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1,2-H Shift in Copper−Chlorocarbenoid Intermediate during CuCl/bpy-Promoted Stereoselective Dechlorination of 2,2,2-Trichloroethyl Alkyl Ethers to (*Z*)-1-Alkoxy-2-chloroethenes

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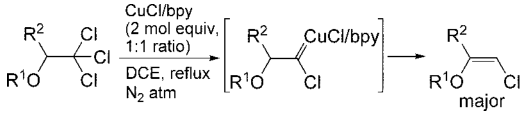
ABSTRACT



Reaction of 2,2,2-trichloroethyl alkyl ethers with 2 molar equiv of CuCl/bpy in refluxing DCE yielded (*Z*)-1-alkoxy-2-chloroethenes stereoselectively as the major product via 1,2-H shift in copper−chlorocarbenoid intermediate. 2,2,2-Trichloroethyl carboxylates undergo a radical 1,2-acyloxy shift under similar conditions.

Recently, we observed a facile dechlorinative rearrangement of 2,2,2-trichloroethyl carboxylates with 2 equiv of CuCl/bpy to give 1-acyloxy-1-chloroalkenes.[1] The reaction was proposed to involve a radical 1,2-acyloxy shift in conformity with the well-known propensity of trichloromethyl compounds to generate radicals under these conditions[2] and that of radicals to undergo this rearrangement, which is known as Surzur−Tanner rearrangement.[3] Subsequently, Falck[4a] and earlier Takai et al.[5] reported the same transformation with 3 and 4 equiv of $CrCl_2$ and proposed a mechanism involving 1,2-acyloxy shift in a chromium−carbenoid intermediate. Falck et al. also reported stereospecific 1,2-H shift in the carbenoid intermediate generated from 2,2,2-trichloroethyl alkyl ethers[4a,b] and trichloromethylalkanes[4b,c] under the same conditions to form (*Z*)-1-alkoxy-2-chloroalkenes and (*Z*)-chloroalkenes, respectively. A rationale based on the steric effect of chromium has been provided for the *Z*-specificity. In the case of trichloroethyl carboxylates[5] and trichloromethylalkanes,[4c] the chromium carbenoid intermediate could be intercepted by nucleophilic addition to aldehydes. Although formation of a carbene or copper−carbenoid intermediate in the reaction of compounds containing a trichloromethyl group with CuCl/bpy has not been reported despite a large number of reported experiments on CuCl/bpy-catalyzed reactions of such compounds,[2] there are a few reports on the formation of copper−carbenoids during the reaction of some *gem*-dichloro and trichloromethyl compounds with metallic copper and Cu_2O.[6] Therefore, it was

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(1) Ram, R. N.; Meher, N. K. *Org. Lett.* **2003**, *5*, 145–147.

(2) (a) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1–11. (b) Ram, R. N.; Kumar, N. *Tetrahedron Lett.* **2008**, *49*, 799–802. (c) Ram, R. N.; Charles, I. *Chem. Commun.* **1999**, 2267–2268. (d) Destarac, M.; Matyjaszewski, K.; Boutevin, B. *Macromol. Chem. Phys.* **2000**, *201*, 265–272.

(3) (a) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, 3273–3312. (b) Lacote, E.; Renaud, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2259–2262.

(4) (a) Bejot, R.; Tisserand, S.; Reddy, L. M.; Barma, D. K.; Baati, R.; Falck, J. R.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2008–2011. (b) Baati, R.; Barma, D. K.; Krishna, U. M.; Mioskowski, C.; Falck, J. R. *Tetrahedron Lett.* **2002**, *43*, 959–961. (c) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *J. Am. Chem. Soc.* **2001**, *123*, 9196–9197.

(5) Takai, K.; Kokumai, R.; Nobunaka, T. *Chem. Commun.* **2001**, 1128–1129.

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considered necessary to re-examine the mechanism of the CuCl/bpy-promoted rearrangement of 2,2,2-trichloroethyl carboxylates and also to investigate the reactions of 2,2,2-trichloroethyl ethers and trichloromethylalkanes under these conditions in order to discern more information about the similarities and differences between CuCl/bpy- and $CrCl_2$-promoted reactions. The possibility of a rare[7] radical 1,2-H shift in trichloroethyl ethers under these seemingly favorable conditions as well as the advantage of lower amounts of the milder reducing agent CuCl/bpy that might be required in these reactions were also envisioned.

