Syntheses of Organic Iodides via Reaction of Organoboranes with Sodium Iodide

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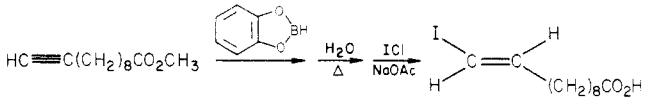
Organic halides are important synthetic intermediates. We recently reported a new method for iodine incorporation utilizing iodine monochloride. We have found that organoboranes react readily with iodide ion in the presence of mild oxidizing agents such as chloramine-T. The reaction is rapid, proceeds under mild conditions, and is ideally suited for the incorporation of radioiodine.

Introduction

Organic halides are important synthetic intermediates in numerous reactions (substitution, alkylation, etc.). They are also important due to the variety of radiohalogen-containing radiopharmaceuticals which have been developed in recent years.[1-3] We recently reported a new method for incorporating iodine stereospecifically via the reaction of iodine monochloride with organoboranes.[4] The

$$R_3B \xrightarrow[NaOAc]{ICl} RI$$

reaction is rapid, proceeds under mild conditions, and is ideally suited for the incorporation of radioiodine. We have synthesized a number of physiologically active radioiodine-containing reagents via the new reaction.[5,6] The reaction is applicable to the synthesis of alkyl, vinyl, and aryl iodides.



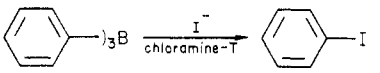
The iodine monochloride reaction is nearly ideal except for the necessity of handling (or preparing) iodine monochloride. In the case of radiopharmaceutical development, the preparation of no-carrier-added iodine monochloride can become a significant problem. We report that organoboranes react readily with iodide ion in the presence of mild oxidizing agents. This new synthesis of organic iodides is ideally suited for the syntheses of functionally substituted molecules and the use of no-carrier-added iodide ion.

Results and Discussion

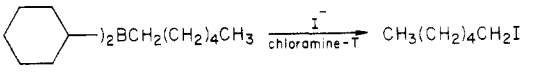
Synthetic chemists have incorporated iodine atoms into organic molecules via oxidation of iodide ions for decades[7,8] and it is clear that the reacting species is some form of electropositive iodine. Since the reaction of organoboranes with iodine monochloride involves an S_E2 reaction of a borate complex with a positively polarized iodine, we postulated that a reaction might occur between a borate complex and iodide ion in the presence of an oxidizing agent.

One of the most extensively studied oxidizing agents is chloramine-T.[9] Chloramine-T presumably reacts with iodide ion to form iodine monochloride or a hydrated iodonium ion; either of these species would be a suitable reactant for the syntheses of organic iodides via organoborane reagents. We have found that organoboranes readily react with iodide ion in the presence of chloramine-T. The reaction proceeds in high yield under extremely gentle conditions. When the trialkylborane is prepared via the hydroboration of terminal alkenes, two of the three alkyl groups react instantaneously. In the case of trialkylboranes derived from internal alkenes, one of the three alkyl groups reacts rapidly. These results parallel those obtained when organoboranes react with iodide ion in the presence of chloramine-T. In addition, triphenylborane reacts with iodide ion in the presence of chloramine-T to yield iodobenzene.

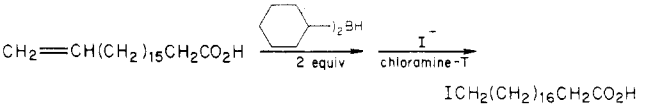
$$R_3B + I^- \xrightarrow{\text{chloramine-T}} RI$$



As noted earlier, primary alkyl groups react more readily then secondary. We investigated the reaction of dicyclohexylalkylboranes with iodide ion in the presence of chloramine-T. As expected the primary alkyl groups reacted preferentially to yield primary alkyl iodides. The



use of the conveniently prepared dicyclohexylborane offers certain advantages since it is a more selective hydroborating and reducing agent than BH_3–THF. The formation of 19-iodononadecanoic acid illustrates the utility of the method.



We have synthesized a variety of functionally substituted organic iodides via this new iodination sequence. Our results are summarized in Table I.

