

Radical Addition of Alkyl Halides to Formaldehyde in the Presence of Cyanoborohydride as a Radical Mediator. A New Protocol for Hydroxymethylation Reaction

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S Supporting Information

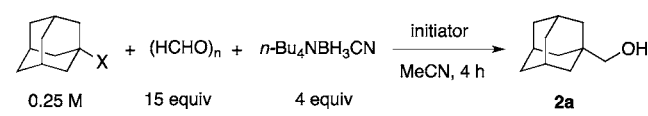
ABSTRACT: Hydroxymethylation of alkyl halides was achieved using paraformaldehyde as a radical C1 synthon in the presence of tetrabutylammonium cyanoborohydride as a hydrogen source. The reaction proceeds via a radical chain mechanism involving an alkyl radical addition to formaldehyde to form an alkoxy radical, which abstracts hydrogen from a hydroborate anion.

Whereas the use of formaldehyde as a C1 synthon is quite common in carbanion reactions,¹ the synthetic use of formaldehyde in radical reactions is rarely reported.^{2–4} In 1958, Fuller and Rust reported di-*tert*-butylperoxide-mediated reaction of cyclohexane with formaldehyde, leading to cyclohexanemethanol in 38% yield.² In 1965, a similar type of reaction with ethanol and formaldehyde to give ethylene glycol was reported by Oyama.^{3a} Later, the work was followed independently by Kollar^{3b–e} and Sanderson.^{3f,g} In 1972, Brown and co-workers reported the reaction of trialkylborane with formaldehyde under air to give one-carbon homologated alcohols, which is thought to involve alkyl radical addition to formaldehyde to form alkyl borate as the precursor to alcohols.⁴ While these reactions were noteworthy as pioneering efforts to use formaldehyde in radical reactions, in order to establish the usefulness of formaldehyde as a radical C1 acceptor,^{5,6} a novel efficient reaction system had to be explored.

Recently we reported that the radical hydroxymethylation of alkyl iodides can be carried out under atmospheric pressure of CO in the presence of borohydride reagents.⁷ We became interested in whether a system in which CO is simply replaced by formaldehyde would work for the hydroxymethylation of alkyl halides. In this Communication, we demonstrate that alkyl iodides and bromides undergo radical-mediated hydroxymethylation with paraformaldehyde in the presence of tetrabutylammonium cyanoborohydride (*n*-Bu₄NBH₃CN) as a radical mediator.⁸

1-Iodoadamantane (**1a**) was chosen as a model substrate for the initial study (Table 1). When a mixture of **1a**, paraformaldehyde, and *n*-Bu₄NBH₃CN in acetonitrile was irradiated with a 15 W black light (peak wavelength at 352 nm) in a Pyrex flask for 4 h under nitrogen, the desired 1-hydroxymethyladamantane (**2a**) was obtained in 85% yield (entry 1).⁹ The reaction using NaBH₃CN also gave **2a** in 70% yield; however, *n*-Bu₄NBH₄, NaBH₄, BH₃·NMe₃, and BH₃·NH₂*t*-Bu did not work, presumably due to rapid reduction of formaldehyde. The reaction using thermal conditions with

Table 1. Hydroxymethylation of 1-Haloadamantane with (HCHO)_n and *n*-Bu₄NBH₃CN



entry	X (1)	initiator	temp, °C	yield, % ^a
1	I (1a)	black light (15 W, Pyrex)	25	85
2 ^b	I (1a)	AIBN (20 mol %)	90	87
3	I (1a)	none	90	0
4 ^c	Br (1a')	black light (15 W, Pyrex)	25	0
5 ^c	Br (1a')	low-pressure Hg lamp (6 W, quartz)	25	85

^aIsolated yield by flash column chromatography on SiO₂. ^b(HCHO)_n, 7.5 equiv; *n*-Bu₄NBH₃CN, 2.0 equiv. ^cReaction time, 12 h.

2,2'-azobisisobutyronitrile (AIBN) as a radical initiator also worked well (entry 2), whereas the reaction with heating without AIBN did not proceed (entry 3). This suggests that the present reaction would proceed via a radical chain process. When 1-bromoadamantane (**1a'**) was irradiated with a 15 W black light, no hydroxymethylation product was obtained. However, irradiation using a 6 W low-pressure Hg lamp (peak wavelength at 254 nm) through a quartz tube effected a smooth hydroxymethylation reaction, which gave 85% yield of **2a** (entry 5).