Scheme 1. Reaction of 2,2,2-Trichloroethyl Ethers **1** and DDT with 2 molar equiv of CuCl/bpy

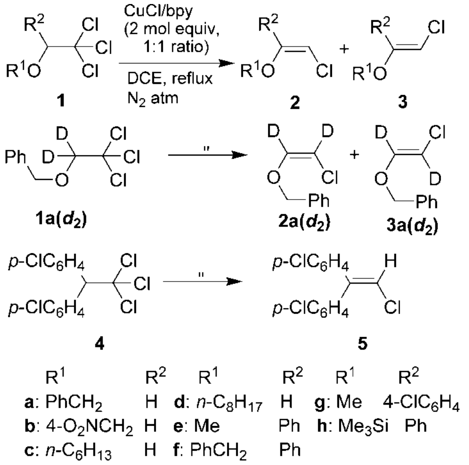


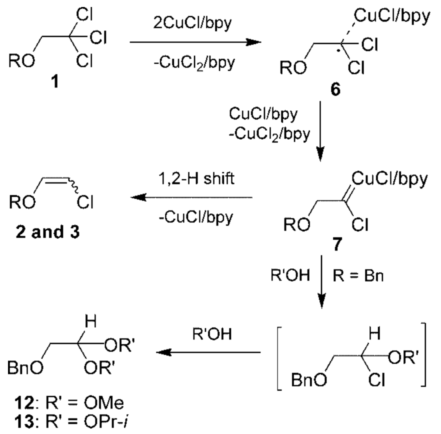
Table 1. Copper(I)-Promoted Dechlorinative 1,2-H Shift in 2,2,2-Trichloroethyl Ethers **1**[a]

entry	ether **1**	solvent	time (h)	isolated (%) **2**	yield (%) **3**	**2**:**3** ratio[b]
1	**a**	DCE	3	70	6	86:14
2	**b**	DCE	3	60	17	78:22
3	**c**	DCE	3	70	6	87:13
4	**d**	DCE	3	71	6	88:12
5	**e**	DCE	15	71[c]		87:13
6	**f**	DCE	14	82[c]		85:15
7	**g**	DCE	14	83[c]		85:15
8	**h**	DCE	14	72[c]		100:0
9	**a**	$CHCl_3$	40	16:84[d]		62:38
10	**a**	PhH	24	67:33[d]		80:20
11	**a**	THF	16	89:11[d]		88:12
12	**a**	DCE	3	60[c,e]		61:39
13	**a**	DCE	4	51:49[d,f]		63:37

[a] All of the experiments were performed in refluxing solvent under a nitrogen atmosphere. [b] Calculated by ^1H NMR. [c] Total isolated yield of (**2** + **3**). [d] (**2** + **3**):**1** as calculated by ^1H NMR. [e] With 2 molar equiv of Cu powder/bpy (1:1 mixture) in place of CuCl/bpy. [f] With N^1,N^1,N^2,N^3,N^3-Pentamethyldiethylenetriamine ligand in place of bpy.

