

## Radical Reactions with Alkyl and Fluoroalkyl (Fluorous) Tin Hydride Reagents in Supercritical CO<sub>2</sub>

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Received April 8, 1997

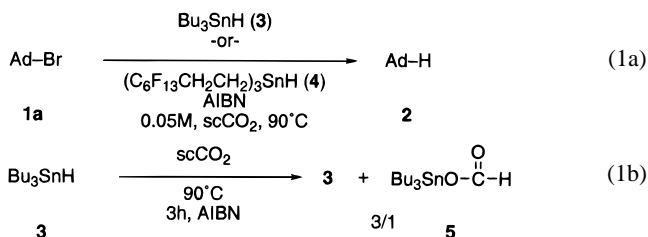
Carbon dioxide in the supercritical state has been touted as a suitable solvent for organic synthesis for an assortment of environmental and practical reasons.<sup>1,2</sup> Carbon dioxide is not classified as a VOC (volatile organic chemical) by the EPA, nor is it regulated in food contact applications by the FDA. In addition, carbon dioxide is inexpensive and nonflammable and has a readily accessible supercritical region ( $P_c = 1044$  psig,  $T_c = 31$  °C).

Despite these and other favorable features, the use of supercritical CO<sub>2</sub> as a reaction solvent<sup>2</sup> has lagged far behind its applications in extraction, chromatography, and other separation processes.<sup>1</sup> This is because there appear to be at least two very broad limitations for many kinds of preparative organic reactions. First, the use of CO<sub>2</sub> as a solvent in polar reactions will be limited because CO<sub>2</sub> is nonpolar and because, even though it is quite unreactive,<sup>2e</sup> it may not be suitable for certain reaction classes that rely on strong nucleophiles or electrophiles. Second, carbon dioxide is a relatively low dielectric fluid that is incapable of dissolving large quantities of many organic compounds at moderate pressures.<sup>3</sup> Most organic reactions require reagents (or catalysts), and problems arise when either or both of the reactants and the reagents are substantially insoluble in CO<sub>2</sub>.

A prospective solution to the first problem is to use radical reactions, which require neither nucleophiles nor electrophiles and proceed well in nonpolar solvents.<sup>4</sup> Tanko and Blackert<sup>5a</sup> have reported benzylic brominations in CO<sub>2</sub>, and DeSimone<sup>5b</sup> has used CO<sub>2</sub> as a medium for radical polymerizations. A

solution to the second problem is to use "fluorous" (highly fluorinated) reagents<sup>6</sup> because organofluorine compounds are well-known to be highly soluble in supercritical CO<sub>2</sub>.<sup>2f,h,3,5b</sup> We report herein the combination of these two solutions: typical radical reactions can be conducted in supercritical CO<sub>2</sub> at moderate pressures with a recently introduced fluorous tin hydride.<sup>6b</sup>

We investigated in some detail the simple reduction of bromoadamantane **1** to adamantane **2** (eq 1a). All radical reactions were conducted by initial pressurization to 850 psig followed by heating to 90 °C (2500 psig) and pressurization to 4000 psig, and the substrate concentration was 0.05 M. It is already known that adamantane **2** is poorly soluble under these conditions.<sup>7</sup> In contrast, bromoadamantane **1a** is soluble in supercritical CO<sub>2</sub> even at 0.22 M. As expected, tris(perfluorohexylethyl)tin hydride **4** was soluble under the reaction conditions (at 0.06 M), but the mixture with tributyltin hydride **3** was not homogenous even at 7000 psig. Thus, with this reagent it is possible that some of the reactions are not occurring in the CO<sub>2</sub> phase. A control experiment under the reaction conditions also showed that tributyltin hydride **3** itself reacts with supercritical CO<sub>2</sub>, albeit inefficiently (eq 1b). Heating of **3** and AIBN in CO<sub>2</sub> at 90 °C for 3 h followed by evaporation of the CO<sub>2</sub> provided a mixture of the starting tin hydride **3** and tributyltin formate **5**<sup>8</sup> in a ratio of 3/1.<sup>9</sup> In contrast, the fluorous tin hydride **4** did not produce a fluorous tin formate but was recovered unchanged.



