Fast, mild, and convenient procedures for iodination and bromination of carbohydrates: reactions of organoboranes with iodine monochloride, sodium iodide, bromine, and bromine chloride

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5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-D-*xylo*-hexofuranosene-5 (**1**), reacts with BH_3–THF to form the tris(glycosyl)borane (**2**) and with dicyclohexylborane to form the dicyclohexylglycosylborane (**3**). The iodination and bromination of **2** and **3** has been investigated using a variety of electrophiles. Iodination of either **2** or **3** with NaI–Chloramine-T/NaOAc is complete within one minute with high percentage uptake of iodine (70–90%) and recovery of the iodinated sugar (**4**). Bromination of **2** in 15 minutes with NaBr–Chloramine-T permits a high percentage uptake of bromine (75%), and bromination of **3** in 15 minutes with Br_2/NaOAc gives the brominated sugar (**5**) with a reasonably good yield (60%) with respect to the starting material (**1**).

LAURANCE D. HALL et JEAN-RICHARD NEESER. Can. J. Chem. **60**, 2082 (1982).

Le didéoxy-5,6 *O*-isopropylidène-1,2 *O*-méthanesulfonyl-3 α-D-*xylo*-hexofurannosène-5 (**1**) réagit avec le complexe BH_3 –THF pour donner accès au tris(glycosyl)borane (**2**), tandis que face au dicyclohexylborane, il conduit au dicyclohexylglycosylborane (**3**). L'iodation et la bromation des composés **2** et **3** ont été étudiées en utilisant divers agents électrophiles. En présence de NaI–Chloramine-T/NaOAc, l'iodation des composés **2** ou **3** est complète au bout d'une minute, le fort pourcentage d'incorporation d'iode (70–90%) conduisant sucre iodé (**4**). La bromation du composé **2** par NaBr–Chloramine-T requiert 15 minutes et donne lieu à un fort pourcentage d'incorporation de brome par le sucre (75%); la bromation du composé **3** par Br_2/NaOAc s'effectue en 15 minutes et permet d'obtenir le sucre bromé (**5**) avec un rendement acceptable (60%) par rapport au produit de départ (**1**).

Introduction

In recent years, a very wide variety of radiohalogen-containing radiopharmaceuticals have been developed (1) for use in diagnostic nuclear medicine and positron emission tomography (PET). Much interest has been aroused in the search for rapid methods of halogenation, compatible with the use of very short half-life radiohalogens. Very recently a new, mild, and rapid method for fluorination of aromatic compounds by treatment of aryl-tin derivatives with ^{18}F-F_2 (2) was developed and similar reactions of other aryl-metal derivatives have been evaluated. Continuing in this general field, we have now adapted new, fast, and mild methods for the iodination and bromination of carbon–boron bonds to the area of carbohydrate chemistry. Recently, Kabalka and co-workers have developed two methods for the iodination (3, 4) and two for the bromination (5) of organoboranes, which work under conditions so mild that they are compatible with a wide range of functional groups.

Kabalka and co-workers have observed that when trialkylboranes, derived from the hydroboration of terminal alkenes, are activated in an electron-rich organoborane–acetate complex, two of the three groups on boron react instantaneously when treated with iodine monochloride (3), or with iodide ion in the presence of an oxidizing agent such as Chloramine-T (4). This latter reaction permits the selective cleavage of a primary alkylboron bond when mixed organoboranes, prepared with dicyclohexylborane, react with iodonium ion (4). Without activation of the trialkylborane, one of the three primary alkyl groups on boron reacts instantaneously when treated with bromine in the presence of water, or with bromine chloride prepared *in situ* (5). This latter reaction permits the preferential cleavage (70%) of a primary alkyl–boron bond, when dicyclohexylborane is used as the hydroborating agent (5). All these reactions are postulated to proceed in an ionic fashion, via an S_E2 mechanism.

