2-Chloro-1,3-dimethylimidazolinium Chloride. 3. Utility for Chlorination, Oxidation, Reduction, and Rearrangement Reactions

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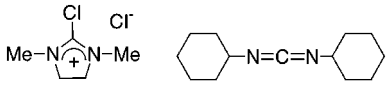
2-Chloro-1,3-dimethylimidazolinium chloride (**1**), which can act as a powerful dehydrating equivalent to DCC (**2**), is also applicable to chlorination, oxidation, reduction, and rearrangement under nearly neutral conditions. The utility of **1** for these reactions is described.

Introduction

In the preceding papers[1] we described the versatility of 2-chloro-1,3-dimethylimidazolinium chloride (DMC) (**1**) as a new dehydrating agent comparable to dicyclohexylcarbodiimide (DCC) (**2**). In this paper, additional reactivities of **1** in chlorination, oxidation, reduction, and rearrangement reactions are discussed.



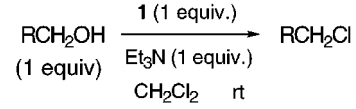
1 **2**

Results and Discussion

Chlorination. As discussed in the first paper of this series,[1a] alcohols are easily acylated with appropriate carboxylic acids in the presence of DMC. It is known that alcohols can be converted to alkyl halides with several reagents containing inorganic halides, such as thionyl chloride or phosphoric chloride.[2] Thus, we found that chloroalkanes were also obtained from alcohols by action of DMC when carboxylic acids were absent in the reaction mixture. Treatment of several types of primary alcohols with **1** in dichloromethane at room temperature in the presence of triethylamine (Et_3N) afforded the corresponding chloroalkanes in excellent yields (runs 1−4 in Table 1[3]). The chlorinations were not affected by the presence of unsaturation or a halogen atom in alcohols. In addition, a good yield was observed even when an acid-sensitive alcohol containing a carbobenzoxy (Cbz) function was used as a starting material (run 5 in Table 1). However, no reaction occurred in the cases of secondary alcohols. Thus, DMC can serve as a selective chlorination reagent for primary alcohols.

Vinylogous acid chlorides were also efficiently synthesized under the same conditions described above when 1,3-diketones were used as starting materials in place of primary alcohols (Table 2[4]).

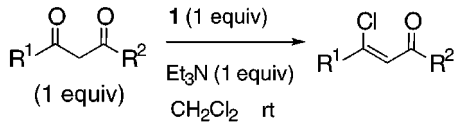
Table 1. Chlorination of Primary Alcohols



run	R	time (h)	yields[a] (%)
1[b]	n-C_7H_{15}	12	93
2[b]	Ph	17	92
3[3]	CH_2=$CH(CH_2)_7$	21	99
4[b]	$Cl(CH_2)_2OCH_2$	17	92
5	CbzNHCH(Bn)CH_2	16	76

[a]Non-optimized, isolated yield. [b]The product is commercially available.

Table 2. Chlorination of 1,3-Diketones



run	R^1	R^2	time (h)	yields[a] (%)
1[4a]	Me	Me	3	84
2[4b]	-$(CH_2)_3$-		3	86
3[4c]	Me	4-(MeO)Ph	24	83

[a]Non-optimized, isolated yield. No establishment of geometries in the products.

(1) Isobe, T.; Ishikawa, T. see the preceding papers; (a) Part 1. (b) Part 2.

(2) Bolmann, R. In *Comprephensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; pp 204−206.

(3) Reference to the product in run 3 in Table 1 is as follows: d'Engenieres, M. D.; Miocque, M.; Gautier, J.-A. *Bull. Soc. Chim. Fr.* **1964**, 2471.

(4) References to the products in Table 2 are as follows: (a) run 1; Gruber, L.; Tomoskozi, I.; Radics, L. *Synthesis* **1975**, 708. (b) run 2; Bateman, L.; Shipley, F. W. *J. Chem. Soc.* **1955**, 1996. (c) run 3; Isobe, T.; Soeda, Y.; Saito, M.; Suzuki, S. Jpn. Kokai Tokkyo Koho JP 04 308547, 1992; *Chem. Abstr.* **1993**, *118*, 233484.

