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Black-Light-Induced Radical/Ionic Hydroxymethylation of Alkyl Iodides with Atmospheric CO in the Presence of Tetrabutylammonium Borohydride

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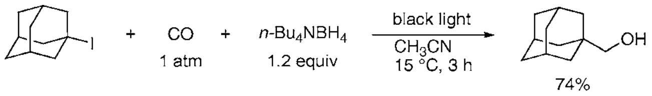
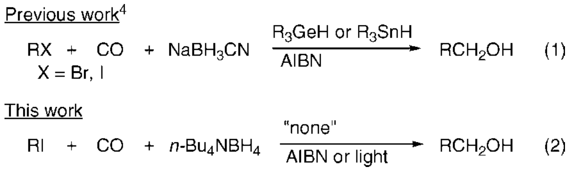
ABSTRACT



Tin-free radical/ionic hydroxymethylation of secondary and tertiary alkyl iodides proceeded efficiently in the presence of tetrabutylammonium borohydride as the hydrogen source under atmospheric pressure of CO in conjunction with photoirradiation using black light. Two possible mechanisms were proposed, both of which involve hybrid radical/ionic processes.

CO is among the most prominent sources of C1 in organic synthesis. A number of valuable transformations utilizing CO have been investigated thus far, irrespective of the reactive species.[1,2] One-carbon homologation generating alcohol derivatives is an important class of synthetic transformations,[3] and the use of CO for such processes is highly desirable. The related hydroxymethylation reaction process using organohalides was achieved by methodologies based on radical carbonylation and in situ reduction. In these processes, a combination of group 14 metal hydrides and cyanoborohydride reagents was used (Scheme 1, eq 1).[4]

Scheme 1. Hydroxymethylation of RX



Recently, we reported that the Giese reaction and the related radical carbonylation reaction proceeded in the presence of cyanoborohydrides under tin-free conditions.[5]

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(1) For reviews on radical carbonylations and acyl radicals, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991. (d) Schiesser, C. H.; Wille, U.; Matsubara, H.; Ryu, I. *Acc. Chem. Res.* **2007**, *40*, 303.

(2) For reviews on metal-catalyzed carbonylation processes, see: (a) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation, Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991. (b) Tsuji, J. *Palladium Reagents and Catalysis: Innovation in Organic Synthesis*; John Wiley & Sons: Chichester, U. K., 1995. (c) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A* **1995**, *104*, 17. (d) In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley: New York, 2002; Vol. 2, p 2309. (e) In *Modern Carbonylation Method*; Kollár, L., Ed.; Wiley-VCH: Weinheim, 2008. (e) Fukuyama, T.; Ryu, I. Carbon Monoxide. In *e-eros, Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, online source.

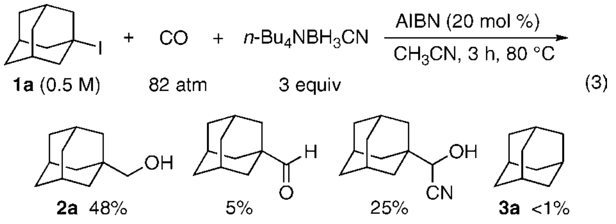
(3) For a recent example, see: Taber, D. F.; Paquette, C. M.; Reddy, P. G. *Tetrahedron Lett.* **2009**, *50*, 2462.

(4) For hydroxymethylation with triphenylgermane-$NaBH_3CN$ system, see: (a) Gupta, V.; Kahne, D. *Tetrahedron Lett.* **1993**, *34*, 591. For hydroxymethylation with a fluorous tin hydride-$NaBH_3CN$ system, see: (b) Ryu, I.; Niguma, T.; Minakata, S.; Komatsu, M.; Hadida, S.; Curran, D. P. *Tetrahedron Lett.* **1997**, *38*, 7883. (c) Matsubara, H.; Yasuda, S.; Sugiyama, H.; Ryu, I.; Fujii, Y.; Kita, K. *Tetrahedron* **2002**, *58*, 4071.

