Chemistry Letters

Dichloromethane as a Chlorination Reagent for α-Bromocarbonyl Compounds in the Presence of a Copper Catalyst

Kentaro Takeuchi, Syo Ishida, and Takashi Nishikata*

Advance Publication on the web February 16, 2017
doi:10.1246/cl.170062

Dichloromethane as a Chlorination Reagent for α-Bromocarbonyl Compounds in the Presence of a Copper Catalyst

Kentaro Takeuchi, Syo Ishida and Takashi Nishikata*
Graduate School of Science and Engineering, Yamaguchi University 2-16-1 Tokiwadai, Ube, Yamaguchi, 755-8611, Japan

E-mail: nisikata@yamaguchi-u.ac.jp

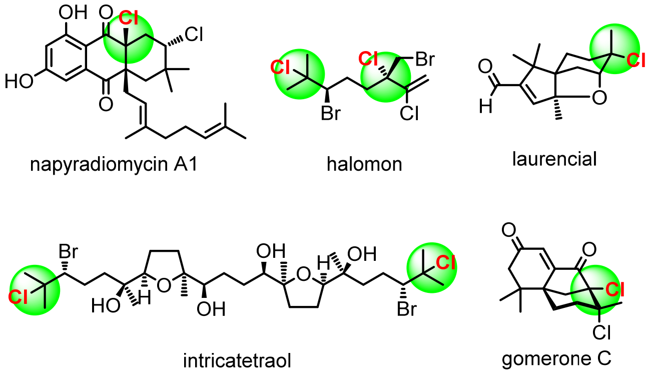
We found that dichloromethane is a powerful chlorinating reagent for the congested 3° and 2°Csp^3–Br bond of α-bromocarbonyl amides, esters, and ketones. In the presence of a proper copper complex as a catalyst, the desired chlorination occurred within an hour. Control experiments revealed that *in situ* generated $CuCl_2$ is a key chlorinating reagent that reacts with the 3° or 2° alkyl radicals generated by the reaction between an α-bromocarbonyl compound and a Cu(I) salt.

Keywords: chlorination, dichloromethane, copper

The 3° Csp^3–Cl bond is a very important fragment which can be seen in various bioactive compounds such as napyradiomycin A1, halomon, intricatetraol, laurencial, and gomerone C (Scheme 1)[1]. Despite its importance, the synthetic methodology for the construction of 3° Csp^3–Cl bonds is limited to the bromochlorination of allylic alcohol with titanium chloride[1b], iridium-catalyzed chlorination of alcohol with chlorosilanes[2], and halogen exchange reaction with $BiCl_3$[3] or $SnCl_4$[4]. These limitations may be attributed to the absence of proper chlorinating reagents. In the synthesis of primary- and secondary-alkyl chlorides, N-chlorosuccinimide (NCS), 2,2,6,6-tetrachlorocyclohexanone[5], trichloromethanesulfonyl chloride[6], trichloroquinolinone[7], alkali chloride[8], and ammonium chloride[9] are useful and reliable chlorination reagents; however, they are not suitable for the construction of 3° Csp^3–Cl bonds. In this context, further development of new concepts and reagents for the synthesis of quaternary carbon centers bearing chlorine atoms would be greatly desired.

During the course of our research on quaternary carbon center construction chemistry using α-bromocarbonyl compounds[10], we discovered that α-chlorocarbonyl compounds were obtained as side products when dichloromethane (CH_2Cl_2) was used as a solvent. This result indicates that CH_2Cl_2 can serve as a good reagent for chlorination of hindered α-carbonyl compounds via a radical reaction.

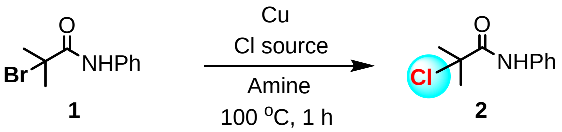
Although there are many organic chlorination reagents described above, chlorination with CH_2Cl_2 is rare. For instance, the Hites group reported on the chlorination of aromatic hydrocarbons using a methane–dichloromethane flame[11]. Herein, we report an unprecedented methodology for the construction of 3° Csp^3–Cl bonds using CH_2Cl_2 as the chlorinating reagent in the presence of a copper catalyst.