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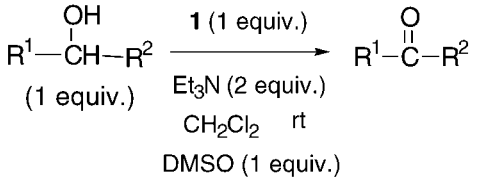
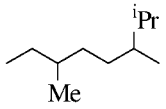
Table 3. Oxidation of Secondary Alcohols



run	R^1	R^2	time (h)	yields[a] (%)
1[b]	Et	n-C_5H_{11}	24	77
2[b]			24	78
3[b]	Me	$Ph(CH_2)_2$	50	92
4[6a]	Me	$Me(CH_2)_3OCH_2$	47	80
5[6b]	$Me(CH_2)_4$	CH_2=CH	72	71

[a]Non-optimized, isolated yield. [b]The product is commercially available.

Scheme 1

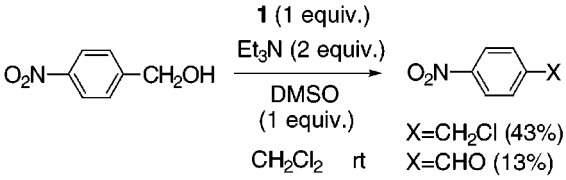
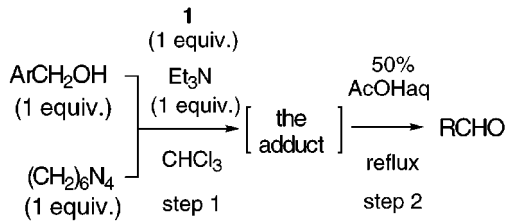


Table 4. Oxidation of Primary Alcohols in the Presence of Hexamethylenetetramine



run	Ar	conditions: step 1 temp/time (h)	conditions: step 2 time (h)	yields[a] (%)
1[b]	4-(Me)Ph	1. rt/2 2. reflux/13	7	63
2[b]	4-(Cl)Ph	1. rt/12 2. reflux/9	3	63
3[b]	4-(MeO)Ph	1. rt/1 2. reflux/7	3	59
4[b]		1. rt/1 2. reflux/15	3	55
5[b]	4-(BuO)Ph	1. rt/1 2. reflux/5	2	47

[a]Non-optimized, isolated yield. [b]The product is commercially available.

Oxidation. It is known that alcohols are converted to aldehydes or ketones with a mixture of DCC, dimethyl sulfoxide (DMSO), and a proton donor such as phosphoric acid.[5] We observed that a variety of secondary alcohols were also oxidized to the corresponding ketones in good to excellent yields when DMSO was used as a coadditive to **1** in the reaction mixture (Table 3[6]). In these cases an additional proton source was not necessary.

As mentioned above, treatment of a primary benzyl alcohol with **1** in the absence of a coadditive produces the corresponding chloride (see run 2 in Table 1). When attempting to oxidize 4-nitrobenzyl alcohol in the presene of DMSO, chlorination at the benzylic carbon predominated (Scheme 1). In contrast, aromatic aldehydes were obtained from primary benzyl alcohols in moderate yields in the presence of hexamethylenetetramine (hexamine) in place of DMSO as an additive (Table 4). In these oxidations hydrolysis of an intermediate with 50% aqueous acetic acid was necessary. It is noteworthy that the yields were not dependent on the substitution of the

Scheme 2

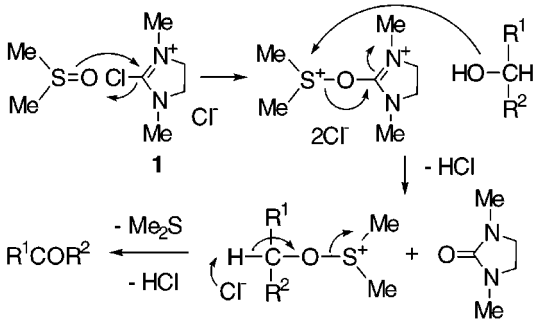
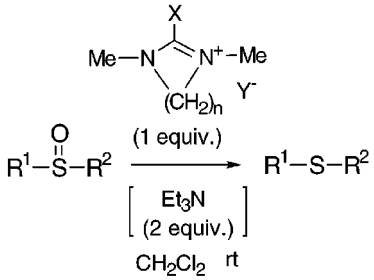


