A Convenient Preparation of Trineophyltin Deuteride and Some Applications Including the Reduction of Organic Halides and α-Halo Ketones

Julio C. Podestá,*,† Nelda N. Giagante,† Adriana E. Zuñiga,† Gerardo O. Danelon,‡ and Oreste A. Mascaretti*,‡

Instituto de Investigaciones en Química Orgánica, Departamento de Química e Ing. Qca., Universidad Nacional del Sur, Avenida Alem 1253, 8000 Bahía Blanca, Argentina, and Instituto de Química Orgánica de Síntesis (CONICET-UNR), Casilla de Correo 991, 2000 Rosario, Argentina

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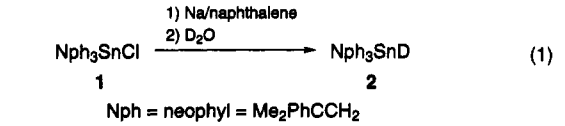
Additions and reductions with organotin deuterides usually proceed without side reactions, and for this reason they have found wide application[1] in organic and organometallic chemistry as highly specific reagents for deuterations. Recently[2] we have shown that the reduction of benzyl and (pivaloyloxy)methyl (abbreviated as Pom) (6*R*)-6-bromo-6-fluoro- and (6*R*)-6-iodo-6-bromopenicillanates with trineophyltin hydride,[3] takes place with very high chemo- and diastereoselectivity to give the corresponding benzyl and Pom 6β-fluoro- or 6β-bromopenicillanates.

The better diastereoselectivity observed in the reductive dehalogenations carried out with this organotin hydride compared with that obtained in the reduction of the same substrates with tri-*n*-butyltin hydride,[4] could be ascribed to a better diastereofacial discrimination by the approaching bulky trineophyltin hydride to donate the hydrogen atom to the unencumbered diastereotopic si face at C-6 position of a penicillin intermediate radical. These results prompted us to attempt a study on the specific deuteration of similar organic substrates using the deuterated equivalent, i.e., trineophyltin deuteride (**2**).

Trineophyltin deuteride (**2**) was conveniently obtained from trineophyltin chloride (**1**), by preparing the corresponding (trineophylstannyl)sodium with the complex sodium/naphthalene,[5] followed by decomposition of the sodium derivative with deuterium oxide. The yield of the reaction, after chromatographic purification, was 93%[6] (eq 1).

In order to determine possible applications of **2** to deuterium labeling of organic compounds, the following reactions were performed. The study of the reaction between trineophyltin deuteride (**2**) and carbon tetrachloride shows that this reaction is very slow. Thus, the



(1)

decomposition of a 0.0077 M solution of **2** in carbon tetrachloride takes ca. 48 h at 25 °C (reaction followed by ^{1}H NMR). Free radical deuterostannation of methyl acrylate (**3**) with **2** takes place in ca. 1 h, to give the corresponding adduct **4** in quantitative yield. The reactions of **2** with both α-bromoacetophenone (**5**) and α-bromo-2-acetonaphthone (**7**) lead to the corresponding deuterated ketones **6** and **8**, respectively, in excellent yields[7] (Scheme 1).

Taking into account these results and our interest in the synthesis of stereospecifically 6α-monodeuterated benzyl and benzhydryl 6β-fluoro- and 6β-bromopenicillanates, we carried out a study of the reactions of **2** with benzyl 6β-bromo-6α-fluoropenicillanate (**9a**)[2b] and benzhydryl 6,6-dibromopenicillanate (**9b**). When **9a** reacted with trineophyltin deuteride in the presence of a catalytic amount of azobis(isobutyronitrile) (AIBN), in anhydrous THF at room temperature, benzyl 6β-bromo-6α-deuteropenicillanate (**10a**, 60% isolated yield) was obtained. Similarly, **9b** reacted with **2** to give 6β-bromo-6α-deuteropenicillanate (**10b**) in 45% isolated yield (Scheme 2).