Thus, the reaction of the trichloroethyl ethers **1** (Scheme 1) with CuCl/bpy (equimolar mixture) in DCE at reflux under a nitrogen atmosphere afforded an isomeric mixture of (*Z*)- and (*E*)-1-alkoxy-2-chloroethenes **2** and **3**, respectively, by *Z*-selective dechlorinative 1,2-H shift. Although the yields of the products were comparable to that of the $CrCl_2$-promoted reactions,[4a,b] the stereoselectivity was observed to be lower. The reaction required 2 molar equiv of CuCl/bpy for completion. The disubstituted ethenes were separated by column chromatography, but the trisubstituted ethenes were relatively less stable[8] on the column and were isolated as a mixture of *Z* and *E* isomers. The structures of the products were determined by IR and ^1H and ^{13}C NMR spectroscopy. The configurations of the disubstituted alkenes **2a**−**d** and **3a**−**d** were established by ^1H NMR and that of the trisubstituted alkene **2e**, **3e**, **2f**, **3f**, and **2h** by NOE. The reaction gave better results in DCE in terms of product yield and reaction time than the other solvents investigated such as $CHCl_3$, benzene, and THF (Table 1, entries 9−11). The reaction of **1a** with copper powder in place of CuCl was less stereoselective and gave the products in lower yields (entry 12). The reaction with N^1,N^1,N^2,N^3,N^3-pentamethyldiethylenetriamine, an efficient ligand in CuCl-catalyzed halogen atom transfer radical cyclization (HATRC),[2a] in place of bpy was found to be slower and less stereoselective (entry 13). The reaction of the dideuteriated ether **1a(*d*$_2$)** did not show any exchange of deuterium with proton in the rearranged enol ethers, as observed by Falck et al.[4a] As expected, CuCl/bpy was found to be milder than $CrCl_2$ because, contrary to $CrCl_2$-promoted reactions,[4c] a hydrocarbon analogue, 1,1,1-trichlorononane, did not form the expected alkenes under similar conditions and the trisubstituted ethenes were formed with significantly slower rate than the disubstituted ones as against nearly equal rates with $CrCl_2$.[4a] Consequently, easily reducible groups, such as nitro, could be safely tolerated (entry 2). Understandably,[9] this

Scheme 2. Mechanism of Dechlorinative 1,2-H Shift



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(7) For the rarity of radical 1,2-H shift in solution, see: (a) Freidlina, R. K.; Kost, V. N.; Khorlina; M. Y., *Russ. Chem. Rev.* **1962**, *31*, 1–18. For some other examples, see: (b) Lendvay, B. V. G.; Kortvelyesi, T.; Seres, L. *J. Am. Chem. Soc.* **1996**, *118*, 3006–3009. (c) Kunz, M.; Retey, J. *Bioorg. Chem.* **2000**, *28*, 134–139.

(8) The compounds tend to decompose to the corresponding aracyl chlorides on standing in open atmosphere.

aspect of selectivity was not examined for $CrCl_2$-promoted reactions. However, 1,1,1-trichloro-2,2-bis-(4-chlorophenyl)ethane **4** (DDT) (Scheme 1), with two aromatic rings at the migration origin, gave the expected product 1-chloro-2,2-bis-(4-chlorophenyl)ethene **5** in 81% yield. 2,2-Dichloroethyl benzyl ether was found to be refractory under similar reaction conditions, as observed by Falck et al.[4a]

A mechanism involving 1,2-H shift in the copper−carbenoid intermediate **7** (Scheme 2) formed by successive abstraction of two chlorine atoms by CuCl/bpy through a free or, more preferably a copper-associated, radical **6** (vide infra) has been proposed for the reaction. The intervention of a free or copper-associated radical **6** was inferred by the fact that the reaction of **1a** was inhibited by excess of TEMPO (2 molar equiv). Further, 2,2,2-trichloroethylcinnamyl ether **8**[2c] (Figure 1), the vinylogous analogue of **1a**, and other trichloroethyl allylic ethers[2b] have been shown to undergo HATRC under similar conditions to give the tetrahydrofurans of the type **9**. Therefore, it was tempting to believe that the products arose by the anticipated radical 1,2-H shift. However, the extreme rarity of 1,2-H shift in alkyl radicals in solution[7] demanded more careful scrutiny. Thus, when the reaction of **1a** with Bu_3SnH/AIBN in refluxing benzene was performed with a view to generate a radical intermediate through a proven and trusted method of free radical generation, no rearrangement products **2a** or **3a** could be detected even under the conditions favorable to 1,2-H shift (slow addition of Bu_3SnH to a solution of **1a** at sufficiently high dilution). Only the elimination product **10** (Figure 1) (at higher concentration) and the reduction product **11** were formed. In a competition experiment between CuCl/bpy and Bu_3SnH, the reaction of **1a** with Bu_3SnH/CuCl/bpy even under the conditions more conducive to reduction (more concentrated solution of **1a**with all the other reactants taken together) yielded the rearranged products **2a** and **3a** (79:21) in nearly double the amount in moles of the reduction product **11**. These results indicated that either a radical intermediate was not involved in the 1,2-H shift or it had a different reactivity from the free radical generated in Bu_3SnH reactions. Similar results were obtained by us[1] during the 1,2-acyloxy shift as mentioned earlier, and it was thought that the difference in the reactivity of the two types of radicals might be due to some sort of association of the radical intermediate with copper in the CuCl/bpy-promoted 1,2-acyloxy shift.[1]

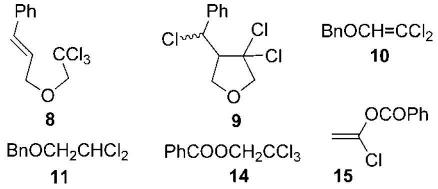

Figure 1. Structures of some relevant compounds.