Table 5. Reduction of Sulfoxides to Sulfides



run	R^1/R^2	DMC analogs X	Y	n	Et_3N	time (h)	yields[a] (%)
1[b]	$PhCH_2$/$PhCH_2$	Cl	Cl	2	-	24	71
2[9a]	4-(Cl)Ph/4-(Cl)Ph	Br	Br	2	+	48	67
3[9a]	4-(Cl)Ph/4-(Cl)Ph	Br	Br	3	+	5	50
4[9b]	$PhCH_2$/3-(Me)Ph	Br	Br	2	-	4	60

[a]Non-optimized, isolated yield. [b]The product is commercially available.

(5) March, J. In *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; pp 1081−1083.

(6) References to the products in Table 3 are as follows: (a) run 4; Yamamoto, Y. *Yakugaku Zasshi* **1953**, *73*, 938; *Chem. Abstr.* **1954**, *48*, 10739. (b) run 5; Sasson, Y.; Rempel, G. L. *Can. J. Chem.* **1974**, *52*, 3825.

Scheme 3

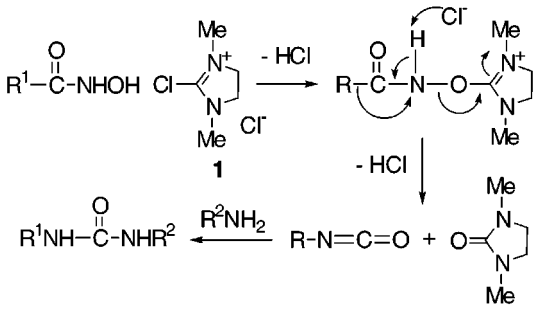
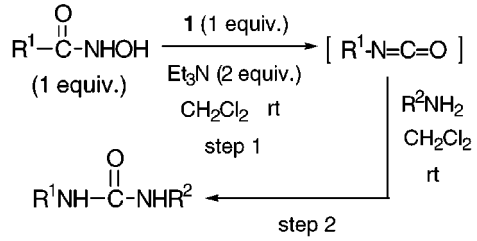


Table 6. Preparation of Ureas from Hydroxamic Acids



run	R^1	R^2	time: step 1 (min)	time: step 2 (h)	yields[a] (%)
1[11a]	Ph	n-Bu	40	48	57
2[11b]	Ph	$Ph(CH_2)_2$	30	19	78
3[11c]	Ph	Ph	900	4	66
4[11d]	$Me(CH_2)_8$	Ph	30	21	67
5[11e]		Ph	30	23	70

[a]Non-optimized, isolated yield.

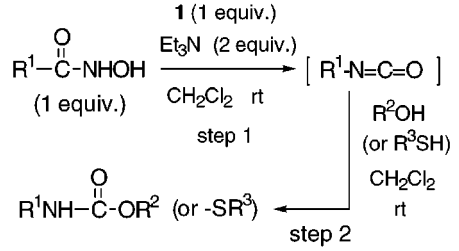
aromatic rings. A mechanism akin to the Swern[7] or the Sommelet[8] oxidation could be in operation, as shown in Scheme 2.

Thus, it was found that ketones could be derived from secondary alcohols by combination of DMC and DMSO, whereas aldehydes were obtained from primary alcohols using hexamine as an additive.

Reduction. In the above oxidation reactions of secondary alcohols, DMSO should be reduced to dimethyl sulfide. This led us to examine the reduction of sulfoxides with DMC (Table 5[9]). Treatment of dibenzyl sulfoxide with **1** yielded the corresponding sulfide in 71% yield (run 1 in Table 5). However, aromatic sulfoxides were inert to **1**, although the use of the more reactive bromo derivative[1b] of **1** with aromatic sulfoxides led to the desired deoxygenated products in moderate yields (runs 2−4 in Table 5). There are no reports on the reduction of sulfoxides with **2**, although a combination of **2** and DMSO can be used for the oxidation of secondary alcohols.[5] Thus, **1** appears to be a more powerful reagent than **2**.