(1) Lambrecht, R. M.; Wolf, A. P. In "Radiopharmaceuticals"; Subramanian, G., Rhodes, B. A., Cooper, J. F., Sodd, V. J. Eds.; Society of Nuclear Medicine: New York, 1975; pp 109-149.
(2) Heindel, N. D., Burns, H. D., Honda, T., Brady, L. W., Eds.; "Chemistry of Radiopharmaceuticals"; Masson: New York, 1977.
(3) Mazaitis, J. K.; Gibson, R. E.; Komai, T.; Eckelman, W. C.; Francis, B.; Reba, R. C. *J. Nucl. Med.* **1980**, *21*, 142.
(4) Kabalka, G. W.; Gooch, E. E. *J. Org. Chem.* **1980**, *45*, 3578.
(5) Kabalka, G. W.; Gooch, E. E.; Otto, C. *J. Radioanal. Chem.*, in press.
(6) Kabalka, G. W.; Gooch, E. E.; Hsu, H.; Sun, T. T.; Washburn, L. C.; Hayes, R. L. In "Applications of Nuclear and Radiochemistry"; Lambrecht, R. M., Morcos, N., Eds.; Pergamon Press: New York, 1981.
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(8) Murray, A.; Williams, D. L. "Organic Synthesis with Isotopes, Part III"; Interscience Publishers: New York, 1958; p 1224.
(9) Campbell, M. M.; Johnson, G. *Chem. Rev.* **1978**, *78*, 67.

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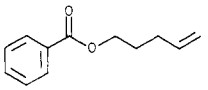
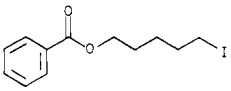
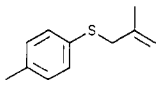
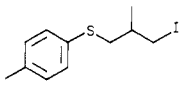
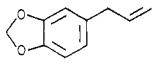
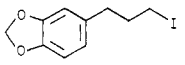
Table I. Conversion of Alkenes to the Corresponding Alkyl Iodides[a]

alkene	product	% yield[b]
$CH_2=CH(CH_2)_3CH_3$	$ICH_2(CH_2)_4CH_3$	99 (96)[c,d]
		99
		94
		99
		78
$CH_2=CH(CH_2)_8CO_2CH_3$	$ICH_2(CH_2)_9CO_2CH_3$	94
$CH_2=CH(CH_2)_{16}CO_2H$	$ICH_2(CH_2)_{17}CO_2H$	89[d,e]
$CH_2=CH(CH_2)_{19}CO_2H$	$ICH_2(CH_2)_{20}CO_2H$	91[d,e]

[a] The alkenes were reacted with BH_3–THF and the resulting organoboranes were reacted with 2 equiv of sodium iodide and 2 equiv of chloramine-T. [b] Isolated yields based on iodide; hexyl iodide and cyclohexyl iodide are GLC yields. [c] Alkene reacted with 2 equiv of dicyclohexylborane to form hexyldicyclohexylborane. [d] 1 equiv of sodium iodide utilized. [e] Alkene reacted with 2 equiv of dicyclohexylborane.

Experimental Section

Routine NMR spectra were recorded on a Varian Associates T-60A spectrometer. All chemical shifts are reported in parts per million downfield from Me_4Si. All melting points and boiling points are uncorrected. The gas chromatography work was performed on a Varian Model 1700 dual-column instrument with a 6 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W column.

Commerically available samples (Aldrich) of 1-hexene, cyclohexene, safrole, methyl 10-undecenoate, and 10-undecynoic acid were used as received. 5-Benzoxy-1-pentene,[4] 3-(*p*-tolylthio)-2-methylpropene,[4] 18-nonadecenoic acid,[5] and 21-docosenoic acid[5] were prepared according to published procedures.

Hydroboration. General Procedure.[10] The alkene (3 mmol) was dissolved in 1 mL of THF in a 10-mL, N_2-flushed, round-bottomed flask equipped with a magnetic stirrer, septum inlet, and reflux condenser. The solution was cooled to 0 °C and BH_3–THF (1 mmol, 0.5 mL of a 2 M solution) was added via a syringe. The solution was stirred at 25 °C for 1 h.

Hydroborations. Dicyclohexylborane Procedure.[10] The alkene (50 mg) was dissolved in 0.5–1.0 mL of THF and then added to 2 equiv of dicyclohexylborane at 0 °C. The solution was stirred at 25 °C for 1 h.