10.1021/ol1002847

The reaction is thought to involve iodine atom transfer from alkyl iodides to Giese adduct radicals followed by hydride reduction of the resulting carbon−iodine bond by cyanoborohydride. These results led us to consider that hydroxymethylation would also be possible without the aid of organotin reagents (Scheme 1, eq 2). Herein, we report that tertiary and secondary alkyl iodides can efficiently undergo a tin-free radical/ionic hydroxymethylation in the presence of tetrabutylammonium borohydride (n-Bu_4NBH_4) as a hydrogen donor. It is important to note that in many cases *carbonylation proceeded under atmospheric pressure of CO*. This method is simple and less toxic compared to the traditional conditions.

n-Bu_4NBH_3CN proved to be optimal in the tin-free Giese reactions;[5] therefore, we initially examined the reaction of 1-iodoadamantane (**1a**) and CO (82 atm) in the presence of n-Bu_4NBH_3CN (3 equiv) under thermal initiation conditions using AIBN as the radical initiator (eq 3). The excepted hydroxymethylation product **2a** was obtained in 48% yield along with 1-adamantane carboxaldehyde (5%) and, unexpectedly, its cyanohydrin (25%). It is noteworthy that the direct reduction product, adamantane (**3a**), was obtained in less than 1% yield and that the expected course of the reaction progressed even with a high concentration of the substrate (0.5 M). Another advantage is that this reaction does not require a very efficient hydrogen source, such as tin hydride. Hydrogen abstraction by alkyl radicals commonly competes with CO trapping, and high dilution conditions are typically required to make the relative concentrations of CO to tin hydride high.[4,6] It is reasonable to assume that **2a** forms by reduction of the initially formed 1-adamantane carboxaldehyde. On the other hand, the unexpected cyanohydrin was thought to form as a result of transfer of the cyano group from the borohydride reagent.[7]



(3)

Table 1. Hydroxymethylation of 1-Iodoadamantane (**1a**) with n-Bu_4NBH_4

$$\underset{0.5\ \text{M}}{\mathbf{1a}} + \text{CO} + \underset{1.2\text{–}1.5\ \text{equiv}}{n\text{-}Bu_4NBH_4} \xrightarrow[\substack{\text{conditions B:}\\ h\nu\ (15\ \text{W black light}),\ \text{rt},\ 3\ \text{h}}]{\substack{\text{conditions A:}\\ \text{AIBN (20 mol \%)},\ 80\ ^\circ\text{C},\ 3\ \text{h}}} \mathbf{2a} + \mathbf{3a}$$

				yield (%)[a]	
entry	CO (atm)	solvent	conditions	**2a**	**3a**
1[b]	85	CH_3CN	A	88	1
2	20	CH_3CN	A	79	2
3	10	CH_3CN	A	76	4
4	5	CH_3CN	A	73	8
5	1	CH_3CN	A	27	33
6[c,d]	1	CH_3CN	B	78	8
7[d]	1	CH_3CN	B	74	16
8	1	DMF	B	74	14
9[d,e]	1	CH_3CN	B	64	12

[a] For **2a**, isolated yield after column chromatography on SiO_2. For **3a**, yield was determined by GC analysis using n-nonane as an internal standard. [b] 3 equiv of n-Bu_4NBH_4 was used. [c] 500 W xenon lamp was used for irradiation. [d] The reaction was performed at a concentration of 0.25 M **1a**. [e] $NaBH_4$ (1.1 equiv) was used instead of n-Bu_4NBH_4.

In an effort to improve the yield of the hydroxymethylation product, screening of borohydride reagents was undertaken. Reductants such as $NaBH_4$, $NaBH(OAc)_3$, or $BH_3{\cdot}NMe_3$ gave poor results, whereas application of n-Bu_4NBH_4 provided the hydroxymethylation product **2a** in 88% yield (Table 1, entry 1). It should be noted that less than 2% yield of the reduction product, adamantane (**3a**), was detected by GC. This suggests that the carbonylation step by adamantyl radical was not hampered by the presence of n-Bu_4NBH_4. Neither aldehyde nor cyanohydrin was detected under the reaction conditions. Acetonitrile was found to be superior to hexane (50% yield), benzene (83% yield), toluene (72% yield), THF (78% yield), tetrahydropyran (73% yield), and EtOH (21% yield).

We next sought to determine whether the present hydroxymethylation would proceed under very low CO pressures. This may be possible because for this reaction an efficient hydrogen source (such as n-Bu_3SnH) is not present to quench alkyl radicals. In order to investigate this, 1-iodoadamantane (**1a**) was exposed to tin-free thermal radical conditions with n-Bu_4NBH_4 under low CO pressures (entries 2−5). Results indicated that hydroxymethylation product **2a** was obtained in 73% yield even under 5 atm of CO (entry 4).

