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Reductions and Radical Cyclizations of Aryl and Alkyl Bromides Mediated by $NaBH_4$ in Aqueous Base

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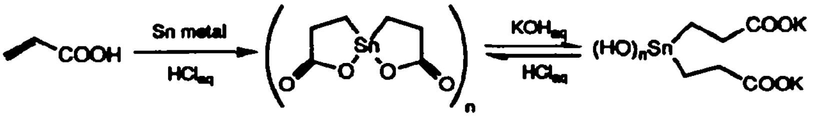
KEY WORDS: radical cyclization; sodium borohydride; aqueous.

Abstract: Reductions and free radical cyclizations of alkyl- and aryl bromides are effected in aqueous base by $NaBH_4$ 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 $NaBH_4$-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 $(MeOCH_2CH_2OCH_2CH_2CH_2)_3SnH$ (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-Bu_3SnH/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* reduction[5] of a more accessible water-soluble tin halide (or pseudo-halide) by $NaBH_4$ might offer a useful alternative to the Breslow-Light protocol.

We prepared dialkyltin(IV) reagent 2 by modifying a literature hydrostannylation protocol[6] 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,[6] 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.



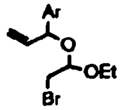
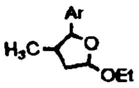
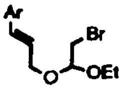
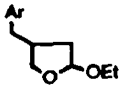
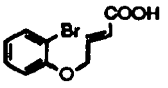
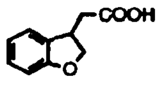
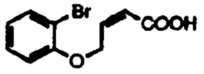
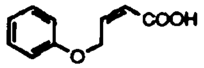
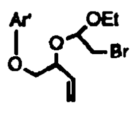
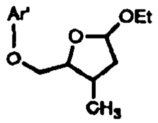
2 3

(1)

Heating a solution of *m*-bromobenzoic acid, 2 (i.e. 3, 1.2 equiv), $NaBH_4$ (2.0 equiv), and ACVA (0.1-1.0 equiv) in degassed 1.5% KOH/H_2O 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-Bu_3SnH/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 $NaBH_4$-sensitive substrates met with little success.

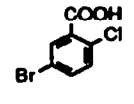
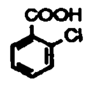
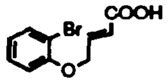
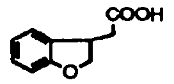
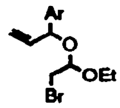
Table I. Reduction of aryl and alkyl bromides by aqueous $NaBH_4$-ACVA-3.

Substrate	Product	Yield
		>90%
		62%[c]
		68%[d]
		75%
		75%
		75%[c]

[a] Ar = p-C_6H_4COOH, Ar' = m-C_6H_4COOH. [b] Substrates (0.04 mmol) were reduced at 90 °C in degassed 1.5% aq KOH (1.33 mL) containing $NaBH_4$ (2.0 equiv), ACVA (1.0 equiv), and 2 (1.2 equiv). Normal extractive workup, esterification with ethereal CH_2N_2 and purification (flash chromatography) afforded the reported yields. [c] Isolated as a mixture containing two of four possible stereoisomers. Equilibrations with $TiCl_4$ 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 $NaBH_4$ 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**, $NaBH_4$, and ACVA. GC-MS analysis of the benzoic acid resulting from reduction of *m*-bromobenzoic acid by $NaBH_4/D_2O$ and $NaBD_4/D_2O$ demonstrate that the hydrogen atom derives from the $NaBH_4$. 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 $PhSnCl_3$ (i.e. $PhSn(OH)_n$). Neither elemental tin nor $SnCl_2$ mediates any detectable reduction. In contrast, *aryl* bromides reduce smoothly, albeit at reduced rates, using $NaBH_4$/ACVA *in the absence of any tin-containing species.* Reduction rates comparable to the tin-mediated examples are observed using excess (8.0 equiv) $NaBH_4$. We are unaware of any reports of catalysis by azo initiators.[9] Additional examples of the $NaBH_4$/ACVA-mediated reductions of aryl halides are listed in Table II.

Table II. Reduction of aryl and alkyl bromides by aqueous $NaBH_4$-ACVA.[a,b]

Substrate	Product	Yield
		>90%
		75%
	--------	0%

[a] Ar = *p*-C_6H_4COOH. [b] Reaction conditions were as described in the text. Yields correspond to purified material after a normal extractive workup and esterification with ethereal CH_2N_2.

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 $NaBH_4$-ACVA variant may find utility due to reagent availability and overall simplicity.

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References and Footnotes

1. Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023
2. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.
3. For selected examples see, Mariaggi, N.; Cadet, J.; Teoule, R. *Tetrahedron* **1976**, *32*, 2385. Fukunishi, K.; Shimda, M.; Hisamune, R.; Akita, M.; Kuwabara, M.; Yamanaka, H.; Momura, M. *Chem. Lett.* **1991**, 337. Haseqawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008. Curran, D. P.; Qi, H.; Porter, N. A.; Su, Q.; Wu, W. X. *Tetrahedron Lett.* **1993**, *34*, 4489.
4. Light, J.; Breslow, R. *Tetrahedron Lett.* **1990**, *21*, 2857. Light, J.; Breslow, R. *Org. Synth.* **1993**, *72*, 199.
5. Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554.
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 H_2O (5 mL). The mixture was heated at 75 ^{o}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 H_2SO_4 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 $C_6H_8O_4Sn \cdot 1/2\ H_2O$: C, 26.52; H, 3.31. Found: C, 26.27; H, 3.33. Dissolution of **2** in aqueous base affords **3**: ^{1}H NMR (D_2O-KOD) δ 2.26 (t, 4, J = 7.4 Hz, $^{2}J[^{1}H\text{-}^{119}Sn]$ 133 Hz), 1.15 (t, 4, J = 7.4 Hz, $^{3}J[^{1}H\text{-}^{119}Sn]$ 105 Hz); $^{13}C\{^{1}H\}$NMR (D_2O-KOD) δ 18.5 ($^{1}J[^{1}H\text{-}^{119}Sn]$ 3736 Hz), 33.1 ($^{2}J[^{1}H\text{-}^{119}Sn]$ 180 Hz), 185.7 ($^{3}J[^{1}H\text{-}^{119}Sn]$ 320 Hz).
7. Calogero, S.; Furlan, P.; Peruzzo, V.; Plazzogna, G. *Inorg. Chim. Acta* **1977**, *22*, 55.
8. Davies, A. G.; Smith, P. J. "Comprehensive Organometallic Chemistry"; Wilkinson, G.; Stone, F.; Abel, E. W., ed.; Pergamon Press, New York **1982**; Vol 2, 519.
9. For related $NaBH_4$-mediated aryl halide reductions see Boisvert, G.; Giasson, R. *Tetrahedron Lett.* **1992**, *33*, 6587.

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