Iodinations. General Procedure. Methanolic sodium acetate (2 equiv, 1 M), aqueous sodium iodide (2 equiv, 1 M), and methanolic chloramine-T (2 equiv, 0.5 M) were added sequentially to the organoborane solution at 25 °C. (For reactions involving dicyclohexylborane derivatives, only 1 equiv of sodium iodide was used.) The mixture was stirred for 1 min at 25 °C and then quenched by adding aqueous sodium thosulfate (1.0 M) and HCl (1.0 N). The mixture was poured into 20 mL of water and 10 mL of pentane. The aqueous layer was separated and was washed with two 5-mL portions of pentane. The combined pentane layers were washed with 5–10 mL of saturated aqueous sodium chloride solution. The pentane was removed by evaporation and the product isolated by flash chromatography[11] (silica gel, ethyl acetate/hexane as eluent).

(*E*)-11-Iodo-10-undecenoic Acid (Via the Iodine Monochloride Method[4]). 10-Undecynoic acid was first converted to its methyl ester via the addition of diazomethane (to avoid reduction of the carboxylic acid). Methyl 10-undecynoate (1.00 g, 5.00 mmol) was placed in a nitrogen-flushed, 25-mL flask. Catecholborane (0.8 mL, 5.84 mmol) was added and the mixture stirred overnight. Water (20 mL) was added to hydrolyze the boronic ester. The solid vinyl boronic acid was isolated by filtration after 10 h and then dissolved in methanol (3 mL). The solution was reacted with 1.0 N NaOH (25 mL) for 3 days at 25 °C. The solution was washed with ether to remove impurities and acidified, and the product extracted into ether. After normal workup, the crude product, a light brown oil, was recrystallized from ethyl ether. The yield of the boronic acid derivative was 1.09 g (94%): mp 99–101 °C; NMR (Me_2SO-d_6) δ 1.3 (s, 12 H, alkane), 2.35 (br envelope, 4 H, CH_2CH=C, CH_2CO_2H), 5.38 (d, 1 H, C=CHB, J = 17 Hz), 6.4 (m, 1 H CH=CHB), 11.9 (s, 1 H, CO_2H).

The boronic acid (135 mg, 0.592 mmol) was dissolved in 1 mL of dry THF contained in a 25-mL round-bottomed flask. Sodium acetate (0.65 mL of a 1.0 M solution in methanol) was added to the solution. The reaction mixture was cooled to −78 °C and then iodine monochloride (0.65 mL of a 1.0 M solution in dry methanol) was added via syringe. the mixture was stirred for 1 h at −78 °C; after 1 h, the mixture was transferred to a separatory funnel and then extracted with three 75-mL portions of ethyl ether. The combined ether layers were washed with aqueous sodium thiosulfate, and dried over magnesium sulfate, and the solvent was removed under reduced pressure. The product was purified by chromatography on neutral alumina, using pentane–ether (5:1) as eluent. The yield of product was 117 mg (64%): mass spectrum, m/e 183 (M − I, calcd 310); NMR ($CDCl_3$) δ 1.35 (s, 12 H, alkane), 2.35 (br envelope, 4 H, CH_2C=C, CH_2CO_2H), 5.85 (d, 1 H, CH=CHI, J = 14 Hz), 6.4 (m, 1 H, CH=CHI), 11.9 (s, 1 H, CO_2H).

1-Iodohexane. 1-Hexene was hydroborated with both BH_3–THF and dicyclohexylborane. The resultant organoboranes were iodinated as described in the general procedure. The yields were determined via GLC analyses. The product exhibited spectral characteristics in accord with a known sample.

Iodocyclohexane. Cyclohexene was hydroborated with BH_3–THF and then reacted with iodide as described in the general procedure. The yield was determined via GLC analyses. The product exhibited spectral characteristics in accord with those of authentic sample.

1-Benzoxy-5-iodopentane. 5-Benzoxy-1-pentene (3 mmol, 570 mg) was hydroborated with BH_3–THF (1 mmol) at 0 °C for 1 h. The resultant organoborane was iodinated as outlined in the general procedure. The product was isolated via column chromatography (silica gel, mixed hexanes eluent) to yield 600 mg (94%). The product exhibited spectral and physical characteristics in accord with those of an authentic sample.[4]

3-(*p*-Tolylthio)-2-methyl-1-iodopropane. 3-(*p*-Tolylthio)-2-methylpropene (3 mmol, 535 mg) was hydroborated with BH_3–THF (1 mmol) at 0 °C for 1 h. The resultant organoborane was iodinated as described in the general procedure. The product was isolated via the column chromatography to yield 610 mg (100%); the product exhibited spectral and physical characteristics in accord with those of an authentic sample.[4]