Interestingly, when the reaction was performed using a CO balloon (1 atm), **2a** was still formed, albeit in low yield (entry 5). In this case, the yield of the reduction product **3a** increased up to 33% yield. This insufficient yield of **2a** was not improved by decreasing the concentration of the substrate or by lowering the reaction temperature to 40 °C with V-70 as the radical initiator.[8] At 1 atm of CO, a simple reduction course plagued the carbonylation. However, notable improvement was achieved by using photoirradiation conditions in place of thermal radical initiation. When a solution of **1a** and n-Bu_4NBH_4 in CH_3CN was irradiated with a 500 W xenon lamp through a Pyrex filter (>280 nm) for 3 h under

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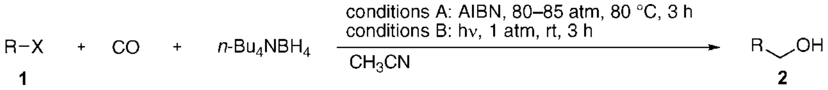
(5) Ryu, I.; Uehara, S.; Hirao, H.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 1005.

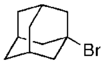
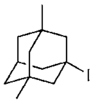
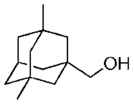
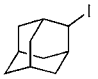
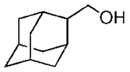
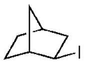
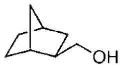
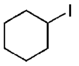
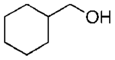
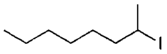
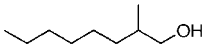
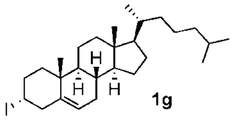
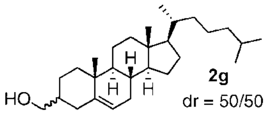
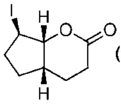
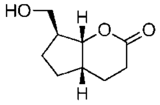
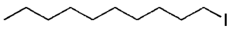
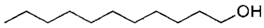
(6) (a) Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, M.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 1295. (b) Ryu, I.; Hasegawa, M.; Kurihara, A.; Ogawa, A.; Tsunoi, S.; Sonoda, N. *Synlett* **1993**, 143.

(7) Although a mechanism to produce cyanohydrin is unclear at this stage, either of the following pathways may be involved: addition of cyanide ion to an intermediate aldehyde or direct cyanation of the acyl radical to produce acylcyanide followed by hydride reduction. Further investigation to obtain the cyanohydrin product as a major component is currently underway in our laboratory.

(8) (a) Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K.; Matsugi, M. *Tetrahedron Lett.* **1997**, *38*, 3549. (b) Kita, Y.; Gotanda, K.; Sano, A.; Oka, M.; Murata, K.; Suemura, M.; Matsugi, M. *Tetrahedron Lett.* **1997**, *38*, 8345.

Table 2. Radical/Ionic Hydroxymethylation of a Variety of Alkyl Iodides



entry	1	conditions	2	yield (%)[b]
1	1a	A, 80 atm	2a	88
2		B, 1 atm		74
3	 **1a'**	A, 80 atm	2a	<3
4	 **1b**	A, 85 atm	 **2b**	91
5		B, 1 atm		70
6[c]	 **1c**	A, 85 atm	 **2c**	82
7		B, 1 atm		64
8	 **1d** *exo*/*endo* = 96/4	B, 1 atm	 **2d** *exo*/*endo* = 93/7	70
9	 **1e**	B, 1 atm	 **2e**	36
10	 **1f**	B, 1 atm	 **2f**	42[d]
11[e]	 **1g**	B, 1 atm	 **2g** dr = 50/50	48
12[f]	 **(±)-1h**	A, 80 atm	 **(±)-2h**	33
13		B, 1 atm		9
14	 **1i**	B, 1 atm	 **2i**	11[g]

[a] Conditions A: [**1**] = 0.5 M, CO (80−85 atm), AIBN (20 mol %), *n*-Bu$_4$NBH$_4$ (3 equiv), 80 °C, 3 h. Conditions B: [**1**] = 0.5 M, CO (1 atm), *n*-Bu$_4$NBH$_4$ (1.2 equiv), black light, 25 °C, 3 h. [b] Isolated yield after column chromatography on SiO$_2$. [c] Reaction time was 6 h. [d] 44% of *n*-octane was detected by GC. [e] Performed in benzene/CH$_3$CN (2:1) for 17 h with 0.17 M **1g**. [f] AIBN (30 mol %), *n*-Bu$_4$NBH$_4$ (1.2 equiv), 5 h. [g] 75% of *n*-decane was detected by GC.

a CO atmosphere, **2a** was obtained in 78% yield (entry 6). A similar result was obtained when a more energy-saving 15 W black light (peak wavelength 352 nm) was used (entry 7). The reaction was also effected in DMF (entry 8). To the best of our knowledge, this is the first example of a highly efficient radical carbonylation under atmospheric pressure of CO.

