A Practical Method for the Removal of Organotin Residues from Reaction Mixtures

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Due to the combination of availability, stability, functional group compatibility, convenient rate constant for hydrogen atom donation to alkyl radicals, and excellent chain carrying properties of stannyl radicals, preparative free radical chemistry is dominated by the use of organotin hydrides (Bu_3SnH and Ph_3SnH).[1] Unfortunately, the triorganotin halide, chalcogenide, and alkoxide byproducts from these reactions show a tendency to hydrolyze slowly on silica gel, which frequently renders purification difficult. This problem, which is particularly prominent in the pharmaceutical industry when such impurities resulting from say the Barton deoxygenation[2] of an aminoglycoside antibiotic must be reduced below the trace level, also extends to the one-[3] and two-electron[4] reactions of allylstannanes and to the use of organotin halides as Lewis acids.[5]

Numerous approaches have been adopted to circumvent this problem. Alternative reagents have been devised and are successful to varying degrees; for example, Bu_3SnH may be replaced in the Barton deoxygenation by hypophosphorous acid[6] or by thiol/silane couples[7] and in the Barton decarboxylation by mercaptans,[8] but none, with the possible exception of tris(trimethylsilyl)silane,[9] are as general or have all the attributes of the tin hydrides. The use of water-soluble tin hydrides,[10] as well as those bearing polar groups to assist purification,[11] has much promise but is not widely applied perhaps due to commercial inavailability. Current polymer-supported tin hydrides suffer from poor recyclability.[12] The fluorous organotin reagents recently described by the Curran group,[13] combined with extraction into an immiscible fluorous phase, show considerable promise, as do the ingenious allylstannylamines developed by Pereyre and co-workers.[14] When the use of Bu_3SnH or Ph_3SnH is mandated, organotin byproducts may be removed from the crude product by oxidative conversion to polymeric, insoluble tin fluorides[15] by coordination to an amine prior to silica gel chromatography[16] and, for polar compounds, by partitioning between acetonitrile and a hydrocarbon solvent.[17] Finally, several protocols have been developed for the use of a catalytic quantity of an organotin reagent with recycling in situ by means of borohydride[18] or silane reagents.[19] Consideration of the various catalytic tin methods suggested that many R_3SnX species must be very rapidly reduced by borohydrides and silanes to R_3SnH. Indeed, Curran and coworkers have reported that $NaBH_3CN$ reduces Bu_3SnCl in *t*-BuOH rapidly and quantitatively in a few minutes at room temperature.[20] Moreover, Bu_3SnH and Ph_3SnH are very nonpolar compounds that can be washed rapidly from silica gel with hydrocarbon eluants. It was apparent, therefore, and readily demonstrated, that for a wide variety of organotin-mediated reactions, a brief borohydride treatment of the crude reaction mixtures should greatly facilitate purification.

In an initial experiment, 9,10-dibromoanthracene (**1**) was reduced with Bu_3SnH and AIBN in benzene at reflux. After concentration, $NaBH_3CN$ and *t*-BuOH were added and the mixture heated to reflux for 1 h. After a further concentration the reaction mixture was applied to a silica gel column and eluted with hexanes when Bu_3SnH was recovered quantitatively. Further elution with hexane/benzene (1:1) yielded analytically pure anthracene, also quantitatively (Table 1, entry 1). In a second experiment, 4,4′-dimethoxytrityl chloride (DMT-Cl, **3**) was reduced with Bu_3SnH and the crude reaction mixture treated with $NaBH_3CN$. After a brief aqueous wash, the reduction product was recovered free of tin residues by filtration on silica gel (Table 1, entry 2). Further examples covering a range of different tin hydride-mediated reductions, classes of substrate, and functionality are presented in Table 1. In each case, the tin hydride could be recovered in excellent yield and the ^{1}H-NMR spectrum of the product, as eluted from the column, revealed the absence of organotin contaminants. Control experiments in which the borohydride treatment was omitted led to the isolation of products with considerable tin contamination (supporting information). We draw special attention to entry 6 of Table 1 in which a hydrocarbon was obtained free of organotin residues by the simple expedient of replacing the coeluting Bu_3SnH by the slightly more polar Ph_3SnH.[21]

The present protocol, involving stoichiometric use of of a triorganostannane followed by a borohydride workup, has clear advantages over the widely used catalytic stannane protocol with in situ regeneration by borohydrides in certain instances. Thus, application of the Stork protocol to **9** resulted in the complete consumption of the substrate but the formation of 0% of **10** (cf. Table 1, entry 5). This is readily understood in terms of the instability of **9** under the reaction conditions. In the case

(1) (a) Neumann, W. P. *Synthesis* **1987**, 665. (b) Pereyre, M.; Quintard, J.-M.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(2) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1575.