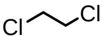
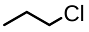
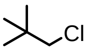


Scheme 1. Chlorinated compounds having 3° Csp3–Cl bonds

For optimization studies, a combination of α-bromocarbonyl compound **1** and a Cl source was employed in the presence of a Cu salt (10 mol%) and amine (1 equiv) at 100 °C for 1 h (Table 1). The effectiveness of the various Cu salts was initially tested, and Cu salts possessing various counter anions showed excellent reactivities (Table 1, runs 1–4). According to our previous works[10], we hypothesized that this reaction involved radical reactions. Therefore, to generate a radical from **1**, Cu(I) (not Cu(II)) must react with **1** via a single-electron transfer[12]. However, $[Cu(H_2O)_6](BF_4)_2$ and $CuCl_2$ (Cu(II)) reacted smoothly with **1** to generate the corresponding chlorinated compound **2** in 90% yield, which is likely produced by the reduction of Cu(II) to Cu(I) in the presence of amine (Run 3)[13]. In this reaction, amines act as a ligand for copper to generate active catalysts. Therefore, multidentate *N*,*N*,*N′*,*N′*,*N″*-pentamethyldiethylenetriamine (PMDETA) was highly effective compared with Et_3N, iPr_2NH, and imidazole (runs 4–7). We also tried to examine various multidentate ligands such as TPMA (tris(2-pyridylmethyl)amine) and Phen (1,10-phenanthroline), but they were not effective. We expected that PMDETA is a ligand for a copper salt. However, reducing the amount of PMDETA (10 mol%) decreased the chemical yield of **2**. Chlorination occurred with various chlorine sources, including $CHCl_3$, 1,2-dichloroethane, and 1-chloropropane, although 1-chloro-2,2-dimethylpropane limited the chlorination activity, and benzyl chloride, allyl chloride, and chlorobenzene lead to sluggish chlorination activities (runs 8–14). The amounts of CH_2Cl_2 can be reduced under appropriate conditions. For example, when the reaction was conducted in toluene with 10 equivalents of CH_2Cl_2, 80% of **2a** was obtained (run 15). Similarly, 5 equivalents of CH_2Cl_2 led to **2a** with 61% yield.

Table 1. Optimization[a]

