J|A|C|S COMMUNICATIONS

Published on Web 09/10/2009

Aromatic Cation Activation of Alcohols: Conversion to Alkyl Chlorides Using Dichlorodiphenylcyclopropene

Brendan D. Kelly and Tristan H. Lambert*

Department of Chemistry, Columbia University, New York, New York 10027

Received August 2, 2009; E-mail: tl2240@columbia.edu

Nucleophilic substitution of alcohols is a concept of broad utility in organic synthesis.[1] Because of the poor leaving-group potential of hydroxide ion, however, an alcohol must typically be converted to a more activated functionality before nucleophilic substitution is feasible. The most widely used strategies to accomplish this goal include protonation;[2] conversion to sulfonate, sulfite, or phosphite esters;[1] or Mitsunobu inversion (via phosphonium ethers).[3] While such strategies have long been a mainstay of organic synthesis, there exists a strong need for the development of alternative approaches to address issues of reactivity, scope, and the use or generation of undesirable reagents or byproducts (e.g., DEAD, Ph_3PO).

In this regard, we have become interested in a novel strategy for the promotion of dehydration reactions based on aromatic cation activation. Aromatic cations are unique molecules that possess the dual properties of aromatic stability and ionic charge.[4] This duality imparts to these carbocycles the facile ability to shuttle between charged and neutral states via reversible association with an anion or a heteroatom lone pair (Figure 1). In fact, many aromatic cations are stable even in aqueous solution, undergoing reversible hydrolysis at solution pH as high as 10.[5] Such facile equilibrium processes suggest intriguing possibilities for the development of novel reaction methods, particularly those involving dehydrative mechanisms.

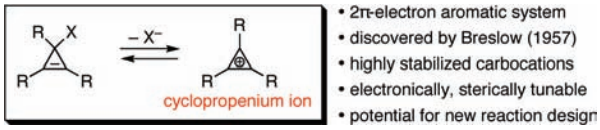


Figure 1. Cyclopropenium ions.

The quintessential class of aromatic cations are the cyclopropenium ions, the first example of which was prepared by Breslow in 1957.[6] Extensive subsequent investigations by Breslow and others revealed much about the unusual properties of this remarkable class of molecules.[4] Inspired by the unique reactivity profile of cyclopropenium ions, we reasoned that activation of alcohols toward nucleophilic displacement should be possible via the following mechanistic design (Figure 2): A cyclopropene **1** with two geminal substituents (X) may exist in equilibrium with cyclopropenium salt **2**. Addition of an alcohol substrate to **2** would produce cyclopropenyl ether **3**, which would be especially prone to reionization via dissociation of the remaining X group. As a cationic ether, the resultant alkoxycyclopropenium ion **4** should then be highly activated toward nucleophilic substitution to furnish the product **5** along with cyclopropenone **6**.[7] Importantly, this strategy would represent a paradigmatic advance for alcohol activation by making use of a simple, sterically and electronically tunable carbon moiety as the dehydrating agent, as opposed to the sulfur- or phosphorus-based reagents typically employed for such purposes.

To implement this strategy, we decided to examine the conversion of alcohols to alkyl chlorides using a 3,3-dichlorocyclopropene.

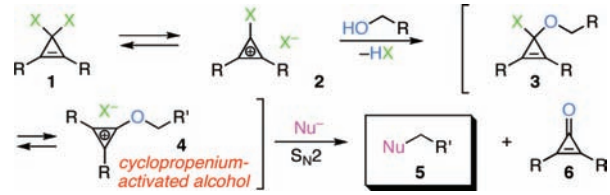
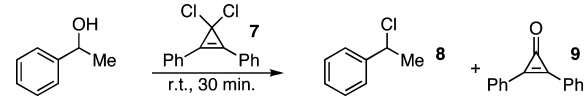


Figure 2. Mechanistic design for alcohol activation by cyclopropenium ion.

In this case, chloride ion would represent both the X groups and the nucleophile in our mechanistic design. We were gratified to find that treatment of 1-phenylethanol with 1.5 equiv of readily available 3,3-dichloro-1,2-diphenylcyclopropene[8] **7** in acetonitrile at room temperature (r.t.) resulted in the formation of (1-chloroethyl)benzene (**8**) in 73% yield along with 1,2-diphenylcyclopropenone **9** (Table 1, entry 1). Screening of solvents revealed that although this conversion also occurred in DMSO, acetone, THF, toluene, and DCE, these media were inferior in terms of reaction efficiency (entries 2−6). On the other hand, CH_2Cl_2 proved to be a very effective solvent, furnishing the product in 91% yield (entry 7). Notably, an identical yield was obtained using only 1.1 equiv of **7** (entry 8). While all of the reactions in Table 1 were run for 30 min in the interest of uniformity, the reaction in entry 8 was complete in only 10 min. Finally, although HCl is generated during this process, treatment of 1-phenylethanol with 1.5 equiv of HCl in CH_2Cl_2 did not produce appreciable amounts of the chloride adduct (entry 9), supporting the notion that a cyclopropenium intermediate is in fact responsible for activation (also see Figure 3).