Prior to this study, organoborane technology had been successfully used in carbohydrate chemistry in hydroboration–oxidation sequences (6). The success generally observed in these applications of organoborane technology in carbohydrate chemistry, and the recent interest in research for very fast methods for the synthesis of halogenosugar derivatives, has prompted us to adapt the new "Kabalka" procedures to an unsaturated carbohydrate model, namely 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-D-*xylo*-hexosene-5 (7) (**1**).

Results and discussion

The triglycosylborane (**2**), obtained by reaction

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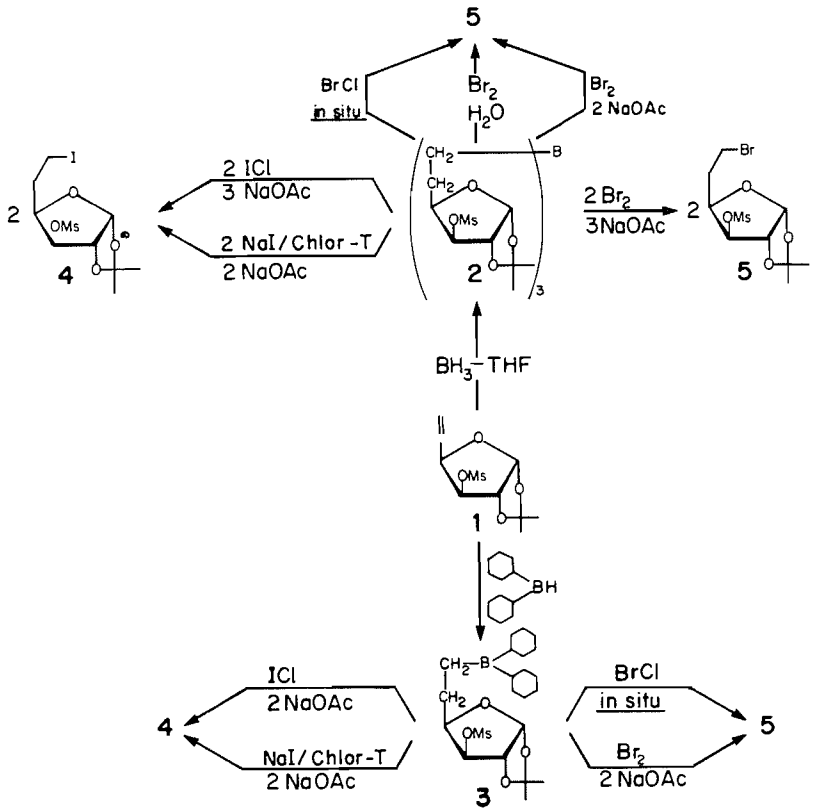


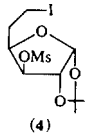
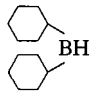
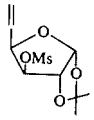
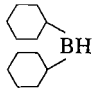
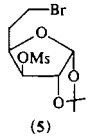
SCHEME 1

of the starting unsaturated carbohydrate (**1**) with BH_3–THF, readily reacts in the presence of sodium acetate with two equivalents of ICl, or with two equivalents of sodium iodide and Chloramine-T; under these conditions 74 and 72%, respectively, of the added iodine is consumed. It seems reasonable to speculate that the first carbohydrate moiety attached on the boron atom reacts quantitatively, whereas the reaction of the second group is incomplete. It was possible to confirm this hypothesis by using dicyclohexylborane as the hydroborating agent. It was found that the dicyclohexylglycosylborane (**3**) reacts quantitatively with one equivalent either of the iodide/Chloramine-T reagent or the ICl reagent, the carbohydrate-containing primary alkyl group being selectively iodinated within one minute by the former reagent to produce the iodo derivative (**4**) in excellent yield (ca. 90%). The results for the iodination reactions are summarized in Table 1.