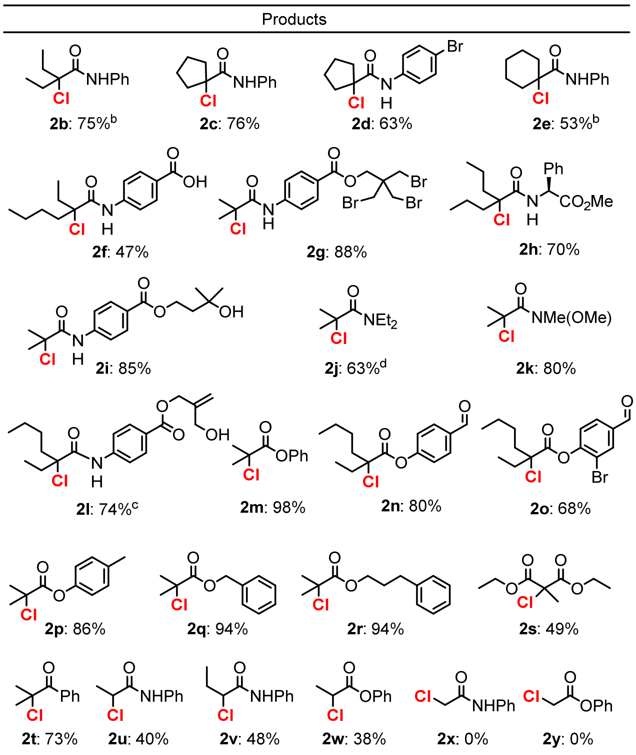


Run	Cu	Amine	Cl source	Yield (%)
1	CuI	PMDETA	CH_2Cl_2	83
2	CuCN	PMDETA	CH_2Cl_2	87
3	$CuCl_2$	PMDETA	CH_2Cl_2	90
4	$[Cu(H_2O)_6](BF_4)_2$	PMDETA	CH_2Cl_2	93
5	$[Cu(H_2O)_6](BF_4)_2$	Et_3N	CH_2Cl_2	0
6	$[Cu(H_2O)_6](BF_4)_2$	iPr_2NH	CH_2Cl_2	0
7	$[Cu(H_2O)_6](BF_4)_2$	imidazole	CH_2Cl_2	0
8	$[Cu(H_2O)_6](BF_4)_2$	PMDETA	$CHCl_3$	93
9	$[Cu(H_2O)_6](BF_4)_2$	PMDETA		75
10	$[Cu(H_2O)_6](BF_4)_2$	PMDETA		73
11	$[Cu(H_2O)_6](BF_4)_2$	PMDETA		trace
12	$[Cu(H_2O)_6](BF_4)_2$	PMDETA	BnCl	25
13	$[Cu(H_2O)_6](BF_4)_2$	PMDETA	allylCl	trace
14	$[Cu(H_2O)_6](BF_4)_2$	PMDETA	PhCl	trace
15[b]	$[Cu(H_2O)_6](BF_4)_2$	PMDETA	CH_2Cl_2	80

[a]Conducted at 100 °C for 1 h with 10 mol% Cu, amine (1 equiv), Cl source (as a solvent 0.5 M) and **1** (1 equiv) in a sealed tube. Yields were isolated. [b]10 equivalents of CH_2Cl_2 was used in toluene.

Under optimized conditions, α-bromoamides, -esters, and -ketones were chlorinated with CH_2Cl_2 (Table 2). The chlorination of various α-bromoamides bearing congested 3° Csp^3–Br, Ar–Br, alkyl–Br, carboxylic acid, alcohol, and amino acid moieties occurred smoothly (**2b**–**2i**). Recently, the Huy group reported a chlorination approach for aliphatic alcohols but our reaction left the alcohol group intact (**2i** and **2l**) [14]. Tertiary amide and Weinreb amide resulted in the corresponding chlorinated product in moderate to good yields (**2j** and **2k**). Similarly, α-bromoesters and ketone possessing various structures provided the desired products in yields ranging from 49% to 94% (**2m**–**2t**). Although α-bromocarbonyl compounds possessing a 2° Csp^3–Br bond reacted with CH_2Cl_2 (**2u**–**2w**), the substrates possessing a 1° Csp^3–Br bond were sluggish (**2x** and **2y**). Overall, our chlorination approach with CH_2Cl_2 showed good functional group tolerances.

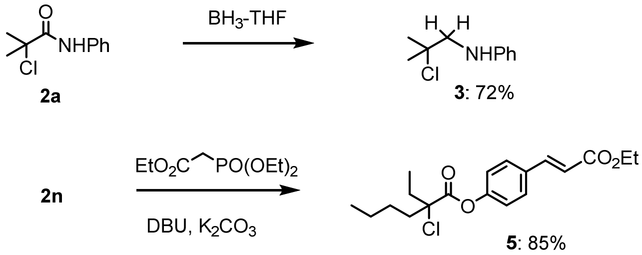
Table 2. Substrate scope[a]



[a]Conducted at 100 °C for 1 h with 10 mol% Cu, PMDETA (1 equiv), CH_2Cl_2 (as a solvent 0.5 M) and **1** (1 equiv) in a sealed tube. Yields were isolated. [b]1.5 equiv of PMDETA was used. [c]2.0 equiv of PMDETA was used. [d] Run for 8 h.

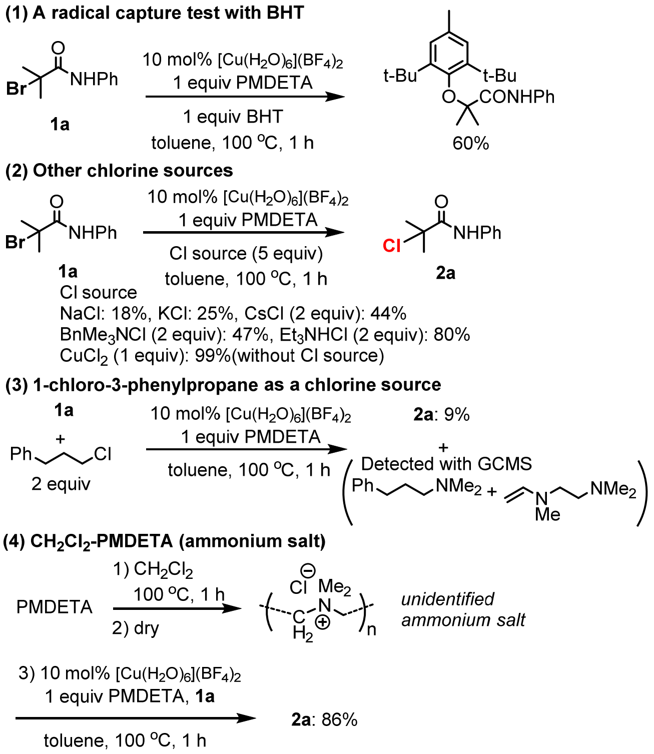
The obtained chlorinated products **2** bearing various active functional groups were easily converted into a wide range of derivatives using conventional organic reactions, including reduction with borane and Horner–Wadsworth–Emmons reactions (Scheme 2).