After identifying the optimal conditions, we next explored the generality of the tin-free radical hydroxymethylation by varying the alkyl iodides (Table 2). Among the substrates tested, tertiary iodides gave the best results (entries 1, 2, 4, and 5). This may be due to the facility of the iodine atom transfer step to cause the generation of the stable tertiary radical. In contrast, alkyl bromide was insusceptible to these conditions (entry 3). When the reactions were carried out with secondary iodides, yields were varied according to the structure of the substrate (entries 6−13). Photoirradiated hydroxymethylation of 2-iodoadamantane (**1c**) and 2-iodonorbornane (**1d**) at atmospheric CO afforded alcohols **2c** and **2d** in 64% and 70% yield, respectively (entries 7 and 8). On the other hand, simpler secondary iodides such as 1-iodocyclohexane (**1e**) and 2-iodooctane (**1f**) resulted in a lower yield, in which the reduction course preceded (entries 9 and 10).

These results suggested that the steric factor played a crucial role in efficient hydroxymethylation; the major side reaction was an S$_N$2-type hydride reduction by *n*-Bu$_4$NBH$_4$, which was suppressed by increasing the bulkiness around the reaction center. It is important to note that functionalized iodides such as cholesteryl iodide **1g** and iodolactone (±)-**1h** underwent hydroxymethylation to give alcohols **2g** and (±)-**2h**, the latter of which is a key synthetic intermediate of the polyketide natural product (entries 11 and 12).[9] We found that primary iodides were not suited for hydroxymethylation, due to competition by hydride reduction (entry 14).

Thus, we have succeeded in efficient hydroxymethylation of tertiary and secondary iodides without the use of group 14 radical mediators. It seems unusual that a significant

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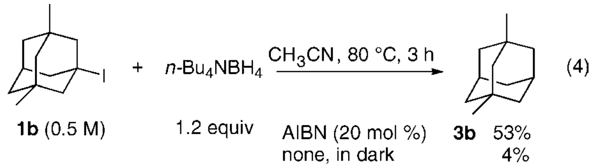
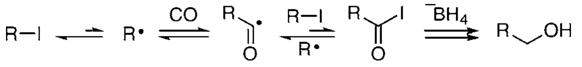
(9) Recently we completed the total synthesis of the polyketide natural product from (±)-**2h**. This report is being prepared.

amount of reduction product was formed in the reaction of a bulky tertiary iodide, such as **1a**, in the absence of a powerful hydrogen donor such as n-$\mathrm{Bu_3SnH}$ (see Table 1). **1a** can not undergo direct reduction through an ionic $\mathrm{S_N2}$ process; therefore, the adamantyl radical arising from **1a** directly abstracted a hydrogen from borohydride and certain electron transfer processes were thought to propagate the radical chain. In an effort to gain further insight, we performed some control experiments without CO. When a mixture of 3,5-dimethyl-1-iodoadamantane (**1b**), AIBN, and n-$\mathrm{Bu_4NBH_4}$ in $\mathrm{CH_3CN}$ was refluxed for 3 h without shading, the corresponding reduction product **3b** was obtained in 53% yield along with 25% recovery of **1b** (eq 4). On the other hand, the reaction in the absence of AIBN under dark conditions afforded a trace amount of **3b** (4%) and the starting iodide **1b** was recovered (85%) (eq 4). Similarly, **3b** was obtained in 35% yield together with 51% recovery of **1b** upon exposure of **1b** to black light in the presence of n-$\mathrm{Bu_4NBH_4}$ for 3 h at room temperature. These results indicated that radical processes were involved in the reduction of **1b** and n-$\mathrm{Bu_4NBH_4}$ served as the hydrogen source.