The triglycosylborane (**2**) reacts readily with one equivalent of BrCl prepared *in situ* from bromide/Chloramine-T, and permits the isolation of the bromo derivative (**5**), in 75% yield with respect to the bromide reagent. However, the fact that, in this reaction, only one of the three carbohydrate groups attached to the boron atom is able to react reduces the yield with respect to the unsaturated starting carbohydrate to 25%. Unfortunately the above reaction conditions appear not to discriminate efficiently between bromination of a glycosyl–boron bond and that of a cyclohexyl–boron bond. Thus it was found that the organoboron derivative (**3**) reacted with one equivalent of BrCl *in situ* to give only 36% of the bromo-sugar (**5**) (mixed with an unidentified carbohydrate-containing by-product) and an equivalent yield of bromocyclohexane. Under the same reaction conditions, Kabalka *et al.* (5) report that tricyclohexylborane utilized 67% of the added halogen.

With one equivalent of Br_2 in aqueous medium, **2** is converted to **5**, utilizing less than half of the bromine in the reaction. In addition, an unresolved mixture of by-products was isolated by lcc (liquid column chromatography); these contain no carbohydrate and probably come from the tetrahydrofuran present in the reaction medium. Consequently, it seems necessary to activate the

TABLE 1. Halogenations of organoboranes derived from **1**

Substrate	Product	Hydroborating agent	Halogenating agent/ Equiv. of organoborane intermediate	Halogenation time (min)	% Isolated yield[a]
	 (4)	BH_3: THF	2 ICl/3NaOAc	45	74 (49)
			1 ICl/2NaOAc	45	88 (88)
 (1)		BH_3: THF	2 NaI/2Chlor-T/2NaOAc	1	72 (48)
			1 NaI/2Chlor-T/2NaOAc	1	91 (91)
	 (5)	BH_3: THF	1 BrCl *in situ*	15	75 (25)
			1 BrCl *in situ*	15	36 (36)[b]
		BH_3: THF	1 Br_2/H_2O	30	48 (16)
		BH_3: THF	1 Br_2/2NaOAc	15	93 (31)
		BH_3: THF	2 Br_2/3NaOAc	15	62 (41)
			1 Br_2/2NaOAc	15	60 (60)

[a]Isolated yields based on the halogenating agent. The numbers in parentheses refer to isolated yields based on starting unsaturated carbohydrate (**1**).
[b]The product (**5**) isolated from this procedure is mixed with an unidentified carbohydrate-containing by-product.

organoboron intermediate (**2**) to obtain a specific reaction with molecular bromine. By analogy with our iodination experiments, **2** was activated with methanolic sodium acetate, and under these conditions one equivalent of Br_2 reacts quantitatively with one sugar moiety to give **5**. However, we observe that under the same conditions, two equivalents of Br_2 are utilized with a 62% yield of **5**, showing that this reaction permits fast cleavage of two of the three primary alkyl groups attached to the boron atom, but with an incomplete migration of the second group in this case. Fortunately, when treated with one equivalent of Br_2, the activated dicyclohexylglycosylborane (**3**) utilizes 60% of the halogen for bromination of the glycosyl group. Thus this latter procedure is more selective for the preferential cleavage of the primary alkyl carbohydrate-containing group than is the BrCl *in situ*. Our results are summarized in Table 1.

In principle, three different products could arise from the hydroboration of **1**: the two, C-5 epimeric 5-bora-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-D-glucofuranose and β-L-iodofuranose, and the 6-bora-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-α-D-*xylo*-hexose (**2** or **3**). The latter is the expected product arising from the normal, anti-Markovnikov hydroboration. Although the fact that only the 6-iodo and 6-bromo derivatives were obtained from the halogenation reactions provides supportive evidence for C-6 boronation, this is not conclusive since it is known that these halogenation methods *preferentially* cleave primary alkyl groups; thus, if small amounts of 5-bora derivatives had been produced by the hydroboration reactions, these products might not be halogenated. The structures of **4** and **5** were unambiguously assigned on the basis of their nmr spectra.

Conclusion

By the standards of conventional organic syntheses the reactions described here are reasonably efficient, but probably not sufficiently so to warrant their selection in preference to other methods for introducing halogen at a primary centre. However, their merit is somewhat more obvious in the context of the constraints of radiolabelling chemistry, where yields are based on the uptake of halogen rather than consumption of the organic substrate, and where time limitations

require that the halogenation reaction plus work-up be completed within the equivalent of 2–3 half-lives; this latter limit requires that the halogen be used in essentially the same atomic form in which it is generated in the cyclotron.