(3) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.

(4) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(5) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063.

(6) Barton, D. H. R.; Jang, J. O.; Jaszberenyi, J. Cs. *J. Org. Chem.* **1993**, *58*, 6838.

(7) Cole, S. J.; Kirwan, J. N.; Roberts, B. P.; Willis, C. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 103.

(8) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

(9) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.

(10) (a) Light, J.; Breslow. R. *Tetrahedron Lett.* **1990**, *31*, 2957. (b) Rai, R.; Collum, D. B. *Tetrahedron Lett.* **1994**, *35*, 6221.

(11) Clive, D. L. J.; Yang, W. *J. Org. Chem.* **1995**, *60*, 2607.

(12) (a) Gerlach, M.; Jördens, F.; Kuhn, H.; Neumann, W. P.; Peterseim, M. *J. Org. Chem.* **1991**, *56*, 5971. (b) Neumann, W. P.; Peterseim, M. *React. Polym.* **1993**, *20*, 189.

(13) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531.

(14) Fouquet, E.; Pereyre, M.; Roulet, T. *J. Chem. Soc., Chem. Commun.* **1995**, 2387.

(15) (a) Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, 44, 449. (b) Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743.

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

(17) Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.

(18) (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.

(19) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4.

(20) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051.

(21) In this one case, as indicated by the control experiment, the borohydride treatment was unnecessary. This is readily understood in terms of the hydrocarbon nature of **10** and its elution from silica gel ahead of any triarylorganotin derivatives.

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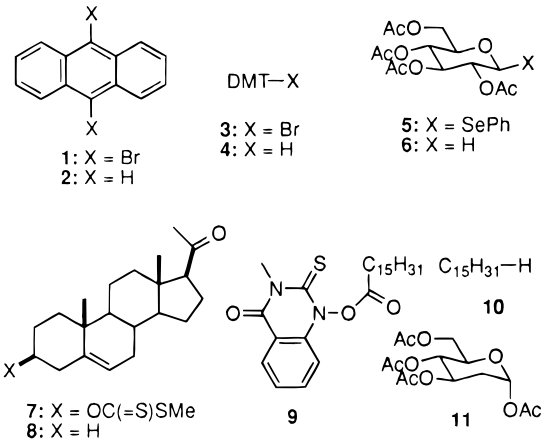
Table 1.

substrate	R_3SnH	treatment	product	% yield	anal. calcd	anal. found	% R_3SnH recovered
1	Bu_3SnH	$NaBH_3CN$	**2**	100	C, 94.35; H, 5.66	C, 94.23; H, 5.61	100
3	Bu_3SnH	$NaBH_3CN$	**4**	100	C, 82.87; H, 6.62	C, 82.92; H, 6.73	97
5	Bu_3SnH	$NaBH_4$	**6**	95	C, 50.60; H, 6.07	C, 50.67; H, 6.03	95
7	Bu_3SnH	$NaBH_3CN$	**8**	84	C, 83.94; H, 10.73	C, 83.81; H, 10.61	83
9	Ph_3SnH	$NaBH_3CN$	**10**	83	C, 84.82; H, 15.18	C, 84.90; H, 15.17	81



of **5**, the catalytic protocol resulted in the isolation of mixtures of **6** and the migration product **11**[24] (cf. Table 1, entry 3) owing to the low concentration of tin hydride in the reaction mixture.

Finally, we note that this new workup protocol permits recovery in very high yield, and thus recycling, of the triorganotin hydride, with obvious economic and environmental implications for large scale work.

Experimental Section[22]

Anthracene (2). A solution of **1** (1.0 g, 2.98 mmol), Bu_3SnH (1.74 mL, 6.55 mmol), and AIBN (98.0 mg, 0.60 mmol) in benzene (60 mL) was heated at reflux for 6 h. After concentration to half volume $NaBH_3CN$ (0.37g, 5.95 mmol) and *t*-BuOH (25 mL) were added, and the mixture was heated to reflux for 1 h. Concentration and column chromatography on silica gel (eluent: hexane → hexane:benzene = 1:1) afforded Bu_3SnH (1.91 g, 100% recovery) and **2** (0.53 g, 100%) free from organotin residues as demonstrated by ^{1}H-NMR spectroscopy.

Bis(*p*-methoxyphenyl)phenylmethane (4). A solution of **3** (1.0 g, 2.95 mmol), Bu_3SnH (0.86 mL, 3.25 mmol), and AIBN (24.0 mg, 0.15 mmol) in benzene (30 mL) was heated at reflux for 12 h. $NaBH_3CN$ (0.21 g, 3.34 mmol) and *t*-BuOH (30 mL) were then added and the reflux continued for 30 min. After cooling, the solution was washed with saturated aqueous sodium bicarbonate and dried with sodium sulfate. Concentration and column chromatography on silica gel (eluent: hexane → hexane: ethyl acetate = 10:1) afforded Bu_3SnH (0.92 g, 97%) and **4** (0.89 g, 100%) free from organotin residues as demonstrated by ^{1}H-NMR spectroscopy.