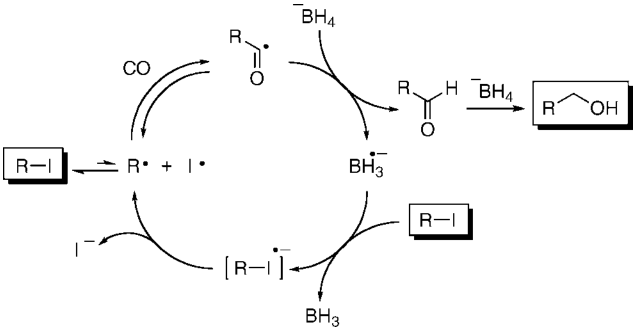


Taking the above results into consideration, two possible reaction mechanisms are conceivable for the present tin-free hydroxymethylation reaction. The first mechanism involves iodine atom transfer from alkyl iodides to acyl radicals followed by hydride reduction of the resulting acyl iodide (Scheme 2).[10−12]

Scheme 2. Atom-Transfer-Based Radical Chain Mechanism



Scheme 3. Alternative Radical Chain Mechanism Involving Electron Transfer



The second mechanism shown in Scheme 3 involves an electron transfer mediated by borohydride reagent[13] ($\mathrm{S_{RN}1}$ mechanism[14]). Thermal initiation or photoirradiation of alkyl iodides generates the initiating alkyl radicals ($\mathrm{R}^\bullet$), which react with CO to form acyl radicals ($\mathrm{RCO}^\bullet$). The acyl radicals abstract hydrogens from borohydride ($\mathrm{BH_4}^-$) to form aldehydes and generates the borane radical anions ($\mathrm{BH_3}^{\bullet -}$). While aldehydes undergo hydride reduction by borohydride anions to give alcohols, the generated borane radical anions ($\mathrm{BH_3}^{\bullet -}$) react with alkyl iodides (R-I) through electron transfer to give radical anions ($[\mathrm{R\text{-}I}]^{\bullet -}$) that fragment to alkyl radicals ($\mathrm{R}^\bullet$) and iodide ions (I^-), thus completing a radical chain. The reduction product formed at low CO pressure gives strong indication that this mechanism is feasible.

In conclusion, we have developed a novel hydroxymethylation reaction using CO and borohydride reagents without the use of toxic radical mediators such as trialkyltin hydrides or its precursors.[15] The reaction can be applied to tertiary and secondary iodides. Furthermore, a combined system involving atmospheric pressure of CO and black light irradiation was successfully employed. We have proposed a mechanism in which the borohydride reagents work both as a hydrogen source and a hydride source, and therefore act as a radical mediator.[16] The reaction conditions are simple and mild. Therefore, this reaction represents a useful method for introducing the hydroxymethyl unit into organic molecules.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from MEXT and JSPS, Japan.

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

OL1002847

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(10) For atom transfer carbonylation, see: (a) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16. Also see: (b) Nagahara, K.; Ryu, I.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1997**, *119*, 5465. (c) Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* **1998**, 1953. (d) Kreimerman, S.; Ryu, I.; Minakata, M.; Komatsu, M. *Org. Lett.* **2000**, *2*, 389. (e) Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *C. R. Acad. Sci., Paris, Chim.* **2001**, *4*, 497.

(11) For theoretical work, see: Matsubara, H.; Ryu, I.; Schiesser, C. H. *Org. Biomol. Chem.* **2007**, *5*, 3320.

(12) For Pd-boosted atom transfer carbonylations, see: (a) Fukuyama, T.; Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I. *Org. Lett.* **2006**, *8*, 1383. (b) Ryu, I.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2002**, *124*, 3812.

(13) A single electron transfer from borane radical anions to aryl halides has been proposed: (a) Barltrop, J. A.; Bradbury, D. *J. Am. Chem. Soc.* **1973**, *95*, 5085. (b) Kropp, M.; Schuster, G. B. *Tetrahedron Lett.* **1987**, *28*, 5295. (c) Liu, Q.; Han, B.; Zhang, W.; Yang, L.; Liu, Z.; Yu, W. *Synlett* **2005**, 2248.

(14) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.

(15) For a review on TEMPO-mediated tin-free radical chemistry, see: Vogler, T.; Studer, A. *Synthesis* **2008**, 1979.

(16) For examples of radical hydrogen abstraction from borane based reagents, see: (a) Ueng, S.-H.; Solovyev, A.; Yuan, X.; Geib, S. J.; Fensterbank, L.; Lacote, E.; Malacria, M.; Newcomb, M.; Walton, J. C.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 11256. (b) Barton, D. H. R.; Jacob, M. *Tetrahedron Lett.* **1998**, *39*, 1331. (c) Baban, J. A.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1195.