Encouraged by the results shown in Table 1, we then applied these reaction conditions to the hydroxymethylation of various alkyl halides (Table 2). Substituted 1-iodoadamantanes **1b** and **1c** gave the corresponding alcohols **2b** and **2c** in good yields (entries 3 and 4). Similarly, 1,3-diiodoadamantane (**1d**) underwent dihydroxymethylation to give diol **2d** in 77% yield (entry 5). Secondary alkyl halides **1e**, **1f**, and **1g** also reacted smoothly with formaldehyde to form the corresponding alcohols **2e**, **2f**, and **2g** in good yields (entries 6–8). However, in the reaction of primary alkyl halides such as 1-iododecane (**1h**) and (2-bromoethyl)benzene (**1i**), the yields of the hydroxymethylated products were low (entries 9 and 10). This is due to the competitive direct S_N2 reduction of the alkyl halides by the hydride anion. 2-Methoxyiodocyclohexane (**1j**) underwent hydroxymethylation to give alcohol **2j** in 50% yield (entry 11). In the case of 2-allyloxyiodocyclohexane (**1k**), a bicyclic alcohol

Received: November 10, 2011

Published: December 20, 2011

Table 2. Radical Hydroxymethylation of Alkyl Halides 1 To Give Alcohols 2

Entry	Alkyl Halide	Method ^a	Alcohol	Yield (%) ^b
1	R ¹ = R ² = H, X = I	1a A	2a	85
2	R ¹ = R ² = H, X = Br	1a' B	2a	86
3	R ¹ = R ² = Me, X = I	1b A	2b	85
4	R ¹ = H, R ² = OH, X = I	1c C	2c	77
5 ^c		1d C	2d	77
6		1e A	2e	80
7		1f A	2f	82 exo/endo = 99/1
8		1g B	2g	57
9	C ₁₀ H ₂₁ I	1h B	2h	25
10		1i B	2i	41
11		1j C	2j	50 trans/cis = 78/22
12		1k C	2k	39 dr = 75/25
13 ^d		1l B	2l	16 dr = 93/7
			3	7
			4	14 dr = 85/15

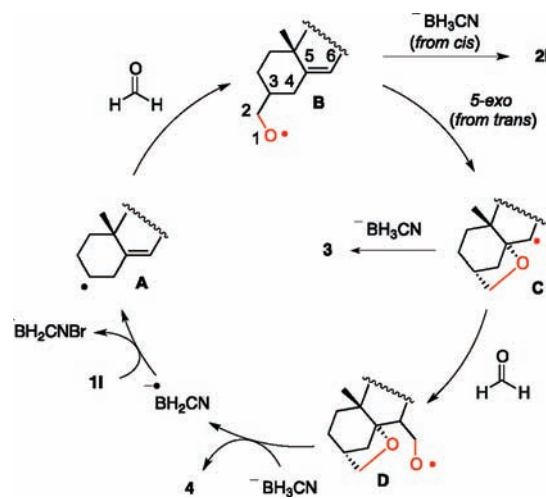
^aMethod A: black light (15 W, Pyrex), rt. For entries 1, 3, and 6, 4 h. For entry 7, 18 h. Method B: low-pressure Hg lamp (6 W, quartz), rt, 12 h. Method C: AIBN (20 mol %), 90 °C. For entries 4 and 12, 6 h. For entry 5, 8 h. For entry 11, 22 h. ^bIsolated yield by flash chromatography on SiO₂. ^c*n*-Bu₄NBH₃CN, 8.0 equiv. ^dPerformed in MeCN/C₆H₆ (2:1).

(2k) was formed in 39% yield via sequential 5-exo radical cyclization and addition to formaldehyde (entry 12). The reaction of cholesteryl bromide (1l) was intriguing in terms of a radical cascade and the stereochemistry (entry 13). Hydroxymethylation product 2l was obtained stereoselectively, along with cyclized products 3 and 4, the latter of which incorporated two molecules of formaldehyde. This is in contrast to our former hydroxymethylation system using CO, which gave inherently a *cis/trans* mixture of a hydroxymethylation product.⁷ It should be noted that acetaldehyde also

reacted with 1a to give the corresponding α -adamantyl ethanol, albeit in low yield.

The mechanistic rationale for the reaction of 1l with formaldehyde and *n*-Bu₄NBH₃CN is summarized in Scheme 1.

Scheme 1. Possible Radical Chain Mechanism



Radical initiation generates the alkyl radical A from 1l, which adds to formaldehyde to give a *cis/trans* mixture of alkoxy radical B. Whereas 3 α -alkoxy radical B (*trans*) undergoes 5-exo cyclization to give C, which would add to a second molecule of formaldehyde to give D, 3 β -alkoxy radical B (*cis*) encounters steric difficulties in undergoing 5-exo cyclization. Thus-formed alkoxy radicals abstract hydrogen from BH₃CN⁻ to form alcohols 2l and 4.^{10–13} The resulting borane radical anion BH₂CN^{•-} would abstract the bromine atom from 1l to form A.^{13,14}

To date, formaldehyde has seldom been utilized in radical chain reactions. However, as the present results demonstrate, when coupled with a judicious choice of radical mediator, such as a borohydride reagent, formaldehyde can serve as a useful C1 radical synthon. Applications of formaldehyde in radical cascade reactions as well as further mechanistic studies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and sample spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas (No. 2105) from the Ministry of Education, Culture, Sports, and Technology (MEXT), Japan.

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