We examined the scope of this method of alkyl chloride synthesis and found it to be quite general (Table 2). Thus benzyl, cinnamyl, and geranyl alcohols were found to undergo rapid and efficient conversion to the corresponding chlorides by treatment with 1.1 equiv of **7** in CH_2Cl_2 at r.t. (entries 1−3). Interestingly, a *cis*-allylic

Table 1. Optimization Studies for Alkyl Chloride Formation[a]



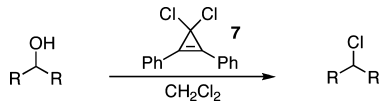
entry	solvent	equiv of **7**	additive (equiv)		% yield of **8**
1	CH_3CN	1.5	–		73
2	DMSO	1.5	–		49
3	acetone	1.5	–		30
4	THF	1.5	–		51
5	toluene	1.5	–		52
6	DCE	1.5	–		71
7	CH_2Cl_2	1.5	–		91
8	**CH_2Cl_2**	**1.1**	–	***10 min***	**91**
9	CH_2Cl_2	–	HCl (1.5)		~5

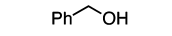
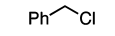
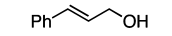
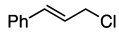
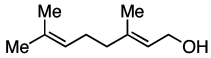
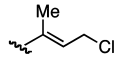
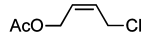
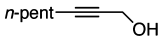
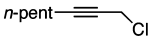
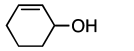
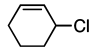
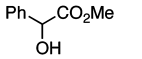
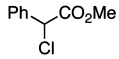
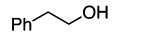
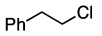
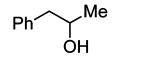
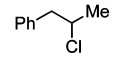
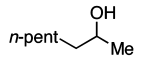
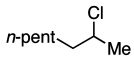
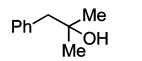
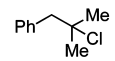
[a] Yields determined by ^1H NMR analysis using Bn_2O as an internal standard.

10.1021/ja906520p CCC: $40.75

alcohol substrate reacted efficiently with no observed olefin isomerization (entry 4). In addition, 2-octyn-1-ol led cleanly to the corresponding propargylic chloride without formation of allenic product (entry 5). Activated secondary alcohols proved to be viable substrates as well, with both cyclohexenol and methyl mandelate serving as efficient participants (entries 6 and 7). Most notably, unactivated substrates could also be employed. Thus, for example, 2-phenylethanol led to the production of (2-chloroethyl)benzene in 15 min (entry 8). Unactivated secondary alcohols were found to undergo efficient conversion, although higher reaction temperatures (80 °C, CH_3CN) were required in these cases (entries 9 and 10). Finally, a tertiary alcohol substrate was investigated and found to lead to the tertiary chloride in modest yield (45%) along with 33% β,β-dimethylstyrene (entry 11).

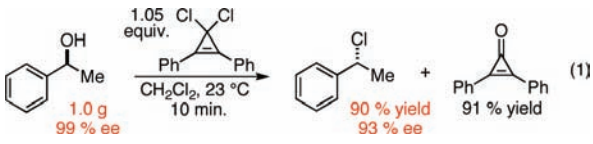
Table 2. Substrate Scope Studies for Alkyl Chloride Formation[a,b]



Entry	Substrate	Product	temp. (°C)	time (min.)	% yield
1			23	10	81
2			23	3	92
3			23	5	95
4			23	5	84
5			23	5	92
6			23	10	88[c]
7			23	65	93
8			23	15	89
9			80[d]	20	95
10			80[d]	30	93[c]
11			23	40	45[c,e]

[a] Reactions were performed by the addition of **7** to a solution of the alcohol in CH_2Cl_2. For entries 1−6, 1.1 equiv of **7** was added. For entries 7−11, 1.5 equiv of **7** was added. [b] Yields were determined on isolated and purified products, unless otherwise noted. [c] Yield was determined by ^{1}H NMR analysis. [d] Reactions were perfomed in CH_3CN. [e] The β,β-dimethylstyrene yield was 33%.