Solutions of bromoadamantane **1a** (0.05 M, 0.85 mmol), AIBN (10%), and either tributyltin hydride **3** (1 mmol) or fluorous tin hydride **4** (1 mmol) were heated for 3 h at 90 °C at 4000 psig of CO<sub>2</sub> in a standard reactor. The bromide was consumed in both reactions. The reactor was cooled, and the CO<sub>2</sub> was vented through ether to collect the entrained products. The crude product from the tributyltin hydride was purified by the "DBU workup"<sup>10</sup> to provide adamantane **2** in 88% yield, while the reaction with the fluorous tin hydride **4** was purified by partitioning between FC-72 (perfluorohexane) and benzene<sup>6b</sup> to provide adamantane **2** in 90% yield.

Similar reduction of a primary iodide and the steroidal iodide, bromide, and phenyl selenide **6a–c** provided the corresponding reduced product **7** in high yields, as indicated in eq 2. Yields were comparable with tributyltin hydride and the fluorous tin hydride, but the reactions with the fluorous tin hydride were easier to purify, and the corresponding fluorous tin byproduct, (C<sub>6</sub>F<sub>13</sub>CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>SnX (**8a–c**, X = I, Br, or PhSe), was isolated in >90% yield by evaporation of the FC-72 phase. No attempt

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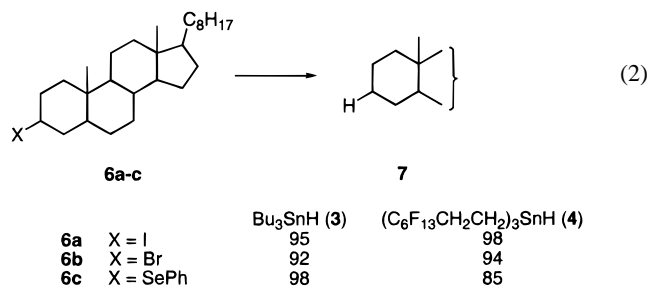
(7) McFann, G. J.; Johnston, K. P.; Hurter, P. N.; Hatton, T. A. *IEC Res.* **1993**, *32*, 2336.

(8) The formate was identified by comparison with authentic material prepared by the direct reaction of bis(tributyltin)oxide with formic acid. Ohara, M.; Okawara, R. *J. Organomet. Chem.* **1965**, *3*, 484.

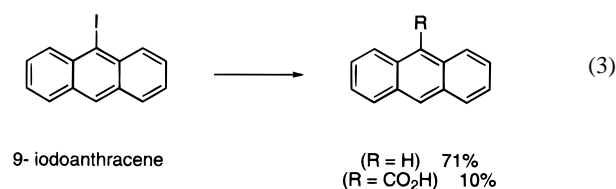
(9) No tin formate was formed in an experiment conducted without AIBN.

(10) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

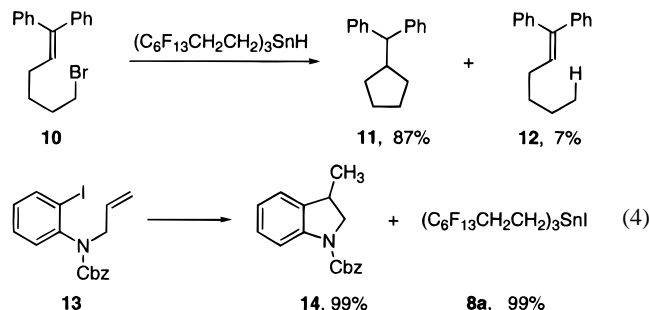
was made to recover the tributyltin products after DBU workup. No evidence for carboxylated products was obtained in these experiments.



In contrast, reduction of 9-iodoanthracene with the fluororous tin hydride **4** provided anthracene in 71% yield along with 10% yield of 9-anthracenecarboxylic acid (eq 3). It thus appears that there is some potential to carboxylate reactive radicals in supercritical CO<sub>2</sub>, and carboxylation could presumably be increased by raising the CO<sub>2</sub> density. This is important because carboxylation is rare in radical chemistry (while decarboxylation is common), and because the use of supercritical CO<sub>2</sub> as a reagent has heretofore been difficult.<sup>2e,f,11</sup>