Next, we conducted the following control experiments (Equations 1–4 in Scheme 3). Equation 1 is a radical capture test with 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT). This chlorination reaction was inhibited by the addition of BHT, which indicated that this reaction involves a radical species. Indeed, we obtained 60% yield of alkylated BHT in the reaction of **1a** with BHT. The other chlorine sources used are shown in Equation 2. When NaCl, KCl, or CsCl was used instead of organic chlorides, **2a** was obtained. Similarly, ammonium chlorides were also effective in the chlorination reaction. These results show that copper chloride may be an active chlorine source. Therefore, a stoichiometric amount of $CuCl_2$ was used instead of organic chlorides as the chlorine source in the chlorination reaction of **1a**[15]. As the result, the product **2a** was obtained in 99% yield. In Equation 3, 1-chloro-3-phenylpropane was used as a chlorine source to understand the role of organic chloride in this reaction. As the result, 9% of **2a**, $PhCH_2CH_2CH_2NMe_2$, and enamine (via Hofmann elimination) were detected with GC-MS. This result indicated that ammonium chloride is formed as a chlorine source during the reaction. In Equation 4, CH_2Cl_2-PMDETA (ammonium salt) was used as the chlorine source. We expected that ammonium chloride may generate from the reaction of CH_2Cl_2 and PMDETA.[16] We obtained a salt after the reaction; but we failed to identify ammonium chloride with HRMS[17]. Although the structure of the resulting salt was unknown, a chloriantion reaction of **1a** was conducted in the presence of this salt. As the result, **2a** was obtained in 86% yield. Based on the results of control experiments, chlorine atom of CH_2Cl_2 can be used after the reaction of PMDETA to generate an ammonium salt.

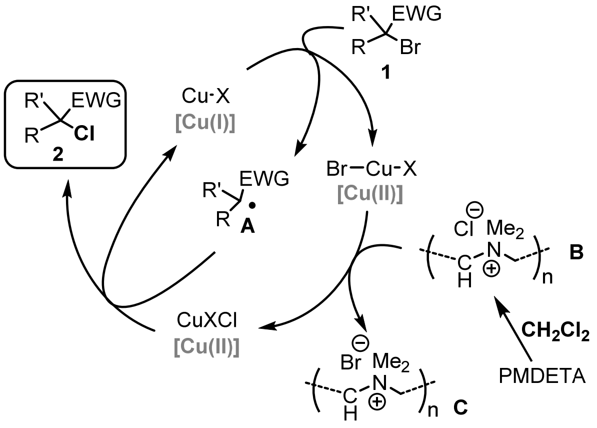


Scheme 2. Utilities of the chlorinated building blocks

One possibility involving a radical pathway is shown in Scheme 4. The reaction starts with the generation of alkyl radical species **A** from the reaction between CuX and **1**. An evidence of this step is the reaction in the presence of BHT, as shown in Scheme 3. The intermediate **A** subsequently reacts with CuClX (generated from the reaction of CuBrX with ammonium chloride **B**) to yield the desired chlorinated product **2**[18]. CH_2Cl_2 was finally converted to **C** in the catalytic cycle.



Scheme 3. Control experiments



Scheme 4. Proposed mechanism

In conclusion, we established a chlorination approach for 3° or 2° Csp^3–Br bonds with CH_2Cl_2 as a chlorinating reagent in the presence of a copper catalyst within an hour. This is an unprecedented example in which simple organic chlorides exhibit chlorination activity by using a metal catalyst. The chlorination mechanism is not fully clear in this communication but further investigations, including mechanistic studies, are currently underway.