Given such constraints and considering the known ease of generating ^{120}I-iodide, the synthesis of **4** from **1** via dicyclohexylboronation and NaI–Chloramine-T/NaOAc, with essentially quantitative uptake of iodine and quantitative yield of **4**, is very encouraging; that the reaction is completed within 1 minute which amounts to ca. 1% of one radioactive half-life for ^{120}I (81 min) is exemplary. The synthesis of the bromo-derivative (**5**) is somewhat less satisfactory, but the yields based on the bromine uptake (75%) in the BH_3–THF/NaBr–Chloramine-T procedure is again encouraging (^{75}Br-bromide being easily generated), as is the time of the reaction, 15 min, 15% of one half life for ^{75}Br (97 min).

Experimental

The nmr spectra were run at 270 MHz using a home-built, pulse Fourier transform nmr spectrometer. All chemical shifts are reported in parts per million downfield from Me_4Si. The mass spectra were recorded at low resolution, on a Varian MAT Atlas CH4-B mass spectrometer. The specific optical rotation $[\alpha]_D$ values were obtained with a Perkin–Elmer 241 MC polarimeter.

*5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-*α*-*D*-xylo-hexosene-5* (**1**) was prepared according to a published procedure (7), modified as follows: 1,2-*O*-isopropylidene-3,5,6-tri-*O*-methanesulfonyl-α-D-glucose (10 g) and NaI (26 g) were dissolved in 500 mL of 2-butanone and heated under reflux (3.5 h). After work-up using the published procedure (7), the crude product was crystallized from methanol to yield pure **1** (5.35 g, 92%).

Hydroborations

Commercially available (Alfa) BH_3–THF (1 *M* solution) was used. Reagent Grade THF was deoxygenated according to a published procedure (8*a*) and kept under N_2 in a bottle stoppered with a septum. Syringes were purged before each use with N_2, according to a published technique (8*b*).

BH_3–THF procedure (synthesis of 1 mmol of 2)

Compound **1** (792 mg, 3 mmol) was introduced under a blanket of N_2 in a round-bottomed flask equipped with magnetic stirrer and septum inlet, which had been flushed hot with N_2. THF (1.5 mL) was added via a syringe, the resultant solution cooled to 0°C and BH_3–THF (1.05 mL of a 1 *M* solution) added via a syringe. The mixture was stirred for 1.5 h at 25°C.

Dicyclohexylborane procedure (synthesis of 2 mmol of 3)

A suspension of dicyclohexylborane in THF at 0°C (4.2 mL of 0.5 *M*) was prepared according to the published procedure (8*c*). During the same time period a solution of **1** (528 mg, 2 mmol) in THF (1 mL) was prepared as above. This solution was added via a syringe to the dicyclohexylborane suspension at 0°C and the mixture was stirred at 25°C for 2 h.

Iodinations:

Iodinations of two groups on boron from 1 mmol of 2 {or one group on boron from 2 mmol of 3}

The published procedures of Kabalka and Gooch (3, 4) were followed. After quenching, the mixtures were poured into water (20 mL) and extracted with 4 × 10 mL of ether. The combined ether extracts were dried ($MgSO_4$) and ether was removed under reduced pressure. Column chromatography on silica with ether/hexane (2:1) as eluant yielded 580 mg (74%) {or 690 mg (88%)} of pure **4** from the *iodine monochloride procedure*, and 565 mg (72%) {or 715 mg (91%)} of pure **4** from the *iodide/Chloramine-T procedure*.

