Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3879–3882

TETRAHEDRON: *ASYMMETRY*

Intramolecular hydrogen abstraction promoted by *N*-radicals: synthesis of chiral 7-oxa-2-azabicyclo[2.2.1]heptane and 8-oxa-6-azabicyclo[3.2.1]octane ring systems

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Received 3 September 2000; accepted 13 September 2000

Abstract

Homochiral 7-oxa-2-azabicyclo[2.2.1]heptane and 8-oxa-6-azabicyclo[3.2.1]octane ring systems can be synthesized by reaction of specifically protected phosphoramidate derivatives of carbohydrates with (diacetoxyiodo)benzene or iodosylbenzene and iodine. The reaction mechanism goes through homolytic fragmentation of a hypothetical iodoamide intermediate. The *N*-radicals so generated participate in an intramolecular hydrogen abstraction reaction (IHA) to give the aforementioned bicycles.

Only a few examples of carbohydrates containing the 8-oxa-6-azabicyclo[3.2.1]octane ring system in their skeleton have been described. They have been synthesized through intramolecular nucleophilic displacement of good leaving groups at C-6 by nitrogen nucleophiles at the anomeric centre.[1] 7-Amino-2,7-anhydro-1,7-dideoxy-D-*gulo*-hept-2-ulopyranose, a mimic of α-L-fucose, is a potent inhibitor of fucosidases which has been prepared by cyclization of the corresponding acyclic hydroxy amino ketone.[2] Moreover, the 8-oxa-6-azabicyclo[3.2.1]octane ring system is present as a substructure in several alkaloids such as samandarine, ribasine and zoanthamine.[3]

As far as we know, the only 7-oxa-2-azabicyclo[2.2.1]heptane system described in carbohydrate chemistry is a by-product formed during the TMSOTf-catalysed reaction of methyl 1,2,3-tri-*O*-acetyl-5-(acetylamino)-5-deoxy-β-D-allofuranuronate with bis-silylated thymine under the conditions of a Vorbrüggen coupling.[4]

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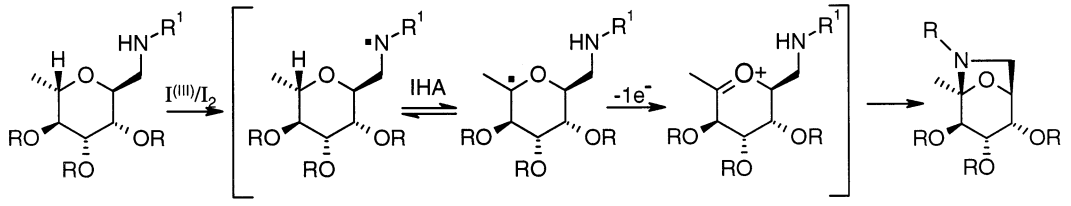
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00364-5

In previous papers,[5] we have described that *N*-nitroamides, *N*-cyanamides and *N*-phosphoramidates react with hypervalent iodine compounds in the presence of iodine to generate *N*-radicals through homolytic fragmentation of a hypothetical iodoamide intermediate. The mechanism is purported to be similar to the radical fragmentation of the hypoiodite reaction and it is outlined in Scheme 1 using a carbohydrate model. Nitrogen radicals generated in this way may participate in an intramolecular hydrogen abstraction (IHA)[6] from unactivated positions to give pyrrolidines, after one electron oxidation and cyclization of the amide group to the oxycarbenium ion intermediate. The reaction, which resembles the Hofmann–Löffler–Freytag synthesis of pyrrolidines,[7] proceeds on the contrary under very mild neutral conditions compatible with the stability of the protecting groups most frequently used in carbohydrate chemistry.



Scheme 1. R = alkyl; $R^1 = P(O)(OPh)_2$

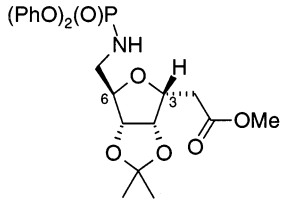
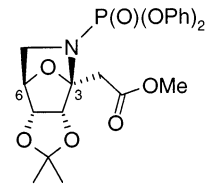
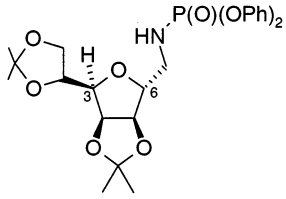
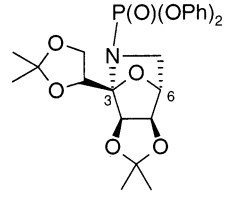
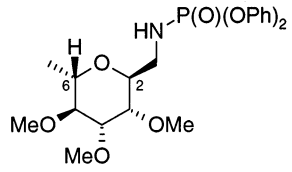
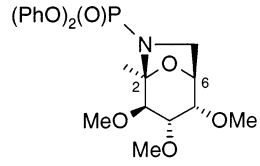
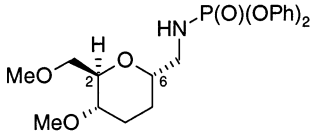
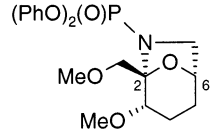
In this communication we describe a convenient synthesis of carbohydrate derivatives of homochiral 7-oxa-2-azabicyclo[2.2.1]heptane and 8-oxa-6-azabicyclo[3.2.1]octane ring systems using this protocol. The amidyl radicals were generated by reaction of the corresponding phosphoramidates with (diacetoxyiodo)benzene (DIB) or iodosylbenzene and iodine under the conditions summarized in Table 1.

