Communications

A New Synthesis of Deoxyiodo Sugars

Summary: Reaction of tetrabutylammonium iodide with carbohydrates containing the trifluoromethanesulfonate (triflate) group has been found to be a very effective means for synthesis of deoxyiodo sugars.

Sir: Deoxyhalogeno sugars are among the most versatile intermediates in carbohydrate synthesis. These compounds have been used in the formation of a variety of substances, including anhydro, aminodeoxy, deoxy, epoxy, and unsaturated sugars.[1] Although several types of reaction have been useful in synthesizing halogenated carbohydrates, displacement processes generally have been the most effective. Many displacement reactions, however, have been subject to one or more of the following limitations: (a) destructively vigorous reaction conditions; (b) inability to effect displacement in some instances (particularly when the leaving group is on a secondary carbon); (c) competing elimination reactions; (d) molecular rearrangements. The purpose of this communication is to report a procedure for the synthesis of deoxyiodo sugars which overcomes many of these limitations by using the remarkably reactive trifluoromethanesulfonate (triflate) leaving group in combination with tetrabutylammonium iodide. This combination has produced substitution in high yield without competition from elimination or rearrangement in each of the molecular systems upon which it has been attempted.

Five partially protected monosaccharides (**1–5**) have been converted into their corresponding iodides (**6–10**) via triflate displacement (Table I). The procedure for this conversion is illustrated by a description of the preparation of 3-deoxy-3-iodo-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**6**). Triflic anhydride[2] (1.68 g, 6.0 mmol) in 20 mL of dichloromethane was added to a solution of 0.52 g (6.5 mmol) of pyridine in 100 mL of dichloromethane maintained at −15 °C. To this solution was added 1.0 g (3.8 mmol) of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[3] (**1**) in 50 mL of dichloromethane and the reaction mixture was stirred for 1.5 h at −15 °C before being poured into 200 mL of 5% sodium bicarbonate solution. The organic layer was separated and dried (anhydrous sodium sulfate) and the solvent was distilled to give a quantitative yield of 1,2:5,6-di-*O*-isopropylidene-3-*O*-triflyl-α-D-glucofuranose[4] (**11**). The triflate **11** was dissolved in 50 mL of benzene, 3.7 g (10 mmol) of tetrabutylammonium iodide[5] was added, and the reaction mixture was refluxed for 18 h. The cooled solution was washed with 50-mL portions of water, 5% sodium bisulfite, saturated sodium bicarbonate, and water and dried over anhydrous sodium sulfate, and the solvent was distilled to leave 1.24 g of noncrystalline material which was homogeneous by TLC and GC analyses. The chemical ionization mass spectrum of this material had an intense parent peak at *m/e* 371 and the ^{1}H NMR spectrum (60 MHz, $CDCl_3$) had absorptions at δ 5.72 (d, 1 H, *J* = 3 Hz), 4.50 (t, 1 H, *J* = 3 Hz), 4.33–3.50 (m, 4 H), 1.57 (s, 3 H), 1.33 (s, 3 H), and 1.23 (s, 6 H). This information suggested structure **6** for the reaction product and excluded **7** (C-3 epimer of **6**), a compound with a quite different ^{1}H NMR spectrum.[6,7] This suggested assignment was confirmed by reduction of the reaction product with lithium aluminum hydride in refluxing ether to 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**12**). The iodides **7–10** were prepared in the same manner as **6** and compared to independently obtained samples (see Table I for yields and references).

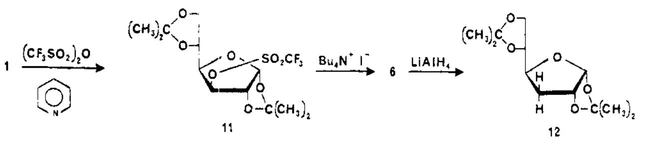
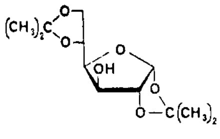
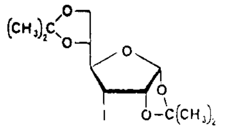
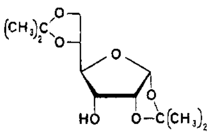
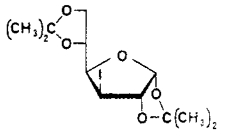
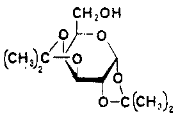
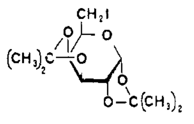
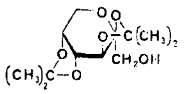
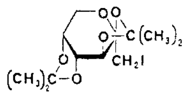
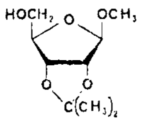
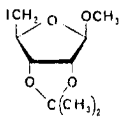


Table I

reactant	product	yield	reference
 1	 6	87%	none
 2	 7	84%	7
 3	 8	94%	3
 4	 9	99%	15
 5	 10	65%	16

The synthesis of **6** from **1** is a significant example of the triflate displacement process because it occurs without rearrangement or elimination. This type of reactivity stands in contrast to other attempts to halogenate **1** via displacement processes; in fact, neither compound **6** nor the corresponding fluoro, chloro, and bromo derivatives previously have been reported. Attempts to synthesize these compounds invariably have led to rearrangement or elimination reactions;[8–14] thus, in addition to being a convenient and relatively mild reaction sequence, triflate displacement has a distinct advantage over other substitution reactions.

We are planning to extend this reaction sequence to other carbohydrate systems and to use it to introduce other halogens.