Brominations:

Brominations of 1 group on boron from 1 mmol of 2 {or 2 mmol of 3}

The published procedures of Kabalka *et al.* (5) were followed. After reacting, the mixtures were extracted with 15 mL of ether; the ether solutions were washed with two 7.5 mL portions of water, dried over $MgSO_4$, and concentrated. Column chromatography on silica with ether/hexane (2:1) as eluant yielded 260 mg (75%) of pure **5** {or 250 mg (36%) of **5** mixed with an unidentified carbohydrate-containing by-product} from the *BrCl* in situ *procedure*, and 165 mg (48%) of pure **5** from the *molecular bromine/water procedure*.

Molecular bromine/methanolic sodium acetate procedure

Methanol (1 mL {or 2 mL}), followed by 2 mL {or 4 mL} of 1 *M* methanolic sodium acetate were added to the organoborane solution in THF. The mixture was cooled to 0°C and shielded from light. Bromine (1 mmol {or 2 mmol}) was added and the mixture stirred 15 min at 0°C; 2 mL of saturated K_2CO_3 solution were added and the mixture poured into 15 mL of water. The mixture was extracted with 4 × 10 mL of ether, the combined ether layers were washed with 2 × 7.5 mL of water and 2 × 7.5 mL of saturated NaCl solution, and dried over anhydrous $MgSO_4$. The product was isolated as described before and 320 mg {or 415 mg} of pure **5** was obtained. The yield was 93% {or 60%}.

Bromination of two groups on boron from 1 mmol of 2

Molecular bromine/methanolic sodium acetate procedure

Three milliliters of 1 *M* methanolic sodium acetate were added to the organoborane solution in THF. The mixture was treated as described previously using 2 mmol of bromine. This method permitted isolation of 430 mg (62%) of pure **5**.

Characterization of 4 and 5

*5,6-Dideoxy-6-iodo-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-*α*-*D*-xylo-hexose* (**4**) was recrystallized from methanol; mp 70–71°C; $[\alpha]_D^{22}$ +4.06° (*c* 1, $CHCl_3$); ^{1}H nmr δ ($CDCl_3$): 1.33 and 1.54 (2s, 2 × 3H, CMe_2), 2.12 and 2.22 (2m, 2 × 1H, H_A- and H_B-C5), 3.08 (s, 3H, SO_2Me), 3.30 (m, 2H, H-C6), 4.43 (ddd, 1H, H-C4, $J_{4,5}$ = 8.1 and 4.0 Hz, $J_{4,3}$ = 3 Hz), 4.77 (d, 1H, H-C2, $J_{2,1}$ = 3.8 Hz), 4.98 (d, 1H, H-C3), 5.92 (d, 1H, H-C1); *m/e*: 377(25) (M^+ − Me), 239(33), 83(16), 79(18), 59(46), 57(16), 55(20), 43(100), 41(26), 32(23), 28(97). *Anal.* calcd. for $C_{10}H_{17}IO_6S$: C 30.62, H 4.37, I 32.36; found: C 30.51, H 4.35, I 32.30.

*6-Bromo-5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-methanesulfonyl-*α*-*D*-xylo-hexose* (**5**) was recrystallized from methanol; mp 74–75°C; $[\alpha]_D^{22}$ +6.50° (*c* 1, $CHCl_3$); ^{1}H nmr, δ ($CDCl_3$): 1.34 and 1.54 (2s, 2 × 3H, CMe_2), 2.14 and 2.29 (2m, 2 × 1H, H_A- and H_B- C5), 3.11 (s, 3H, SO_2Me), 3.54 (m, 2H, H-C6), 4.52 (ddd, 1H, H-C4, $J_{4,5}$ = 8.2 Hz and 3.8 Hz, $J_{4,3}$ = 2.9 Hz), 4.78 (d, 1H, H-C2, $J_{2,1}$ = 3.8 Hz), 4.99 (d, 1H, H-C3), 5.94 (d, 1H, H-C1); *m/e*: 331–329 (18-18) (M^+ − Me), 193–191 (23-23), 79(17), 59(53), 55(14), 43(100), 41(22), 28(20). *Anal.* calcd. for $C_{10}H_{17}BrO_6S$: C 34.79, H 4.96, Br 23.15; found: C 34.95, H 5.02, Br 22.95.

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