3-[3,4-(Methylenedioxy)phenyl]-1-iodopropane. Safrole (3 mmol, 490 mg) was hydroborated with BH_3–THF (1 mmol) at 0 °C for 1 h. The organoborane was iodinated as described in the general procedure. The product was isolated via column chromatography to yield 452 mg (78%); the product exhibited spectral and physical characteristics in accord with those of an authentic sample.[4]

Methyl 11-Iodoundecanoate. Methyl 10-undecenoate (3 mmol, 595 mg) was hydroborated with BH_3–THF (1 mmol) of 0 °C for 1 h. The iodination was carried out as described in the general procedure. The product was isolated via column chromatography: yield 614 mg (94%); mass spectrum, m/e 199 (M − I, calcd 326); IR (neat) 1740 cm^{-1} (C=O); NMR ($CDCl_3$) 1.1–1.2 δ (br s, 16 H, alkane), 2.25 (t, 2 H, CH_2CO_2), 3.28 (t, 2 H, CH_2I), 3.58 (s, 3 H, OCH_3).

19-Iodononadecanoic Acid. 18-Nonadecenoic acid (100 mg, 0.34 mmol) was hydroborated with dicyclohexylborane (0.7 mmol) at 0 °C. The organoborane was iodinated with sodium acetate (0.7 mmol), sodium iodide (0.35 mmol), and chloramine-T (0.7 mmol). The product was isolated by column chromatography on silica gel (10% ethyl acetate–hexane): yield 129 mg (89%); mass spectrum, m/e 424.5 (calcd 424.5); NMR ($CDCl_3$) δ 1.2 (s, 30 H,

(10) Brown, H. C. "Organic Synthesis via Boranes"; Wiley interscience: New York, 1975; Chapter 2.
(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

alkane), 2.1 (m, 4 H, CH_2CO_2H, CH_2CH_2I), 3.0 (t, 2 H, CH_2I), 11.9 (s, 1 H, CO_2H).

22-Iododocosanoic Acid. 21-Docosenoic acid (55 mg, 0.16 mmol) was hydroborated with dicyclohexylborane (0.32 mmol) at 0 °C. The organoborane was iodinated with a mixture of sodium acetate (0.32 mmol), sodium iodide (0.16 mmol), and chloramine-T (0.32 mmol). The product was isolated by column chromatography on silica gel (10% ethyl acetate–hexane): yield 68 mg (91%); mp 71–72 °C; mass spectrum, *m/e* 466.5 (calcd for 466.5); NMR ($CDCl_3$) δ 1.2 (s, 36 H, alkane), 2.1 (m, 4 H, CH_2CO_2H and CH_2CH_2I), 3.0 (t, 2 H, CH_2I, 11.9 (s, 1 H, CO_2H).

Iodobenzene. Triphenylborane was prepared according to a published procedure.[12] The triphenylborane (247 mg 1.02 mmol) was placed in a 5-mL, dry, nitrogen-flushed flask containing 1.5 mL of THF. Sodium acetate, sodium iodide, and chloramine-T (1.02 mmol) were added at room temperature. The yield of iodobenzene (100%) was determined via GLC analysis (yield based on the migration of one phenyl group per organoborane molecule).

(12) Koster, R.; Binger, P.; Fenzye, W. *Inorg. Synth.* 1941, *15*, 134.

Acknowledgment. We thank the National Institutes of Health (1-R01-GM-25187-02) for support of this research.

Registry No. 1-Hexene, 592-41-6; 1-iodohexane, 638-45-9; cyclohexene, 110-83-8; iodocyclohexane, 626-62-0; 5-benzoxy-1-pentene, 29264-40-2; 1-benzoxy-5-iodopentane, 74203-20-6; 3-(*p*-tolylthio)-2-methylpropene, 54844-24-5; 3-(*p*-tolylthio)-2-methyl-1-iodopropane, 74203-21-7; safrole, 94-59-7; 3-[3,4-(methylenedioxy)phenyl]-1-iodopropane, 74203-22-8; methyl 10-undecenoate, 111-81-9; methyl 11-iodoundecanoate, 929-33-9; 18-nonodecenoic acid, 76998-87-3; 19-iodononodecanoic acid, 76998-88-4; 21-docosenoic acid, 53821-23-1; 22-iododocosanoic acid, 76998-89-5; iodobenzene, 591-50-4; triphenylborane, 960-71-4; methyl 10-undecynoate, 2777-66-4; (*E*)-11-iodo-10-undecenoic acid, 76998-90-8; catecholborane, 274-07-7; (*E*)-11-(1,3,2-benzodioxaborol-2-yl)-10-undecenoic acid, 76998-91-9; iodine monochloride, 7790-99-0; dicyclohexylborane, 1568-65-6; sodium iodide, 7681-82-5; BH_3–THF, 14044-65-6.

