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Intramolecular 1,5-hydrogen atom transfer reaction promoted by phosphoramidyl and carbamoyl radicals: synthesis of 2-amino-*C*-glycosides

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Abstract—The preparation of 2-amino-*C*-glycosides of the hexahydro-2*H*-furo[3,2-*b*]pyrrole and octahydropyrano[3,2-*b*]pyrrole systems is described. A tandem 1,5-hydrogen atom transfer–radical oxidation–nucleophilic cyclisation mechanism is proposed for the intramolecular hydrogen atom transfer reaction promoted by carbamoyl and phosphoramidyl radicals employing hipervalent iodine oxidants.
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The intramolecular hydrogen atom transfer (IHAT) reaction promoted by alkoxyl radicals has attracted considerable interest in organic synthesis.[1] In contrast, comparatively, less effort has been devoted to the IHAT reaction generated by N-centred radicals.[1a,2] Since the pioneering works on IHAT processes promoted by aminyl or amidyl radicals developed by Hoffmann-Löffler-Freytag[3] and Barton,[4] a number of procedures have been reported for the generation of N-radicals.[5] In previous papers from this laboratory, we have reported that *N*-nitroamines, *N*-cyanamides, *N*-phosphoramidates and *N*-*tert*-butoxycarbonylamides react with hypervalent iodine reagents in the presence of iodine to generate *N*-centred radicals through homolytic fragmentation of a hypothetical iodoamide intermediate.[6] Nitrogen thus-formed radicals may participate in an intramolecular 1,5-hydrogen abstraction from remote carbons to generate pyrrolidines. These results have provided an excellent opportunity to demonstrate the synthetic potential of this methodology for the preparation of 2-hemiaminals related to 2-amino-*C*-glycosides.

C-Glycosides have gained considerable importance in recent years as carbohydrate mimetics and in view of the increased detection of the C-glycosidic bond in natural products.[7] Among them, 2-amino-*C*-glycosides have been widely investigated as synthons for the preparation of a variety of biologically active compounds, in particular, glycopeptide mimics, glycosidase inhibitors and analogues of tumour-associated carbohydrate antigens.[8] Unfortunately, some difficulties have been encountered in the synthesis of these compounds. The presence of the nitrogen-containing functionality at C-2 does not seem to be fully compatible with standard C-glycosidation methodologies. It is therefore not surprising that current methods for their preparation are somewhat limited.[9]

In this Letter, we disclose an efficient way to prepare interesting oxa-azabicyclic systems such as hexahydro-2*H*-furo[3,2-*b*]pyrrole and octahydropyrano[3,2-*b*]pyrrole structures (Scheme 1). The electrophilic N-radical, attached to a dimethylene tether extended from the C-1 of a carbohydrate, abstracts a hydrogen atom at C-2 through a favourable six-membered transition state. The nucleophilic C-radical thus formed is subsequently oxidised to a carbenium ion which is intramolecularly trapped by the nucleophilic amide to give pyrrolidines fused to furanose or pyranose rings.[10] Precedent for this reaction comes from previous works from this laboratory, where a similar carbohydrate system with one methylene tether abstract exclusively from C-4 (furanoses) or C-5 (pyranoses), thus the length of the side chain constitutes a major determinant of the regioselectivity of the reaction.[6b]

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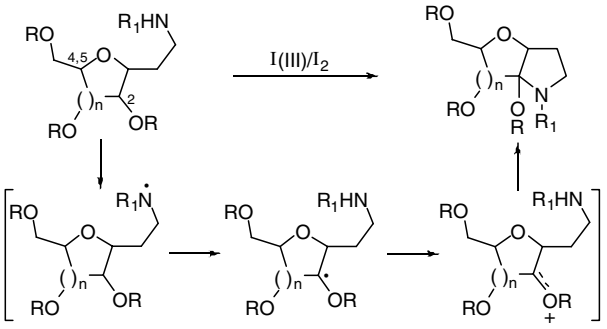


Scheme 1. Synthesis of 2-amino-*C*-glycosides. R = Protective group; $R_1 = PO(OPh)_2$, Boc; $n = 1,2$.