In summary, the specific and smooth monodeuteration reactions of trineophyltin deuteride reported herein show promise of considerable practical value because **2** can be handled in the air and kept at room temperature without noticeable decomposition for months. It is soluble in most organic solvents such as ether, THF, benzene, toluene, etc., and its thermal stability is very good.

Experimental Section

NMR spectra were obtained partly at IQUIOS (^{1}H and ^{13}C), Rosario, Argentina, using a Bruker AC 200 instrument and partly with a Bruker AM 300 instrument (^{1}H, ^{13}C, and ^{119}Sn) at Dortmund University (Germany); IR spectra were recorded with a Perkin-Elmer 599B spectrophotometer. Melting points were determined on a Kofler hot-stage and are uncorrected. Low and high resolution mass spectra were recorded on a Varian MAT 112S mass spectrometer. Microanalyses (C, H) were performed at Dortmund University. All solvents and reagents used were analytical reagent grade, and the compounds were purified by column chromatography using silica gel 60 (70–230 mesh). Trineophyltin chloride (**1**),[8] α-bromoacetophenone (**5**),[9] α-bromo-2-acetonaphthone (**7**),[9] benzyl 6β-bromo, 6α-fluoropenicillanate (**9a**),[2b] and benzyl 6,6-dibromopenicillianate (**9b**)[10] were obtained according to known procedures.

Trineophyltin Deuteride (2). To a solution of trineophyltin chloride (**1**) (2 g, 3.6 mmol) in dry THF (4 mL), placed in a two-necked round-bottom flask with a nitrogen seal and a pressure-equalizing addition funnel attached, and with magnetic stirring, was added dropwise a solution of the sodium–naphthalene complex prepared from sodium (930 mg, 40 mmol) and naphthalene (3.7 g, 28.8 mmol) in THF (13 mL) according to ref 5. The mixture was left 12 h at room temperature under nitrogen, and deuterium oxide (1 mL) was then added. The organic layer was decanted and the aqueous layer was extracted with hexane. The combined organic layers were dried over sodium sulfate. The

† Universidad Nacional del Sur.

‡ Instituto de Química Orgánica de Síntesis.

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(2) (a) For the reductive dehalogenation of Pom penicillanates see: Mata, E. G.; Setti, E. L.; Mascaretti, O. A. *J. Org. Chem.* **1990**, *55*, 3674. (b) For the reductive dehalogenation of benzyl penicillanates see: Danelon, G. O.; Laborde, M.; Mascaretti, O. A.; Boggio, S. B.; Roveri, O. A. *Bioorg. Med. Chem.* **1993**, *1*, 447.

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(6) It is to note that although we have used deuterium oxide 99.8 atom % D, this product contains ca. 5.8% of trineophyltin hydride as shown by ^{119}Sn NMR spectroscopy.

(7) Deuterated ketones **6** and **8** contain ca. 5% of the corresponding non-deuterated ketones as shown by ^{1}H and ^{13}C NMR spectroscopy.

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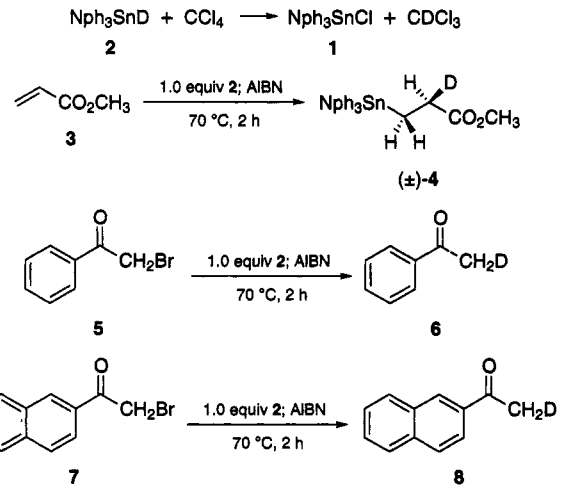
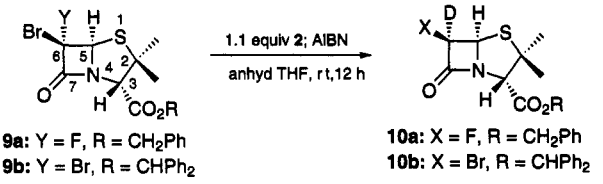
Scheme 1