The evidence for the involvement of a carbene, or more preferably, the copper−carbenoid intermediate **7** (vide infra) was obtained when the reaction of **1a** was performed in the presence of a protic quencher with a view to ascertain whether this association is organometallic type or coordination through a heteroatom. Thus, the reaction of **1a** in the presence of 20 molar equiv of methanol yielded the dimethyl acetal **12** (Scheme 2) as the major product, about 5 times of the rearranged products **2a** and **3a**, along with small amounts of the unreacted **1a** and some other minor unidentified products (Table 2, entry 1). The structure of the acetal **12** was confirmed by comparison with an authentic sample. It did not arise from the rearranged products **2a** and/or **3a** because the latter were found to be stable under the conditions as well as toward the action of $CuCl_2$/bpy or its equimolar mixture with CuCl/bpy, even in a 1:1 v/v mixture of DCE−MeOH. The reaction of **1a** in *i*-PrOH DCE (1:1 v/v) (Scheme 2) yielded the corresponding acetal **13** (Table 2, entry 2). However, the reaction of **1a** in the presence of a lower amount (2 molar equiv) of methanol gave only **2a** and **3a** (85:15) in 72% combined isolated yield. No acetal could be detected. The formation of the acetals **12** and **13** from **1a** indicated that 1,2-H shift in the ethers might be taking place through a chlorocarbene or copper−chlorocarbenoid intermediate which, in the presence of an alcohol, underwent insertion into the O−H bond of the alcohol followed by solvolysis of the α-chloro ether thus formed to give the acetal.[12] In contrast, only benzoyloxy shift occurred in the case of the trichloroethyl benzoate **14** to give **15** (Figure 1) even in a (1:1 v/v) mixture of DCE−MeOH (Table 2, entry 3). 2,2,2-Trichloroethylcinnamyl ether **8** also afforded only the HATRC product **9** (Figure 1) on reaction with CuCl/bpy in refluxing DCE−MeOH (1:1 v/v) (Table 2, entry 4); no acetal was detected in the reaction mixture. The insertion of free chlorocarbenes into O−H bond of methanol is known to be a fast diffusion-controlled reaction.[10,11] The fact that this was not observed in the case of 2,2,2-trichloroethyl benzoate **14** and 2,2,2-trichloroethylcinnamyl ether **8** suggested that probably the acyloxy shift and HATRC involve a nonorganometallic type copper-associated/free-radical intermediate as proposed earlier.[1,2] The fact that no acetal was detected in the reaction of **1a** at lower concentration of methanol (2 mol equiv) indicated that the 1,2-H shift was also very fast probably due to the known powerful rate accelerating effect of the bystander alkoxy group on the 1,2-H shifts in carbenes[12] Consequently, intramolecular C−H insertion in the case of **1c** and **1d** was not observed and attempts to intercept the carbenenoid intermediate in the reaction of **1a** by cyclopropanation with excess of cyclohexene or methyl acrylate failed (Table 2, entries 5 and 6). Intra- or intermolecular cyclopropanation with alkenes was complicated by a preceding radical reaction, such as

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(9) For reviews on $CrCl_2$-promoted reductions, see: (a) Ho, T.−L. *Synthesis* **1979**, 1–20. (b) Hanson, J. R. *Synthesis* **19**, *74*, 1–8.

(10) Griller, D.; Liu, M. T. H.; Scaiano, J. C. J. C. *J. Am. Chem. Soc.* **1982**, *104*, 5549–5551.