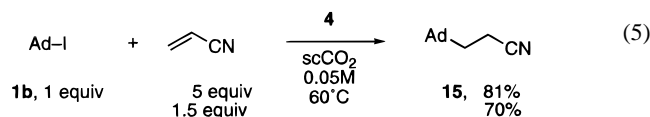


Reduction of 1,1-diphenyl-6-bromo-1-hexene **10** under the standard conditions with the fluororous tin hydride **4** provided the 5-*exo* cyclized product **11** in 87% isolated yield along with 7% of the reduced product **12** (eq 4). Interestingly, reduction of **10** under the standard conditions in liquid benzotrifluoride (1 atm) provided only the cyclized product **11**, which was isolated in 75% yield.<sup>12</sup> The absence of the reduced product is expected since all the relevant rate constants are known,<sup>13</sup> and hydrogen transfer cannot compete with cyclization under these conditions. Although effects of phase separation cannot be firmly ruled out, we speculate that some reduced product **12** forms in supercritical CO<sub>2</sub> because diffusion in supercritical solvents is faster than in liquids.<sup>12</sup> This would allow bimolecular reduction to compete more efficiently with cyclization. Significantly, the reduction of **10** with tributyltin hydride **3** produced neither **11** nor **12** but returned **10** and **3** along with some tin formate **5**. Although additional solubility studies are needed, this failure may be due to the insolubility of **10** and **3**. Reduction of the aryl iodide **13** with **4** provided **14** in 99% yield along with 99% of the tin iodide **8a**.



(11) Anionic carboxylations under electrochemical conditions: Sullenberger, E. F.; Dressman, S. F.; Michael, A. C. *J. Phys. Chem.* **1994**, *98*, 5347.

The standard Giese reaction shown in eq 5 was also conducted. Addition of iodoadamantane **1b** to acrylonitrile (5 equiv) provided the radical adduct **15** in 81% yield after flash chromatography. Also formed in this experiment was an acetone-soluble material that we assume is polyacrylonitrile.<sup>5b</sup> When 1.5 equiv of acrylonitrile was used, compound **15** was isolated in 70% yield, and the formation of the acetone-soluble material was not observed.



The simplicity of these experiments belies their significance. Although the favorable features of using supercritical CO<sub>2</sub> as a reaction medium for organic synthesis have been widely cited for over a decade, it is still not very clear what kinds of reactions to run in supercritical CO<sub>2</sub> and how to run them. Tin hydrides and related reagents are now commonly used in synthesis to make C–H, C–C, and (to a lesser extent) C–N and C–O bonds. Although further studies are surely needed, wholesale porting of this reaction class to supercritical CO<sub>2</sub> now seems like a viable possibility. Furthermore, the use of highly CO<sub>2</sub>-soluble fluororous reagents and catalysts<sup>2b</sup> should prove to be a valuable strategy to transport other reaction classes to CO<sub>2</sub>. In addition, there are now fluororous protecting groups available,<sup>6c</sup> and these could be used to confer additional solubility on the reaction substrates themselves. The solubility problem can also be viewed from the other side: fluororous chemistry is providing useful new options in both traditional and parallel synthesis,<sup>6e,14</sup> but one of the main problems in this field is choosing a reaction solvent. Supercritical CO<sub>2</sub> provides a valuable addition to the existing complement of solvents available to dissolve both fluororous and organic compounds.

Ultimately, the biggest advantage of coupling fluororous reagents with synthetic chemistry may be at the separation stage. At the end of many reactions, the problem of separating products from spent and unspent reagents remains. The use of environmentally friendly reaction solvents like supercritical CO<sub>2</sub> makes little sense if the reactions are followed by standard extractions or chromatographies with traditional organic solvents—extractions and chromatographies invariably require more solvent volumes than the reactions that precede them. However, it seems probable that the large differences in solubility in supercritical CO<sub>2</sub> between fluororous and organic compounds can be translated into practical separation procedures. In the long run, the CO<sub>2</sub> should serve as both the reaction and the separation solvent.

**Acknowledgment.** We thank the National Institutes of Health for funding this work.

**Supporting Information Available:** A representative experimental procedure for the reductions, a summary of the solubility experiments, and representative spectra of crude products (7 pages). See any current masthead page for ordering and Internet access instructions.

JA971120I

(12) Heating of **10** and **4** for 12 h at 90 °C with AIBN returns mostly recovered starting materials, presumably because **10** and **4** are not miscible. This suggests that reactions with **4** are occurring in the CO<sub>2</sub> phase. Heating of **10** and **4** with a minimal amount of benzotrifluoride (estimated concentration 0.6 M) provided the following yields: **11**, 62%; **12**, 6%; **10**, 21%.

(13) Curran, D. P.; Hadida, S.; Horner, J. H.; Martinez, F. N.; Newcomb, M. *Tetrahedron Lett.* **1997**, *38*, 2783.

(14) Curran, D. P. *Chemtracts—Org. Chem.* **1996**, *9*, 75.