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References and Notes

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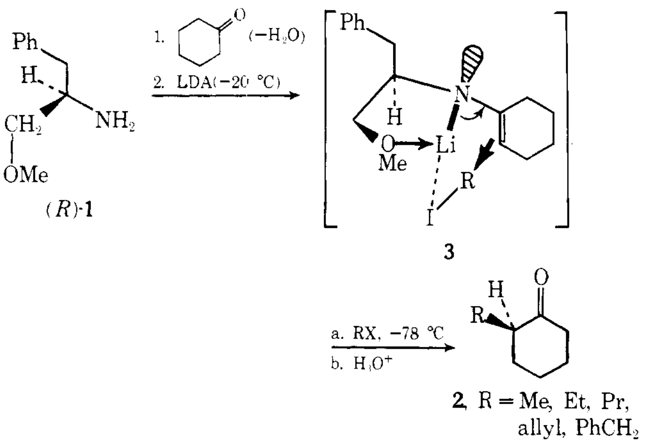
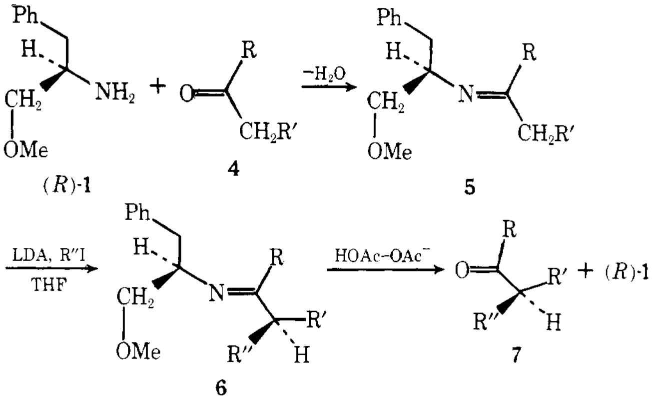
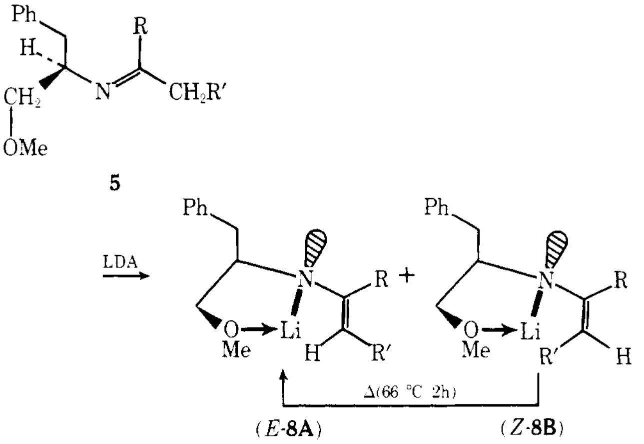
Asymmetric Alkylation of Acyclic Ketones via Chiral Metallo Enamines. Effect of Kinetic vs. Thermodynamic Metalations

Summary: Chiral imines of acyclic ketones have been metalated and alkylated to afford α-alkyl ketones in 20–98% ee after equilibration of the metallo enamines.



Scheme I





Sir: We recently described an asymmetric synthesis of 2-alkylcyclohexanones (**2**) via the chiral methoxyamine **1**.[1] The process was based upon the premise that the intermediate metallo enamine **3** would exist as a rigid five-membered ring through chelation of the methoxyl group with the lithium cation, providing favorable topological features for specific sites of alkylation. In order to account for the configurations obtained, it was suggested that the alkyl halide may approach from the front side of the cyclohexene moiety, leading to 2-alkylcyclohexanones in high enantiomeric purity.[2] It seemed reasonable that this rigid metallo enamine should also provide α-alkyl ketones of high enantiomeric purity in the acyclic series. We now report that the conditions utilized above with acyclic ketones gave very poor results with regard to enantioselective alkylation, but a minor modification of the experimental procedure led to α-alkyl ketones **7** in generally high enantiomeric purity (Table I) within the constraints of certain structural features (vide infra). When the reaction conditions utilized for **2** (LDA, −20 °C; $R''I$, −78 °C) were employed for the acyclic imines **5**, alkylation occurred with no difficulty, furnishing **6** (Scheme I). However, hydrolysis to the ketones **7** gave products in 3–44% enantiomeric excess (Table I, % ee's in parentheses). The possibility that the lithiated enamines were kinetically formed as mixtures of *E* and *Z* isomers (**8A**, **8B**), a situation not possible in the cyclohexene system **3**, was therefore considered. When the lithio enamines, formed at −20 °C, were heated to reflux (THF) prior to alkylation, and the alkyl halide was added after cooling at −78 °C (first three entires, Table I), the ketones were obtained in 76–98% ee! In the case where R (in **4** or **5**) was phenyl or benzyl (last four entries, Table I), the % ee of the ketones **7** was less dramatically affected. Thus, the kinetic or the thermodynamic ratio of lithio enamines **8** is dependent upon the bulk of the substituents present. It may, therefore, be assumed that metalation of **5** produces **8A** and **8B** kinetically; however, heating **8** (**A, B**) allows equilibration which favors the most stable lithio enamine. The relative size of the three substituents about the double bond will dictate whether the thermodynamic ratio of enamines is very different from the kinetic ratio.[3] As seen from the table, the progression of high % ee to a relatively lower one follows the increasing size of substituents on the ketone or lithio enamine **8**. Larger groups, such as phenyl, may decrease the thermodynamic stability of the *E* relative to the *Z* isomer, resulting in ketones of lower enantiomeric purity. In the last entry of Table I, two phenyl groups are present in **8** and from the absolute configuration of the ketone isolated, we may assume that the (*Z*)-enamine is slightly favored (60:40) to give 20% ee with an *S* configuration. The previous conditions for generating lithio enamines (∼−20 °C) were obviously insufficient to effect their equilibration

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