To further demonstrate the utility of this method, we performed the conversion of 1-phenylethanol to (1-chloroethyl)benzene on a 1.0 g scale (eq 1): The yield of this transformation was 90%, and



1,2-diphenylcyclopropenone was readily recovered in approximately the same yield. Most interestingly, the chloride product was obtained with an enantiomeric excess of 93% (starting material 99% ee), demonstrating that substitution occurred primarily via the S_N2 pathway. Notably, other more traditional methods of chlorination often proceed with retention ($SOCl_2$) or with poor stereoselectivity (MsCl).[9]

Finally, as further support for the claim that substitution occurs by way of a cyclopropenium-activated intermediate, we used ^{1}H NMR spectroscopy to monitor the reaction of 2-phenylethanol (**10**) in CD_3CN, a solvent in which the reaction is relatively slow. When alcohol and **7** were mixed, the two starting-material methylene triplet peaks immediately disappeared, and two new triplets took their place (Figure 3). We attribute these new peaks to cyclopropenium ion **11**. Notably, the oxygen-bearing methylene was shifted downfield to δ 5.47, which is consistent with an alkoxycyclopropenium prepared by Breslow via an alternative method.[10] Over the course of the reaction, these new peaks decreased in intensity and were replaced by the two methylene triplets of the chloride product **12**.

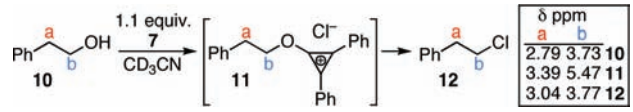


Figure 3. Chemical shifts of the alkoxycyclopropenium intermediate.

In conclusion, this work offers a convenient and efficient method for converting alcohols to alkyl chlorides based on a novel paradigm for the promotion of substitution reactions. Importantly, we have also found aromatic cation activation to be effective for a broad range of dehydration manifolds. The results of these studies will be disclosed shortly.

Acknowledgment. We are grateful to the Turro Group for generous use of their GC and Arun Sundaresan for his assistance.

Supporting Information Available: Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 6, Chapter 1.1−1.9, pp 1−284.
(2) For recent examples, see: (a) Motokura, K.; Nakagiri, N.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* **2007**, *72*, 6006. (b) Sanz, R.; Martínez, A.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Eur. J. Org. Chem.* **2006**, 1383.
(3) (a) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (b) Mitsunobu, O. *Synthesis* **1981**, 1.
(4) For selected reviews, see: (a) Komatsu, K.; Kitagawa, T. *Chem. Rev.* **2003**, *103*, 1371. (b) Komatsu, K.; Yoshida, Z. In *Methods of Organic Chemistry (Houben-Weyl)*; de Meijere, A., Ed.; Thieme: Stuttgart, 1996; Vol. E17d, pp. 3079−3192. (c) Khimii, U. *Russ. Chem. Rev.* **1967**, *36*, 557. (d) Yoshida, Z.-i. *Top. Curr. Chem.* **1973**, *40*, 47. (e) Krivun, S. V.; Alfërova, O. F.; Sayapina, S. V. *Russ. Chem. Rev.* **1974**, *43*, 835.
(5) For example, see: (a) Moss, R. A.; Shen, S.; Krogh-Jespersen, K.; Potenza, J. A.; Schugar, H. J.; Munjal, R. C. *J. Am. Chem. Soc.* **1986**, *108*, 134. (b) Kerber, R. C.; Hsu, C.-M. *J. Am. Chem. Soc.* **1973**, *95*, 3239. (c) Agranat, I.; Aharon-Shalom, E. *J. Org. Chem.* **1976**, *41*, 2379.
(6) Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 5318.
(7) A related addition of bromide ion to tropyl benzyl ether has been observed: Parnes, Z. N.; Mur, G.; Kudryavtsev, R. V.; Kursanov, D. N. *Dokl. Akad. Nauk SSSR* **1964**, *155*, 1371.
(8) This compound is readily prepared by the action of sulfonyl chloride or oxalyl chloride on 2,3-diphenylcyclopropenone, which is commercially available or may be prepared on large scale: (a) Föhlisch, B.; Bürgle, P. *Liebigs Ann. Chem.* **1967**, *701*, 67. (b) Breslow, R.; Posner, J. *Org. Synth.* **1967**, *47*, 62.
(9) *Comprehensive Organic Transformations*, 2nd ed.; Larock, R. C., Ed.; Wiley-VCH: New York, 1999; pp 689−702. (b) Copenhaver, J. E.; Whaley, A. M. In *Organic Syntheses*; Wiley and Sons: New York, 1941; Collect. Vol. I, pp 144−145.
(10) Breslow, R.; Eicher, T.; Krebs, A.; Peterson, R. A.; Posner, J. *J. Am. Chem. Soc.* **1965**, *87*, 1320.

JA906520P