Radical Fragmentation of β-Hydroxy Azides. Synthesis of Chiral Nitriles

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In previous papers, we have described the preparation of chiral building blocks by fragmentation of anomeric alkoxy radicals of carbohydrates.[1] Moreover, nitriles have proven to be extremely versatile functional groups.[2] They may undergo a variety of reactions, especially reduction, alkylation of their enolates, enzymatic hydrolysis to acids and amides by nitrile hydratase,[3] Ritter reaction,[4] and many other synthetically useful transformations.

In this paper, we develop a new protocol for the synthesis of nitriles by β-fragmentation of alkoxy radicals by reaction of β-hydroxy azides with (diacetoxyiodo)benzene (DIB) and iodine. In particular, this reaction has been applied to the synthesis of chiral nitriles by β-fragmentation of anomeric alkoxy radicals from 2-azido-2-deoxy sugars, as shown in Scheme 1.

Related methodologies for the synthesis of cyano ketones by cleavage of trisubstituted cyclic olefins with DIB−trimethylsilyl azide, LTA−trimethylsilyl azide,[5] or photooxygenation in the presence of NaN$_3$/Cu(OTf)$_2$ have been described.[6] Moreover, an interesting synthesis of aldononitriles by reaction of N-bromoglycoxylimines with Zn/Ag−graphite or C$_8$K has been reported.[7]

Several excellent methods exist in the literature for the synthesis of β-hydroxy azides in general by electrophilic or radical addition reactions to olefins.[8] We have prepared 3,4,6-tri-O-acetyl-2-azido-2-deoxy-D-glucose[9] (**1**) by reaction of 3,4,6-tri-O-acetyl-D-glucal with sodium azide/ceric ammonium nitrate[10] and subsequent anomeric denitration[11] with hydrazine acetate of the β-nitro azide obtained. Reaction of this compound with DIB and iodine
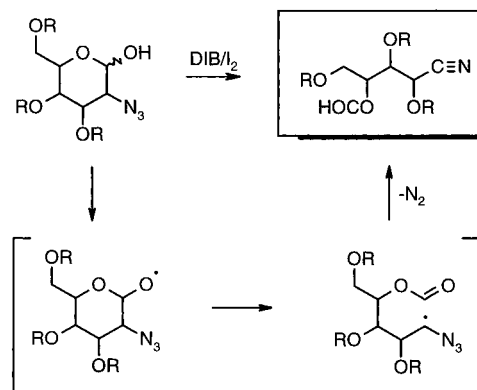
Scheme 1

Table 1. Nitriles by β-Fragmentation of β-Hydroxy Azides[a]

entry	substrate	T (°C)	time (h)	product	yield (%)
1	**1**	20	2	**2**	88
2	**3**	20	0.5	**4**	71
3	**5**	20	2	**6**	65
4	**7**	25-30	1.5	**8**	79
5	**9**	25-30	1.5	**10**	82

[a] All reactions were performed in dry dichloromethane with (diacetoxyiodo)benzene (1.2 mmol) and iodine (1 mmol) per mmol of substrate. The monoterpene substrates **7** and **9** were irradiated with 2 × 80W tungsten-filament lamps.

under the conditions shown in Table 1 (entry 1) gave the arabinonitrile derivative **2**.

In a typical procedure, a solution of β-hydroxy azide **1** (102 mg, 0.31 mmol) in CH$_2$Cl$_2$ (20 mL) containing DIB (120 mg, 0.37 mmol) and iodine (79 mg, 0.31 mmol) was stirred at 20 °C for 2 h. The reaction mixture was then

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poured into a 10% aqueous sodium thiosulfate solution and extracted with CH$_2$Cl$_2$, dried (Na$_2$SO$_4$), and concentrated in vacuo. Chromatotron chromatography of the residue (hexanes−EtOAc, 70:30) yielded **2** (82.3 mg, 88%).

The reaction can also be performed with carbohydrates in furanose form as can be observed from Table 1 (entry 2). The 2-azide-2-deoxy-5,6-*O*-isopropylidene-3-*O*-methyl-D-mannofuranose (**3**) obtained starting from 1,4-anhydro-2-deoxy-5,6-*O*-isopropylidene-D-arabino-*hex*-1-enitol[12] by azidophenylselenation with *N*-(phenylseleno)-phthalimide and trimethylsilyl azide followed by anomeric dephenylselenation with *N*-iodosuccinimide[13] gave the arabinonitrile derivative **4**. The arabinonitrile derivatives **2** and **4** possess very different patterns of protection and have been synthesized in order to explore the utility of this methodology for the synthesis of chiral synthons.

As can be seen in Table 1 (entry 3), the reaction was also applied to carbohydrates of the threose series, so the 2-azido-2-deoxy-galactose derivative **5**, obtained from the commercially available 3,4,6-tri-*O*-acetyl-D-galactal by an analogous azidophenylselenation−hydrolysis,[13] gave the lyxonitrile derivative **6**.

The reaction can be extended to noncarbohydrate compounds such as the monoterpenes **7** and **9**. Both β-hydroxy azides were prepared by photooxygenation in the presence of sodium azide of the corresponding olefins, (+)-limonene and (−)-α-pinene, and subsequent reduction, with sodium sulfite, of the azidohydroperoxides formed.[14] The radical fragmentation reaction gave 1,5-cyano ketones **8** and **10** in similar yields (entries 4 and 5). Although, in both cases, the reaction may proceed

Scheme 2
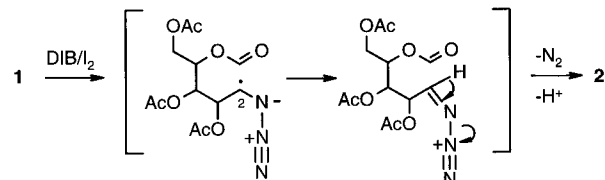
under natural light conditions, assisted irradiation with 2×80W tungsten-filament lamps reduced reaction times.

The reaction mechanism deserves special comment. As shown in Scheme 2, the C2 radical initially formed must be oxidized by the reagent to a carbocation in order for the nitrile group to be formed after loss of a molecule of nitrogen. Another transformation of azides into nitriles can be observed during the thermal or photochemical decomposition of vinyl azides.[15]

As may be inferred from Table 1, the reaction proceeds under similar conditions to other anomeric alkoxy radical fragmentations.[1] These conditions are mild enough to be compatible with the protective groups most widely used in carbohydrate chemistry. The obtained products possess an easily hydrolyzable formate group at a position that only depends on the pyranose or furanose form of the starting carbohydrate. This may be of interest when products are to be employed as chiral templates or chiral auxiliaries and further chemical transformations are required.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2**−**4**, **6**, **8**, and **10** (5 pages).

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