2,3,4,6-Tetra-*O*-acetyl-1-deoxy-D-glucose (6). A solution of **5**[23] (91.0 mg, 0.188 mmol), Bu_3SnH (74.2 μL, 0.28 mmol), and AIBN (6.2 mg, 0.04 mmol) in benzene (3 mL) was heated at reflux for 4 h. After concentration to dryness, $NaBH_4$ (8.0 mg, 0.21 mmol) and EtOH (4 mL) were added, and the mixture was stirred for 5 min at room temperature. After evaporation of the volatiles, the crude product was extracted with dichloromethane, and the extracts were purified by preparative TLC (eluent: hexane:ethyl acetate = 1:1) to afford Bu_3SnH (77.4 mg, 95%) and **6**[24] (59.3 mg, 95% yield) free from organotin residues as demonstrated by ^{1}H-NMR spectroscopy.

***S*-Methyl *O*-(3*β*-pregn-5-en-20-onyl) dithiocarbonate (7)** was prepared in the standard manner:[2] mp 160−170 °C dec; ^{1}H-NMR δ 0.59 (3 H, s), 0.97 (1 H, m), 1.02 (3 H, s), 1.15 (3 H, m), 1.35−1.75 (9 H, m), 1.90 (1 H, m), 1.90−2.20 (4 H, m), 2.10 (3 H, s), 2.45 (2 H, m), 2.50 (3 H, s), 5.35 (2 H, m); ^{13}C-NMR δ 13.1, 18.7, 19.2, 20.9, 22.7, 24.4, 27.0, 31.4, 31.7, 36.5, 36.8, 37.3, 38.7, 42.2, 43.8, 49.7, 56.7, 83.2, 122.8, 139.1, 209.2, 214.9. Anal. Calcd for $C_{23}H_{34}O_2S_2$: C, 67.93; H, 8.43. Found: C, 68.35; H, 8.84.

Pregn-5-en-20-one (8). A solution of **7** (156.3 mg, 0.384 mmol), Bu_3SnH (153.0 μL, 0.576 mmol), and AIBN (12.6 mg, 0.077 mmol) in toluene (6 mL) was heated at reflux for 4 h. After concentration, $NaBH_3CN$ (72.5 mg, 1.15 mmol) and *t*-BuOH (8 mL) were added, and the mixture was stirred at room temperature for 2 h. After evaporation of the volatiles, the crude product was extracted with dichloromethane, and the extracts were purified by preparative TLC (eluent: hexane:ethyl acetate = 6:1) to give Bu_3SnH (139 mg, 83%) and **8**[25] (97.0 mg, 84%) free from organotin residues as demonstrated by ^{1}H-NMR spectroscopy.

Pentadecane (10). A solution of **9**[26] (91.0 mg, 0.204 mmol), Ph_3SnH (143.0 mg, 0.41 mmol), and AIBN (17 mg, 0.1 mmol) in xylenes (4 mL) was heated at reflux for 20 h. Further portions of Ph_3SnH (143.0 mg, 0.41 mmol) and AIBN (17 mg, 0.1 mmol) were added after 5 and 10 h. After concentration, $NaBH_3CN$ (120.0 mg, 1.91 mmol) and *t*-BuOH (10 mL) were added, and the mixture was heated to reflux for 0.5 h. After evaporation of the volatiles, the crude product was extracted with dichloromethane, and the extracts were purified by column chromatography on silica gel (eluent: hexane) to give Ph_3SnH (347.5 mg, 81%) and **10** (36.0 mg, 83%) free from organotin residues as demonstrated by ^{1}H-NMR spectroscopy.

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Supporting Information Available: ^{1}H-NMR spectra of **2**, **4**, **6**, **8**, and **10** as isolated by silica gel chromatography showing absence of organotin residues and the corresponding spectra from the control experiments omitting the borohydride treatment (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(22) For general experimental procedures see: Crich, D.; Sun, S.; Brunckova, J. *J. Org. Chem.* **1996**, *61*, 605.
(23) Bonner, W. A.; Robinson, A. *J. Am. Chem. Soc.* **1950**, *72*, 354.
(24) Beckwith, A. L. J.; Duggan, P. J. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1673.
(25) Gonzalez, M. D.; Burton, G. *Z. Naturforsch.* **1985**, *40b*, 639.
(26) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39.