ORGANIC LETTERS

1999
Vol. 1, No. 8
1275−1277

Convenient Catalytic Free Radical Reductions of Alkyl Halides Using an Organotin Reagent on Non-Cross-Linked Polystyrene Support

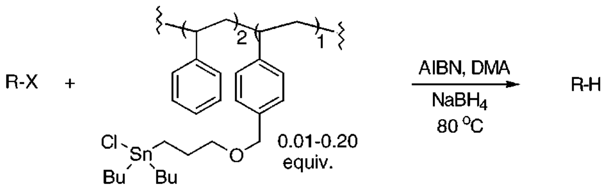
Eric J. Enholm* and James P. Schulte II

Department of Chemistry, University of Florida, Gainesville, Florida 32611

enholm@chem.ufl.edu

Received August 13, 1999

ABSTRACT



A highly efficient and catalytic organotin reagent on soluble support has been developed for free radical reactions. The non-cross-linked polystyrene copolymer support allows solubility in most organic solvents such as $CHCl_3$, benzene, THF, dimethylacetamide (DMA), DMF, and EtOAc; however, the tin reagent can be readily obtained as a white powder from cold methanol. A variety of alkyl halides (1°, 2°, 3°, aryl) underwent radical reductions in good isolated yields (60–93%) using only 0.01–0.2 equiv of the polymer catalyst.

The reduction of alkyl halides with tributyltin hydride is one of the most common and highly successful free radical transformations in organic synthesis.[1] Removal of excess tin reagents, byproducts, and impurities has been a tenacious problem with these reactions, even on a small laboratory scale.[2] Moreover, tributyltin hydride has been avoided in the manufacturing industry and in the synthesis of medicinal agents and pharmaceuticals, due to the environmental and physiological toxicity of organotin compounds.[2a]

One way to avoid these difficulties is with catalytic tin hydride radical reactions, using only very small substoichiometric amounts of tin hydride. Significant efforts have been advanced in this area; however, some organotin compounds persistently remain in solution.[3] Recently, a few reports have focused on preparing tin reagents on solid resin support, where the tin reagents can be removed by a mechanical separation such as filtration.[4] Unfortunately, most of these reactions require manyfold excesses of tin reagents on resin support and up to 3−4 equiv of AIBN inititator, normally used catalytically, to go to completion. These resins are *insoluble* polymer supports, requiring long reaction times (often >12 h), because a two-phase reaction is involved.[5]

It had occurred to us that a *soluble* support for free radical reactions would have several advantages (vide infra). Reactions using linear copolymers of poly(ethylene glycol) and polystyrene have recently been investigated, particularly in

---

[1] (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press: New York, 1986. (b) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (c) Curran, D. P. *Synthesis* **1988**, *417*, 489. (d) Hart, D. J. *Science* **1984**, *223*, 883. (e) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: New York, 1992.

[2] (a) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200. (b) Farina, V. *J. Org. Chem.* **1991**, *56*, 4985. (c) Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140. (d) Berg, S. M.; Roberts, S. M. *Synthesis* **1979**, 471.

[3] (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. (c) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4.

[4] (a) Miller, B. L.; Hershberger, J. W. *J. Polym. Sci.* **1987**, *25*, 219. (b) Gerik, M.; Jurdens, F.; Kuhn, H.; Neumann, W. P.; Peterseim, M. *J. Org. Chem.* **1991**, *56*, 5971. (c) Dumartin, G.; Ruel, G.; Kharboutli, J.; Delmond, B.; Connil, M.-F.; Jousseaume, B.; Pereyre, M. *Synlett* **1994**, 952. (d) Chemin, A.; Deleuze, H.; Malliard, B. *Eur Polym. J.* **1998**, 1395. (e) Dumartin, G.; Pourcel, M.; Delmond, B.; Donard, O.; Pereyre, M. *Tetrahedron Lett.* **1998**, 4663.

[5] Narita, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1477.

10.1021/ol990945p CCC: $18.00

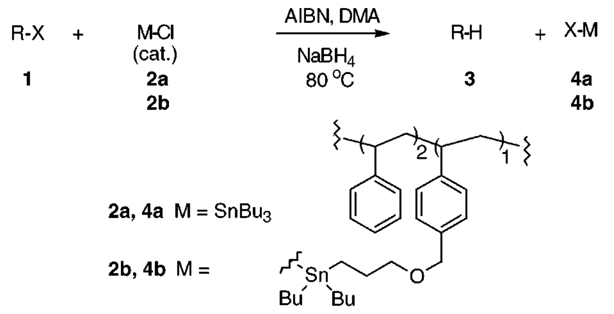
the laboratories of Janda.[6] The application of these polymers to free radical reactions, however, has currently not been reduced to practice. These studies will show that an organotin reagent can be mounted on soluble support and react in catalytic amounts with alkyl halides in a free radical reaction. These reactions appear to rival solution phase catalytic reactions with $^n\mathrm{Bu}_3\mathrm{SnH}$, both in short reaction times (typically <2 h) and similar sub-stoichiometric amounts of tin reagents.[3]

