiv), Et_3N (2.5 equiv), CH_2Cl_2, 0 °C → rt
Cond. B: triphosgene (1.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 0 °C → rt

entry	cond.	starting material[a]	product(s) (yield[b,c])		
1	A	 **8a**	 **9a** (40%)	 **10a** (50%)
2	B	 **8b**	 **9b** (23%)	 **10b** (69%)
3	B	 **8c**		 **10c** (91%)
4	B	 **8d**	 **9d** (32%)	 **10d** (42%)
5	A	 **8e**	 **9e** (27%)	 **10e** (45%)

[a] Alcohols **8b**–**8d** are racemic. [b] Yield based on product isolated by flash chromatography. [c] Lower yields attributed to the volatility of the alkyl chloride.

primary alcohol with triphosgene and triethylamine initially generates chloroformate **11**.[7,16a] In the absence of α-branching, the *in situ* generated chloride ion then rapidly attacks at the C1 carbon to provide alkyl chloride **5** by extruding CO_2 and another equivalent of chloride ion. However, steric hindrance imposed by α-branching significantly reduces the rate of substitution by chloride. The addition of triethylamine to the acyl carbon becomes competitive and produces the putative acylammonium ion intermediate **12**. An ethyl group is then lost rapidly via nucleophilic attack by a chloride ion to produce the observed diethylcarbamate **7**.[13,16b] The use of amine bases other than triethylamine (viz. pyridine and Hünig's base) did not lead to chlorination.[7,17a,b] This might be taken as support for the intermediacy of **12** en route to alkyl chloride **5**,[16b] and an alternative mechanism involving C1 substitution by a chloride ion on this intermediate cannot be disregarded. Another noteworthy observation is that the byproduct of this chlorination reaction is diethylcarbamoyl chloride **13** which is most likely produced upon consumption of excess phosgenic species with triethylamine.[17c] The role of this species in affecting direct alcohol carbamoylation to diethylcarbamate **7** was readily ruled out.[17b]

Scheme 1. Proposed Mechanism



In summary, we have reported our findings in relation to the previously underexplored activation of aliphatic primary alcohols with triphosgene and triethylamine. The propensity for chlorination vs diethylcarbamoylation is influenced by steric demands at the carbon adjacent to the reactive center. The versatility and chemoselectivity exhibited by this incredibly mild and operationally simple chlorination method will appeal to the general synthetic community, and it should favorably complement the existing repertoire of reagents for this useful and important transformation. Applications of the method, including the construction of pertinent motifs for chlorine-rich natural products and other alkyl halides, are ongoing in our laboratories.

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Supporting Information Available. Full experimental and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) (a) The intermediacy of chloroformate species **11** was readily observed by GC-MS of the reaction mixture by simply modulating the amount of triethylamine introduced in the reaction mixture. See SI. (b) Acylammonium ion **12** was not detected by GC-MS and pressumed short-lived, if it existed.

(17) (a) Alcohol **4a** did not react with triphosgene in the absence of triethylamine. (b) Addition of alcohol **4a** to a premixed solution of triphosgene and triethylamine did not produce any reactions. See SI. (c) The presence of diethylcarbamoyl chloride **13** was readily detected by both GC-MS and NMR of the crude reaction mixtures.