Rearrangement. It is well-known that the O-acyl derivatives of hydroxamic acids give isocyanates when

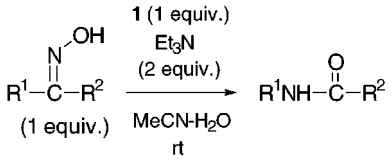
Table 7. Preparation of Carbamates (or Thiocarbamate) from Hydroxamic Acids



run	R^1	R^2 [or R^3]	time: step 1 (min)	time: step 2 (h)	yields[a] (%)
1[12a]	Ph	Me	20	21	82
2[12b]	Ph		30	48	81
3[12c]	Ph	$Ph(CH_2)_2$	30	5	82
4[12d]	Ph		30	6	88
5[12e]	$Me(CH_2)_8$	Me	30	12	93
6[12f]		Me	30	12	87
7[12g]	Ph	[2-(Me)Ph]	30	12	83

[a]Non-optimized, isolated yield.

Table 8. Preparation of Carboxamides from Oximes



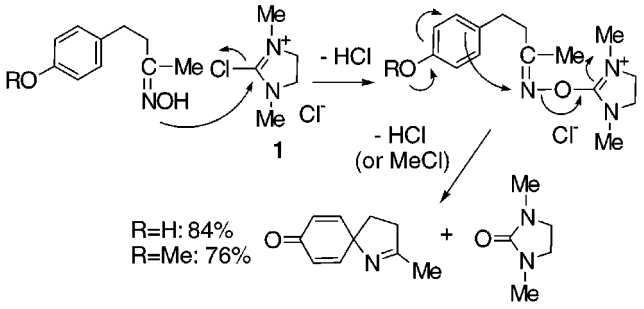
run	R^1	R^2	time (h)	yields[a] (%)
1[b]	Ph	Me	2	80
2[b]	Ph	Ph	16	85
3[b]	4-(F)Ph	Me	2	77
4[14]			16	85

[a]Non-optimized, isolated yield. [b]The product is commercially available.

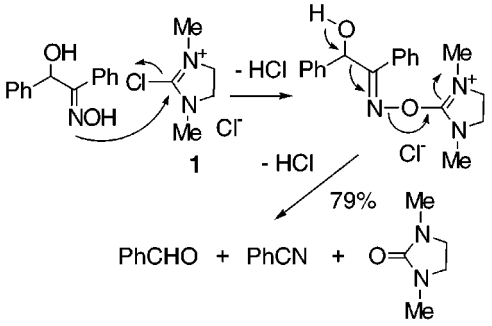
treated with bases.[10] This Lossen-type rearrangement was observed in the reaction of **1** with hydroxamic acids (see Scheme 3). Thus, urea derivatives were obtained in moderate to good yields by treatment of hydroxamic acids with **1** followed by trapping of the intermediate isocyanates with primary amines (Table 6[11]). The use of either

(7) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
(8) Angyal, S. J. *Org. React.* **1954**, *8*, 197.
(9) References to the products in Table 5 are as follows: (a) runs 2 and 3; Ho, T.-L.; Hall, T.-W.; Wong, C. M. *Synthesis* **1973**, 206. (b) run 4; Vowinkel, E. *Synthesis* **1974**, 430.
(10) Wallis, E. S.; Lane, J. F. *Org. React.* **1946**, *3*, 267. Smith, P. A. S. *Org. React.* **1946**, *3*, 337.
(11) References to the products in Table 6 are as follows: (a) run 1; Davis, T. L.; Constan, N. D. *J. Am. Chem. Soc.* **1936**, *58*, 1800. (b) run 2; Carothers, W. H.; Jones, G. A. *J. Am. Chem. Soc.* **1925**, *47*, 3051. (c) run 3; Davis, T. L.; Blanchard, K. C. *Org. Synth. Coll. Vol. I* **1941**, 453. (d) run 4; Isobe, T.; Hosogai, A. Jpn. Kokai Tokkyo Koho JP 07 89926, 1995; *Chem. Abstr.* **1995**, *123*, 111681. (e) run 5; Skita, A.; Rolfes, H. *Chem. Ber.* **1920**, *53*, 1242.