We have recently started a program of liquid phase organic chemistry (LPOC) using non-cross-linked polystyrene supported reactions and reagents.[7] This soluble polymer support differs markedly from the standard 2−3% divinylbenzene cross-linked resin polymers currently used in solid phase organic chemistry (SPOC).[3,4] The use of non-cross-linked polystyrene allows for the complete organic solubility (EtOAc, benzene, $CHCl_3$, CH_2Cl_2, and THF) of each product in the synthesis and in subsequent free radical reactions of the stannane reagent.[6,7] Because a single phase is utilized with non-cross-linked polystyrene, the reactions have rates up to 100 times faster than those of standard cross-linked solid-phase methods.[5]

Unlike classic cross-linked resins, these reactions can be conveniently monitored by standard ^{1}H NMR spectroscopy without cleavage from polymer support.[6,7] Intermediate product steps used to prepare a stannane reagent and tin halide byproducts obtained after the radical reaction are virtually quantitatively obtained as white crystalline-like solids filtered from cold methanol.[6,7] Also, commercial resins are often found to have a very low percentage of reactive sites available (Wang resin = 1.0−1.5 mmol/g of resin; Merrifield resin = 1.0−1.5 mmol/g of resin). This means that for a prep-scale reaction to occur, a significant amount of resin would be needed.

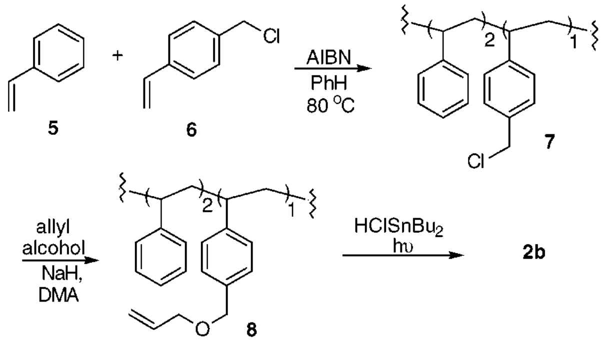
Scheme 1 shows the reaction we wished to investigate involving the simple catalytic reduction of an alkyl halide **1** with polystyrene-supported tin chloride reagent **2b**.[8] Corey and Suggs originally developed the solution phase procedure for use with $^n\mathrm{Bu}_3\mathrm{SnCl}$ (**2a**) with $NaBH_4$, which would allow for catalytic use of the tin reagent in these studies.[3a] Because polystyrene readily precipitates from the ethanol solvent used in this method, DMA, which allows the polymer to remain in solution, was substituted. Of initial concern in this regard was the limited solubility of the sodium borohydride under these conditions.

Scheme 1



The polymer was constructed as shown in Scheme 2. To obtain a large amount of reactive sites and reduce the amount of polymer used in each reaction, styrene and *p*-chloromethylstyrene were reacted in a 2:1 ratio to prepare the non-cross-linked copolymer **7** in 94% yield.[5] Confirmation of the presence and content of the CH_2Cl functionality was corroborated by direct proton ^{1}H NMR integration in $CDCl_3$, giving an active content value (ACV) of 2.77 mmol/g of chloride **7**. Subsequent formation of allyl ether **8** by S_N2 displacement (74%) and photochemical hydrostannylation using $HClSnBu_2$ gave the desired tin chloride **2b** in 93% yield with an active content value of 2.62 mmol/g.[9] It is worth noting that all of these intermediates are precipitated white powders. The crystalline-like nature of non-cross-linked polymers allows for convenient handling of potentially toxic tin reagents.

Scheme 2



It can be seen from Table 1 that the reductions of alkyl halides with **2b** were highly successful. Yields ranging from 60% to 93% were obtained from isolated products. Typically, the alkyl halide was dissolved in DMA and heated to 80 °C with 0.1 equiv of **2b** and 1.5 equiv of $NaBH_4$. After stirring for 2.5 h and then cooling, the reaction solution could be directly applied to a flash column to isolate the pure product without tin impurities. Except for the special cases, such as some aromatic halides discussed below, most reactions were complete in 2.5 h.