Scheme 2



9a: Y = F, R = CH_2Ph
9b: Y = Br, R = $CHPh_2$

10a: X = F, R = CH_2Ph
10b: X = Br, R = $CHPh_2$

solution was filtered and the solvent was removed under reduced pressure. The naphthalene in the crude product was removed by sublimation using a cold-finger. After being purified by column chromatography (eluent hexane), **2** (1.74 g, 93%) was obtained as a white solid: mp 54–56 °C; IR (film) 1290 (Sn–D) cm^{-1}; ^1H NMR (C_6D_6) δ 0.95 (s, $^2J_{Sn,H}$ = 49.2 Hz, 6H), 1.23 (s, 18H), 7.15 (m, 15H); ^{13}C NMR (C_6D_6) δ 30.42 ($^1J_{Sn,C}$ = 345.8 Hz), 32.37 ($^3J_{Sn,C}$ = 34.4 Hz), 37.68 ($^2J_{Sn,C}$ = 20.1 Hz), 125.62, 125.70, 128.28, 151.11 ($^3J_{Sn,C}$ = 22.9 Hz); ^{119}Sn NMR (C_6D_6) δ (vs Me_4Sn) −156 (t, $^1J_{Sn,D}$ = 508.0 Hz). Anal. Calcd for $C_{30}H_{39}DSn$: C, 69.24; H, 7.55. Found: C, 69.74; H, 7.60.

Methyl 2-Deutero-3-(trineophylstannyl)propanoate (4). Methyl acrylate (0.5 g, 5.8 mmol) was treated with trineophyltin deuteride (**2**) (2.71 g, 5.22 mmol), using azobis(isobutyronitrile) (AIBN) as a catalyst, in a nitrogen atmosphere, at 70 °C, and with stirring for 2 h. Under these reactions conditions, the ^1H NMR spectrum showed that **4** was obtained in quantitative yield. The crude product was purified by column chromatography (hexane–benzene 97:3), and **4** was isolated as a white solid: mp 46–48 °C: IR (film) 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.39 (d, $^2J_{Sn,H}$ = 46.4 Hz, $^3J_{H,H}$ = 9.2 Hz, 2H), 0.87 (s, $^2J_{Sn,H}$ = 48.3 Hz, 6H), 1.12 (s, 18H), 1.77 (m, 1H), 3.55 (s, 3H), 7.12 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 6.91 ($^1J_{Sn,C}$ = 294.2 Hz), 30.31 ($^1J_{Sn,C}$ = 316.4 Hz), 29.78, 30.18, 30.56 (these three signals belong to the C–D bond), 33.06 ($^3J_{Sn,C}$ = 35.4 Hz), 37.77 ($^2J_{Sn,C}$ = 18.2 Hz), 51.19, 125.06, 125.30, 127.90, 150.95 ($^3J_{Sn,C}$ = 18.5 Hz), 175.61 ($^3J_{Sn,C}$ = 72.4 Hz). Anal. Calcd for $C_{34}H_{45}DO_2Sn$: C, 67.33; H, 7.48. Found: C, 67.40; H, 7.50.

