Reductions and Radical Cyclizations of Aryl and Alkyl Bromides Mediated by NaBH₄ in Aqueous Base

Roopa Rai and David B. Collum*  
Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, N.Y. 14853-1301

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Abstract: Reductions and free radical cyclizations of alkyl- and aryl bromides are effected in aqueous base by NaBH₄ in conjunction with a base-soluble dialkyltin(IV) reagent and 4,4'-azobis(4-cyanovaleric acid) (ACVA). The aryl bromides reduce at lower rates under tin-free conditions using simply NaBH₄-ACVA.

As part of a developing interest in aqueous organic chemistry,¹ our attention was drawn to the chemistry of carbon centered radicals.² Although many water-compatible reactions likely involve radical intermediates, explicit aqueous radical chemistry is not well developed.³ The most prominent example is that reported by Breslow and Light entailing aqueous reductions using the water-soluble (MeOCH₂CH₂OCH₂CH₂CH₂SnH (1) with the aid of a commercially available, water soluble initiator 4,4'-azobis(4-cyanovaleric acid) (ACVA).⁴ Mixtures of 1 and ACVA certainly offer extremely viable water-compatible equivalents to the n-Bu₃SnH/AIBN combination used so frequently in organic solvents. However, the requisite 5-step synthesis of 1 proved restrictive for our needs. We had the notion that in situ reduction⁵ of a more accessible water-soluble tin halide (or pseudo-halide) by NaBH₄ might offer a useful alternative to the Breslow-Light protocol.

We prepared dialkyltin(IV) reagent 2 by modifying a literature hydrosstannylation protocol⁶ as shown in eq 1. The identity of 2 was difficult to establish due to its insolubility in water and the standard organic solvents. The assignment is based upon elemental analysis,⁷ IR data,⁷ and the propensity of tin acylates to form insoluble polymers.⁸ Compound 2 readily dissolves in aqueous base, affording a species exhibiting NMR spectroscopic properties consistent with 3. Furthermore, acidification causes immediate precipitation of 2.

Heating a solution of m-bromobenzoic acid, 2 (i.e. 3, 1.2 equiv), NaBH₄ (2.0 equiv), and ACVA (0.1-1.0 equiv) in degassed 1.5% KOH/H₂O at 80 °C for several hours affords benzoic acid in near quantitative yield.
Photolysis does not measurably influence the reaction rates or yields. A limited survey of radical cyclizations (Table I) revealed rates and isolated yields that are comparable to those obtained using n-Bu₃SnH/AIBN on the corresponding esters in benzene. We observed no unusual effects of the water. A resistance of alkyl- and aryl chlorides to reduce should be noted. Additionally, efforts to generate a preformed tin-hydride species analogous to the Breslow-Light reagent for reduction of NaBH₄-sensitive substrates met with little success.

Table I. Reduction of aryl and alkyl bromides by aqueous NaBH₄-ACVA-3.

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Substrates (0.04 mmol) were reduced at 90 °C in degassed 1.5% aq KOH (1.33 mL) containing NaBH₄ (2.0 equiv), ACVA (1.0 equiv), and 2 (1.2 equiv). Normal extractive workup, esterification with ethereal CH₂N₂ and purification (flash chromatography) afforded the reported yields. Isolated as a mixture containing two of four possible stereoisomers. Equilibrations with TiCl₄ and analogy with literature reports (Stork, G.; Mook, R.; Billen, S. A.; Rychnovsky, S. D. J. Am. Chem. Soc. 1983, 105, 3741) implicate trans 1,2 stereochemistry with a mixture at the acetal. Mixture of both stereoisomers.
Control experiments revealed that the ACVA radical initiator and NaBH₄ are both essential components. While the reduction is catalytic in both 2 and ACVA, the rates reflect a qualitative proportionality to the concentrations of 2, NaBH₄, and ACVA. GC-MS analysis of the benzoic acid resulting from reduction of m-bromobenzoic acid by NaBH₄/D₂O and NaBD₄/D₂O demonstrate that the hydrogen atom derives from the NaBH₄. However, the role of the tin hydride precursor is more complex than first anticipated. Omission of 2 completely precludes reductions of aliphatic bromides. Sluggish reduction of the aliphatic bromides is observed when 2 is replaced by PhSnCl₃ (i.e. PhSn(OH)₃). Neither elemental tin nor SnCl₂ mediates any detectable reduction. In contrast, aryl bromides reduce smoothly, albeit at reduced rates, using NaBH₄/ACVA in the absence of any tin-containing species. Reduction rates comparable to the tin-mediated examples are observed using excess (8.0 equiv) NaBH₄. We are unaware of any reports of catalysis by azo initiators. Additional examples of the NaBH₄/ACVA-mediated reductions of aryl halides are listed in Table II.

**Table II. Reduction of aryl and alkyl bromides by aqueous NaBH₄-ACVA.**

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<tr>
<th>Substrate</th>
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<sup>aAr = p-C₆H₄COOH. bReaction conditions were as described in the text. Yields correspond to purified material after a normal extractive workup and esterification with ethereal CH₂N₂.</sup>

The role of the tin(IV) species and the mechanism of the reduction are not at all clear at this time. However, both the tin-catalyzed reduction protocol as well as the tin-free NaBH₄-ACVA variant may find utility due to reagent availability and overall simplicity.
Acknowledgement. This work was generously supported by the Johnson & Johnson Focussed Giving Program and Pfizer, Inc. We also thank Professor Ned Porter (Duke University) for a helpful discussion.

References and Footnotes
1. Li, C.-J. Chem. Rev. 1993, 93, 2023
6. Hutton, R. E.; Oakes, V. Adv. Chem. Series 1976, 157, 123. 2 and 3 were prepared as follows: Six equiv of conc HCl were added dropwise to a suspension of tin (25.2 mmol) and acrylic acid (50.5 mmol) in H2O (5 mL). The mixture was heated at 75 °C for 4 h. The reaction mixture was concentrated and treated with 20% aq KOH (exotherm). The nearly homogeneous mixture was filtered and the filtrate acidified with 1 N H2SO4 with slow formation of a white solid. The solid was filtered, washed successively with water and methanol, and then dried in vacuo to afford 4.5 g of 2 (68% yield). IR (Nujol, in cm⁻¹) 1550, 1435, 625; Anal. Calcd. for C₅H₅O₄Sn-1/2 H₂O: C, 26.52; H, 3.31. Found: C, 26.27; H, 3.33. Dissolution of 2 in aqueous base affords 3: ¹H NMR (D₂O-KOD) 6 2.26 (t, 4, J = 7.4 Hz, 2J¹H-¹¹⁹Sn) 133 Hz), 1.15 (t, 4, J = 7.4 Hz, 3J¹H-¹¹⁹Sn) 105 Hz); ¹³C(¹H)NMR (D₂O-KOD) 6 18.5 (1J¹H-¹¹⁹Sn) 3736 Hz), 33.1 (2J¹H-¹¹⁹Sn) 180 Hz), 185.7 (3J¹H-¹¹⁹Sn) 320 Hz).

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