Products of tertiary halides such as adamantane (**10**) could be isolated in 60% yield (GC yield = 99%) in 2 h. Primary alkyl halides in entries 2 and 3 reacted quickly, requiring only 0.5−1 h. To test the catalyst's limitations, some reactions had only 0.01 equiv of polymer **2b** present (entries 4−6 and 9) and some reactions took longer; for example,

---

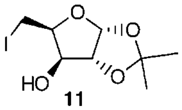
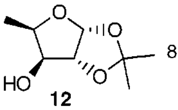
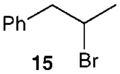
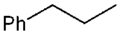
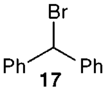
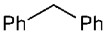
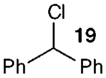
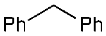
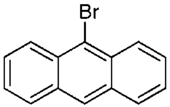
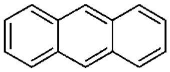
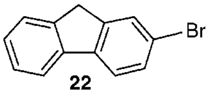
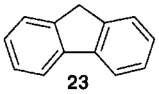
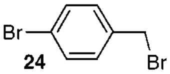
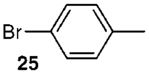
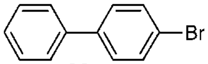
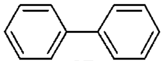
(6) For a review, see: Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. See also: Chen, S.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 3943.

(7) Enholm, E. J.; Gallagher, M.; Moran, K. M.; Lombardi, J. S.; Schulte, J. P., II. *Org. Lett.* **1999**, *1*, 689.

(8) For a "fluorous" approach to this problem, see: Curran, D. P.; Hadida, S.; Kim, S.-Y.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 6607.

(9) Gerigk, U.; Gerlach, M.; Neumann, W. P.; Vieler, R.; Weintritt, V. *Synthesis* **1990**, 448.

Table 1. Catalytic Reduction of Alkyl Halides by a Non-Cross-Linked Polymer Supported Tin Chloride

Entry	Substrate	Time (h)	**2b** (equiv.)	Product	Yield
1	adamantyl bromide (**9**)	2	0.20	adamantane (**10**)	60% (99%)[a]
2	 **11**	1	0.10	 **12**	85%
3	dodecyl iodide (**13**)	0.5	0.10	dodecane (**14**)	88%
4	 **15**	6.5[b]	0.01	 **16**	93%
5	 **17**	1	0.01	 **18**	88%
6	 **19**	6	0.01	 **18**	74%[c]
7	 **20**	2.5	0.1	 **21**	80%
8	 **22**	24	0.2	 **23**	74%[d]
9	 **24**	1	0.01	 **25**	86%
10	 **26**	7	0.2	 **27**	96%

[a] GC yield. [b] GC shows the reaction complete in 0.5 h when 0.1 equiv of catalyst is used. [c] Nonisolated yield by GC, 74% conversion with 26% starting material remaining. [d] Under identical conditions without **2b**, the reaction was 30% complete after 24 h.

15 needed 6.5 h. Increasing the catalyst to 0.1 equiv afforded total conversion in 0.5 h, by GC analysis.

A comparison was made to appraise the efficiency of the catalyst at reducing 2-bromofluorene (**22**) to fluorene (**23**). Using 0.2 equiv of the polymer catalyst and 2.5 equiv of $NaBH_4$, GC and TLC analysis showed that the reaction went to completion in 24 h. Under the exact same conditions, without use of catalyst **2b**, only 30% conversion to product occurred after the same amount of time. In all reactions, ^{13}C NMR and ^{1}H NMR analysis indicated no contamination by tin byproducts. This method was also found to be very convenient for the regioselective reaction of *p*-bromobenzylbromide (**24**) in entry 9 (86% yield). When just 0.01 equiv of the tin polymer catalyst was used, *p*-bromotoluene (**25**) was obtained in 1 h.

Tin chloride reagent **2b** was investigated for residual tin pollution in a typical free radical reaction.[4e] Dodecyl iodide (**13**) and aromatic bromide **26** were each reacted with **2b**, and reduction products dodecane (**14**) and biphenyl (**27**) were obtained, respectively, by flash column chromatography. Compounds **14** and **27** were each dissolved in nitric acid and tested for ppm tin using ICP-MS. We obtained 5.4 (± 0.1) ppm and 11.1 (± 0.1) ppm for the reactions of **14** and **27**, respectively. A test sample of unreacted precipitated **2b** was also dissolved in nitric acid and ICP MS which gave 540 (± 10) ppm. We conclude from these studies that the catalytic tin byproducts from the reactions are readily reduced to extremely minute levels using our simple procedure.

In summary, the new and highly effective catalyst **2b** was designed for free radical reduction of alkyl halides in high yields without substantial byproducts. Non-cross-linked polystyrene supported the tin chloride catalyst as a white solid which was soluble in organic solvents.

Acknowledgment. We gratefully acknowledge support by the National Science Foundation (Grant CHE-9708139) for this work. We also thank B. W. Smith, E. E. Austin, and the NSF Engineering Research Center for Particle Science and Technology at the University of Florida for the ICP-MS results.

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

OL990945P