Notes

Dehydroaporphines. Enamine-Type Michael Additions

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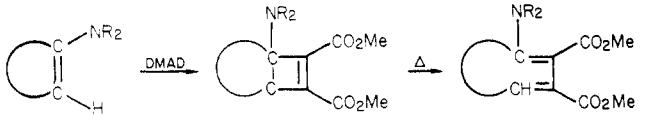
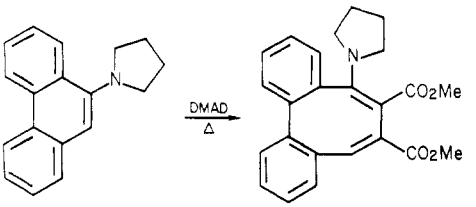
We have shown previously that dehydroaporphines show a certain degree of enamine-type character, as evidenced by their behavior on protonation,[1] Reimer–Tiemann formylation,[2] and acylation.[3] We now report the first study of the reactions of a typical dehydroaporphine, dehydronuciferine (1), with Michael acceptors and the resulting synthesis of some new types of 7-substituted aporphines of potential pharmacological interest.

Results and Discussion

Enamines derived from cyclic ketones are known to undergo [2 + 2] cycloadditions to dimethyl acetylenedicarboxylate (DMAD) to give thermally labile cyclobutenes which, on heating, are transformed into diene diesters; the overall process affords a simple bishomologation of the carboxylic ring of the original enamine.[4]



This process has been carried out successfully even in the case of 9-(dialkylamino)phenanthrenes. For example, a dibenzocyclooctatetraene derivative was produced smoothly when 9-pyrrolidinophenanthrene was heated in dioxane with DMAD, as shown below.[5]



The analogous reaction of dehydronuciferine (1) with DMAD in refluxing dioxane proceeded very sluggishly and required over 5 days for the consumption of the original alkaloid. Chromatographic separation afforded none of the *C*-dihomoaporphine **2**; the isomeric diesters **3** and **4** were produced in good yield in hot benzene–methanol, the reaction going largely to completion in 30 min. The stereochemistry of esters **3** and **4** was clearly revealed by their NMR spectra. As predicted by molecular models, one of the ester methoxyls of the trans isomer **4** lies over the lower aromatic ring of the phenanthrene system and appears at the rather shielded position of δ 3.43. In addition, the olefinic proton of **4** is deshielded by the adjacent carbomethoxyl and appears δ 7.20, as compared to the more normal value of δ 6.43 in the cis isomer **3**. The esters **3** and **4** were slowly interconverted in refluxing benzene–methanol. After 4 days of heating, the cis isomer **3** yielded a mixture of **3** and **4** containing about 35% **4**; after 4 days of similar treatment, the far more stable trans isomer **4** was converted to **3** to an extent of only about 1%.

The mechanism of formation of **3** and **4** merits some comment. The initial product of addition of dehydronuciferine to DMAD may be formulated as the dipolar species **5**. Cyclization of **5** to the cyclobutene **6** involves no unusual steric problems, but ring opening of **6** to the strained tetracyclic diene **2** is a process of high enough energy that ring cleavage back to **5** occurs instead (Scheme

(1) A. Venkateswarlu and M. P. Cava, *Tetrahedron*, **32**, 2079 (1976).
(2) J. M. Saá and M. P. Cava, *J. Org. Chem.*, **42**, 347 (1977).
(3) J. M. Saá and M. P. Cava, *J. Org. Chem.*, **43**, 1096 (1978).
(4) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963).
(5) D. Becker, L. R. Hughes, and R. A. Raphael, *J. Chem. Soc., Perkin Trans 1*, 1674 (1977).

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