(11) For a review, see: (a) Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811–10843. For some other examples, see: (b) Jiang, N.; Wang, J.; Chan, A. S. C. *Tetrahedron Lett.* **2001**, *42*, 8511–8513. (c) Motschiedler, K.; Gudmundsdottir, A.; Toscano, J. P.; Platz, M.; Garcia-Garibay, M. A. *J. Org. Chem.* **1999**, *64*, 5139–5147.

(12) Nickon, A. *Acc. Chem. Res.* **1993**, *26*, 84–89.

Table 2. Experiments toward Mechanistic Investigation[a]

entry	reactants (molar equiv)/solvent	time (h)	products (% isolated yield)
1	**1a**/CuCl/bpy/MeOH (1:2:2:20)/DCE	3	**2a/3a/12/1a** (11:5:79:5)[b]
2	**1a**/CuCl/bpy (1:2:2)/DCE/*i*-PrOH (1:1 v/v)	3	**13** (45)
3	**14**/CuCl/bpy (1:2:2)/DCE/MeOH (1:1 v/v)	3	**15** (88)
4	**8**/CuCl/bpy (1:2:2)/DCE/MeOH (1:1 v/v)	3	**9** (73)
5	**1a**:CuCl: bpy: cyclohexene (1: 3: 3: 40)/DCE	6	**2a/3a/9/1a** (38:10:13:39)[b]
6	**1a**/CuCl/bpy/methyl acrylate (1:2:2:50)/DCE	3	**2a** (19), **3a** (3), telomers (major)

[a] All the experiments were performed in refluxing solvent under a nitrogen atmosphere. [b] Product ratio as calculated by ^{1}H NMR.

cyclization[2a–c] (Table 2, entry 4), reduction (Table 2, entry 5), or telomerization[2d] (Table 2, entry 6).

Thus, it appears that the formation of the carbene or copper−carbenoid intermediate occurs stepwise succeeding the formation of a free radical or copper-associated radical only in the absence of availability of an easier route for a radical reaction, such as HATRC or 1,2-acyloxy shift. The direct formation of chromium−carbenoid intermediate in the $CrCl_2$-promoted reactions might be due to higher reactivity of $CrCl_2$ than CuCl/bpy which would give little time to the radical intermediate, if formed,[13] to undergo 1,2-acyloxy shift. Though the involvement of a free carbene has not been ruled out, the intermediacy of a copper carbenoid is preferred. It is less likely for a free carbene to exist in the presence of CuCl/bpy in the medium. It also seems likely that the abstraction of the second chlorine atom by CuCl/bpy occurs from a radical stabilized by association with copper rather than a more reactive unassociated free radical.

Unlike chromium−carbenoids, these copper−carbenoids appear to be less nucleophilic, as attempted trapping of the copper−carbenoid generated from **1a** with 4-nitrobenzaldehyde led only to 1,2-H shift and recovery of the aldehyde. It could also be due to faster 1,2-H shift which precluded its reaction with the aldehyde.

In conclusion, the CuCl/bpy-promoted reaction of 2,2,2-trichloroethyl ethers is advantageous over the $CrCl_2$-promoted reaction for stereoselective synthesis of (*Z*)-2-chloroenol ethers[14] in terms of the amount and chemoselectivity of the metal promoter used, though the *Z*-selectivity is lower. The CuCl/bpy-promoted 1,2-H and acyloxy shifts probably occur in a carbenoid and radical intermediate, respectively, as against the reported involvement of carbenoids in both the reactions promoted by $CrCl_2$. We could not find a literature precedent for 1,2-H shift under the present reaction conditions.[15]

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Supporting Information Available: Experimental procedures, spectral data, and NMR spectra of all new and relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] For $CrCl_2$-promoted radical cyclization of trihaloethyl allyl/propargyl ethers, see: Nakagawa, M.; Saito, A.; Soga, A.; Yamamoto, N.; Taguchi, T. *Tetrahedron Lett.* 2005, *46*, 5257−5261.

[14] For their potential as AD prodrugs, see: Yoshimatsu, M.; Sakai, M.; Moriura, E. *Eur. J. Org. Chem.* **2007**, 498–507.

[15] The copper−carbenoid was generated by the reaction of methyl 2,2-dichloropropanoate with copper powder in DMSO; the only reported example with such a possibility yielded dimerization product (ref 6a).