Scheme 4



Scheme 5



alcohols or a thiol in place of amines afforded carbamates (runs 1−6 in Table 7[12]) or a thiocarbamate (run 7 in Table 7[12]).

Beckmann-like rearrangements[13] were also observed when oximes were treated with **1** (Table 8[14]). Carboxamides were obtained in good yields. Interestingly a spiroimine was obtained as a sole product when the oximes derived from 4-(4-hydroxy- or 4-methoxyphenyl)-2-butanones were used (Scheme 4). The yield was high in each case. Recently Narasaka and co-workers[15] reported the same intramolecular cyclization of oximes affording azaspirodienones by treatment with a mixture of tetrabutylammonium perrhenate and trifluoromethanesulfonic acid. In this case the conditions (in 1,2-dichloroethane at reflux for 1 h) used were more drastic than ours (in dichloromethane at room temperature for 20 min). However, benzoin oxime yielded a cleavage product through an alternative path (Scheme 5).

Conclusions

As mentioned above, DMC (**1**) can be used in chlorination, oxidation, reduction, and rearrangement reactions. These reactions are caused by the strong electrophilicity of **1**, as well its activity as a dehydrating reagent. In summary, DMC is a more versatile reagent than DCC because of not only its ability to act as an electrophile but also simple product isolation.

Experimental Section

General comments and a basic procedure for the reaction using **1** were given in the preceding paper.[1a]

(*S*)-*N*-Carbobenzoxy-1-benzyl-2-chloroethylamine (run 5 in Table 1). Colorless prisms (from hexane−ethyl acetate); mp 72−73 °C. Anal. Calcd for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.97; N, 4.61. Found: C, 67.26; H, 6.02; N, 4.54. FABMS *m*/*z*: 304 (MH^+), 306 ($MH^+ + 2$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.86−3.00 (m, 2H), 3.50 (dd, J = 11.3, 3.1 Hz, 1H), 3.64 (dd, J = 11.3, 3.8 Hz, 1H), 4.20 (br s, 1H), 5.05 (m, 1H), 5.10 (s, 2H), 7.22−7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.7, 46.7, 52.6, 66.9, 126.9, 128.1, 128.2, 128.6, 128.7, 129.3, 136.2, 136.8, 155.5; IR (KBr): 1685 cm^{-1} (C=O); $[\alpha]^{25}_D$ −17.8 (*c* 1.00, $CHCl_3$).

Supporting Information Available: Selected spectroscopic data for compounds described in our patents. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) References to the products in Table 7 are as follows: (a) run 1; Hofmann, A. W. *Ann.* **1850**, 74, 1. (b) run 2; Meiser, W. *Chem. Ber.* **1899**, *32*, 2049. (c) run 3; Oeda, H. *Bull. Chem. Soc. Jpn.* **1935**, *10*, 531. (d) run 4; Van Zyl, G.; Langenberg, R. J.; Tan, H. H.; Schut, R. N. *J. Am. Chem. Soc.* **1956**, *78*, 1955. (e) run 5; Huang, X.; Keillor, J. W. *Tetrahedron Lett.* **1997**, *38*, 313 (f) run 6; Kienzle, F. *Tetrahedron Lett.* **1972**, 1771. (g) run 7; Bourne, N.; Williams, A.; Douglas, K. T.; Penkava, T. R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1827.

(13) Heldt, W. Z. *Org. React.* **1960**, *11*, 1. Gawley, R. E. *Org. React.* **1988**, *35*, 1.

(14) Reference to the product in run 4 in Table 8 is as folows: Dickerman, S. C.; Besozzi, A. J. *J. Org. Chem.* **1954**, *19*, 1855.

(15) Kusama, H.; Uchiyama, K.; Yamashita, Y.; Narasaka, K. *Chem. Lett.* **1995**, 715.