α-Deuteroacetophenone (6). A mixture of α-bromoacetophenone (**5**) (199 mg, 1 mmol), trineophyltin deuteride (**2**) (520 mg, 1 mmol), and a catalytic amount of AIBN, placed in a two-necked round-bottom flask with a nitrogen seal, was left at 70 °C with magnetic stirring during 2 h. The crude product was purified by column chromatography, **6** (0.118 g, 98% yield) being eluted with hexane, after elution of trineophyltin bromide. ^1H NMR showed that this product contained ca. 5% of acetophenone.[7] **6** showed the same spectroscopic characteristics already reported by Neumann et al.[11]

α-Deutero-2-acetonaphthone (8). Under the same conditions as above, a mixture of α-bromo-2-acetonaphthone (**7**) (478 mg, 1.92 mmol), trineophyltin deuteride (**2**) (1 g, 1.92 mmol), and a catalytic amount of AIBN, was left during 3 h. Purification of the crude product by column chromatography (hexane–benzene 97:3) gave **8** (284 mg) in 86.5% yield. As previously, the compound contained ca. 5% of 2-acetonaphthone:[7] IR (film) 1660 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70 (m, 2H), 7.89 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 25.69, 26.08, and 26.47 (these three signals belong to CH_2D), 123.57, 126.46, 127,47, 128.08, 128.16, 129.25, 129.86, 132.22, 134.19, 135.28, 197.74.

Benzyl 6α-Deutero-6β-fluoropenicillanate (10a). A solution of trineophyltin deuteride (**2**) (125 mg, 0.24 mmol) in dry THF (1 mL) was added to a solution of benzyl 6β-bromo-6α-fluoropenicillanate (**9a**) (79 mg, 0.2 mmol) and AIBN (1 mg) in dry THF (4 mL). The reaction mixture was stirred overnight at room temperature and then the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate, 85:15) leading to **10a** (38 mg, 60% yield) as colorless oil:[12] IR (film) 1795 (C=O, β-lactam), 1746 (C=O, ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 3H), 1.64 (s, 3H), 4.55 (s, 1H), 5.2 (s, 2H), 5.5 (d, $^3J_{F,H}$ = 4.0 Hz, 1H), 7.38 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 26.2, 31.71, 64.28, 66.47 ($^2J_{C,F}$ = 21.7 Hz), 67.45, 70.7, 128.6, 134.48, 167.25, 169.26 ($^2J_{C,F}$ = 23.85 Hz); LRMS (El$^+$) *m/e* 310 (M^+, 6%), 253 (2), 219 (2), 147 (2.2), 115 (10), 91 (100); HRMS calcd for $C_{15}H_{15}DFNO_3S$ 310.0901, found 310.0913.

Benzhydryl 6β-bromo-6α-deuteropenicillanate (10b). A solution of **2** (158 mg, 0.3 mmol) in dry THF (1 mL) was added to a solution of benzhydryl 6,6-dibromopenicillanate (**9b**) (107 mg, 0.2 mmol) and AIBN (1 mg) in dry THF (4 mL). The reaction was stirred overnight at room temperature, and then the solvent was evaporated and the residue purified by column chromatography (hexane/ethyl acetate, 85:15) to give **10b** (41 mg, 45% yield) as a colorless oil:[12] IR (film) 1793 (C=O, β-lactam), 1744 (C=O, ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.66 (s, 3H), 4.61 (s, 1H), 5.58 (s, 1H), 6.9 (s, 1H), 7.34 (s, 10H); ^{13}C NMR ($CDCl_3$) δ 26.06, 32.3, 64.65, 68.1, 70.84, 78.4, 127.5, 138.0, 166.4, 168.4.[13]

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Supplementary Material Available: Copies of ^{13}C NMR spectra of **2**, **4**, **8**, **10a**, and **10b**, ^1H NMR spectra of **10a** and **10b**, and ^{119}Sn NMR spectrum of **2** (8 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.

(12) Deuterated penicillanates **10a** and **10b** contain ca. 10% of the corresponding non-deuterated compounds, according to ^1H NMR spectroscopy.

(13) LRMS and HRMS spectra of compound **10b** cannot be obtained due to its instability.