Financial support was provided by the Program to Disseminate Tenure Tracking System, MEXT, Japan and the Grant-in-Aid for Scientific Research for Challenging

Exploratory Research and Tosoh Award (SOCJ). We also thank Mr. Ryo Fujimoto for supplying the starting materials.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

References and Notes

1 (a) J. B. Burreson, F. X. Woolard, R. E. Moore, *Chem. Lett.* **1975**, *4*, 1111; (b) D. X. Hu, F. J. Seidl, C. Bucher, N. Z. Burns, *J. Am. Chem. Soc*. **2015**, *137*, 3795; (c) W. J. Chung, C. D. Vanderwal, *Angew. Chem. Int. Ed*. **2016**, *55*, 4396.

2 M. Yasuda, S. Yamasaki, Y. Onishi, A. Baba, *J. Am. Chem. Soc*. **2004**, *126*, 7186.

3 B. Boyer, E. M. Keramane, S. Arpin, J. L. Montéro, J.-P. Roque, *Tetrahedron*, **1999**, *55*, 1971.

4 A. Amrollah-Madjdabadi, T. N. Pham, E. C. Ashby, *Synthesis*, **1989**, 614.

5 E. C. Lee, K. M. McCauley, G. C. Fu, *Angew. Chem., Int. Ed*. **2007**, *46*, 977.

6 C. Jimeno, L. Cao, P. Renaud, *J. Org. Chem.* **2016**, *81*, 1251.

7 G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre, L. Sambri, *Angew. Chem., Int. Ed.* **2005**, *44*, 6219.

8 (a) D. C. Braddock, R. H. Pouwer, J. W. Burton, P. Broadwith, *J. Org. Chem*. **2009**, 74, 6042; (b) G. Cahiez, O. Gager, A. Moyeux, T. Delacroix, *Adv. Synth. Catal*. **2012**, *354*, 1519.

9 G. Cahiez, N. Lefèvre, M. Poizat, A. Moyeux, *Synthesis,* **2013**, *45*, 231.

10 (a) T. Nishikata, Y. Noda, R. Fujimoto, T. Sakashita, *J. Am. Chem. Soc*. **2013**, *135*, 16372; (b) T. Nishikata, K. Nakamura, K. Itonaga, S. Ishikawa, *Org. Lett*. **2014**, *16*, 5816; (c) T. Nishikata, S. Ishida, R. Fujimoto, *Angew. Chem., Int. Ed*. **2016**, *55*, 10008.

11 S. Krishnan, R. A. Hites, *Chemosphere*, **1980**, *9*, 679.

12 (a) K. Matyjaszewski, J. Xia, *Chem. Rev*. **2001**, *101*, 2921; (b) M. Kamigaito, T. Ando, M. Sawamoto, *Chem. Rev*. **2001**, *101*, 3689; (c) T. Pintauer, *Eur. J. Inorg. Chem*. **2010**, 2449; (d) W. T.; Eckenhoff, T. Pintauer, *Cat. Rev. Sci. Eng*. **2010**, *52*, 1; (e) J. M.; Muñoz-Molina, T. R. Belderrain, P. J. Pérez, *Eur. J. Inorg. Chem*. **2011**, 3155; (f) T. Pintauer, K. Matyjaszewski, *Chem. Soc. Rev*. **2008**, *37*, 1087.

13 J. F. Weiss, G. Tollin, J. T. Yoke, *Inorg. Chem*. **1964**, *3*, 1344.

14 P. H. Huy, S. Motsch, S. M. Kappler, *Angew. Chem., Int. Ed*. **2016**, *55*, 10145.

15 N.Sakai, T. Nakajima, S. Yoneda, T. Konakahara, Y. Ogiwara, *J. Org. Chem*. **2014**, *79*, 10619.

16 (a) B. Almarzoqi, A. V. George, N. S. Isaacs, *Tetrahedron*, **1986**, *42*, 601; (b) A. B.Rudine, M. G. Walter, C. C. Wamser, *J. Org. Chem*., **2010**, *75*, 4292. (c) X. Chen, T. Chen, Y. Zhou, C.-T. Au, L.-B. Hana, S.-F. Yin, *Org. Biomol. Chem*., **2014**, *12*, 247; (d) Y. Zhao, X. Chen, T. Chen, Y. Zhou, S.-F. Yin, L.-B Han. *J. Org. Chem*., **2015**, *80*, 62.

17 We took ^{1}H NMR of the crude. It looks like ammonium polymers and oligomers.

18 E. M. Zubanova, E. N. Golubeva, G. M. Zhidomirov, *Organometallics*, **2014**, *33*, 121.