The starting models **1**, **3**, **5** and **7** were synthesized using established methodology for the preparation of *C*-glycosides.[8] Thus, compound **1** was obtained from methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropyliden-D-*altro*-heptonate[9] and heptitols **3**, **5** and **7** from 2,5-anhydro-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-*manno*-heptitol,[10] 2,3,4-tri-*O*-methyl-β-L-rhamnopyranosyl cyanide[11] and 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl cyanide,[12] respectively. The amine groups were introduced through the respective azides in the first two cases and by $LiAlH_4$ reduction of the nitrile in the last two. The reaction of the free amines with diphenyl chlorophosphate in the presence of TEA gave the required diphenyl phosphoramidates.[13]

The synthesis of the 7-oxa-2-azabicyclo[2.2.1]heptane ring system was accomplished in two ways: from a phosphoramidate group at the C-6 of a D-*ribo* substrate **1** (Entry 1) or by placing the phosphoramidate group on a tether attached to the C-1 of a D-mannofuranose derivative **3** (Entry 2). In both cases we avoided the interaction with the neighbouring isopropylidene group, and the IHA reaction proceeded smoothly to give azabicycles **2** and **4** in good-to-excellent yields. In the first case the hydrogen abstraction occurred on the β-side of the molecule, while in the second this happened on the α-side. The structures were confirmed by ^1H and ^{13}C NMR spectra (DEPT, COSY and HMBC experiments), showing in both cases a selective abstraction of the C-3 protons.

The 8-oxa-6-azabicyclo[3.2.1]octane ring system can be obtained from 2,6-anhydro-1,7-dideoxy-7-[(diphenoxyphosphoryl)amino]-3,4,5-tri-*O*-methyl-L-*glycero*-L-*manno*-heptitol **5** (Entry 3). The IHA reaction proceeded on the β-side of the molecule through a chairlike

Table 1
Synthesis of homochiral 7-oxa-2-azabicyclo[2.2.1]heptane and 8-oxa-6-azabicyclo[3.2.1]octane ring systems[a]

Entry	Substrate	Reagent[b] (mmol)	I_2 (mmol)	Solvent	Time (min)	Product	Yield (%)
1	 **1**	PhIO (2)	1.2	CH_2Cl_2	75	 **2**	75
2	 **3**	PhIO (2)	1.2	CH_2Cl_2/ CCl_4 1:1	60	 **4**	95
3	 **5**	DIB (1.3)	1	CH_2Cl_2	75	 **6**	66
4	 **7**	DIB (1.5)	1	CH_2Cl_2	50	 **8**	65

[a]All reactions were performed in dry solvents (20 ml/mmol) at room temperature.
[b]Per mmol of substrate.
DIB = (diacetoxyiodo)benzene.

six-membered transition state to give the L-*altro*-hept-2-ulopyranose derivative **6**. The carbohydrate ring was in a more stable $^1C_4$ chair conformation which allowed a 1,3-diaxial relationship between the phosphoramidate tether at C-2 and the hydrogen atom at C-6.

The D-*arabino*-heptitol **7** was cyclized under the conditions shown in Table 1 (Entry 4) to 2,7-anhydro-4,5,7-trideoxy-7-[(diphenoxyphosphoryl)amino]-1,3-di-*O*-methyl-D-*threo*-hept-2-ulopyranose **8**. The reaction proceeded this time on the α-side of the molecule, while the

carbohydrate ring was in its more stable $^4C_1$ chair conformation. This allowed the required approach between the *N*-radical and the hydrogen at C-2 for the IHA reaction to take place.

Notable features of this one-step methodology in comparison with the Hofmann–Löffler–Freytag reaction are the following: (a) the in situ generation of the unstable iodoamide intermediates; (b) the mildness of the reaction conditions which permit the synthesis of these sensitive *N*,*O*-protected ulose derivatives and which are compatible with a wide variety of protective groups used in carbohydrate chemistry;[14] (c) the iodoamide homolysis proceeds thermally at room temperature, irradiation with ultraviolet light being unnecessary.

Acknowledgements

This work was supported by Investigation Programme PB96-1461 of the Direction General de Investigación Científica y Técnica. A.J.H. thanks the Ministerio de Educación y Ciencia, Spain, for a fellowship.

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