The starting amines were prepared through a sequence involving (a) Lewis acid-mediated C-glycosidation with allyltrimethylsilane to afford the non-8-enitols, in general with high stereoselectivity,[11] (b) olefin ozonolysis followed by reductive ($NaBH_4$) opening of the ozonide to give the octitols, (c) transformation of the primary unprotected alcohols into the corresponding mesyl-derivatives and subsequent nucleophilic substitution with azide ion, (d) reduction (H_2, Pd/C 10%, AcOEt) followed by treatment of the resulting crude amine with the corresponding protecting group reagent: with diphenyl chlorophosphate and TEA to give phosphoramidates **3**, **6**, **11**, **13**, **15**, **18** and **19** and with di-*tert*-butyl dicarbonate to give *N*-Boc-protected derivatives **1** and **9**. It is noteworthy that the use of carbamates is interesting regarding further manipulation at the nitrogen centre because of its facile deprotection.[12]

The phosphoramidyl and carbamoyl radicals were generated by reaction of the corresponding phosphoramidates and carbamates with (diacetoxyiodo) benzene (DIB) or iodoxyl benzene and iodine under the reaction conditions mentioned in Table 1.

In entry 1, we describe an IHAT reaction over a C-glycoside derived from D-mannose **1** possesing a three-atoms side chain. In this case, with the pyranose ring in a restricted $^4C_1$ conformation, the amidyl radical would preferentially abstract the hydrogen located at either the C-4 or C-7 position.[13a] Taking into account that the abstraction from C-7 evolves through a seven-membered transition state (TS) and that from C-4 through in principle, a more favourable six-membered

Table 1. 1,5-HAT reaction promoted by N-radicals[a]

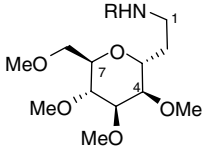
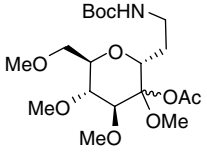
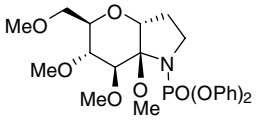
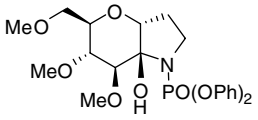
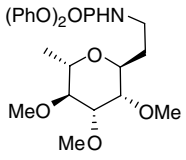
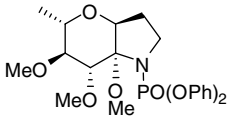
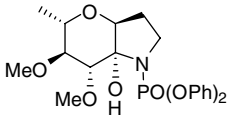
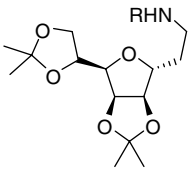
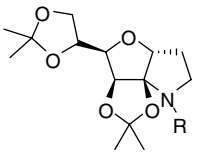
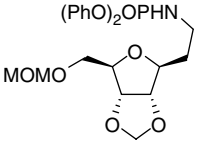
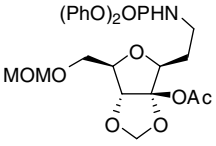
Entry	Substrate	Reagent (mmol)	Time (h)	Products yield (%)
				
1	1R = Boc	2.5	5	**2** (61, *S*/*R* 2:1)
				
2[b]	3R = $PO(OPh)_2$	2.2	3	**4** (75)
				
3[c]	3R = $PO(OPh)_2$	4	5	**5** (74)[d]
				
4[b]	**6**	2.1	5.5	**7** (66)
				

Table 1 (*continued*)

Entry	Substrate	Reagent (mmol)	Time (h)	Products yield (%)
5[c]	**6** 	3.2	6	**8** (91)[d] 
6[b]	**9**R = Boc	2.5	6	**10**R = Boc (55)
7[b,e]	**11**R = $PO(OPh)_2$	1.5	12	**12**R = $PO(OPh)_2$ (64)
				
8[f]	**13**	3.7	7	**14** (51)

[a] A solution of the amide (1 mmol) in dry DCM or CH_3CN (20 mL) containing (diacetoxyiodo)benzene (DIB) and iodine (1 mmol) was irradiated with two 80 W tungsten-filament lamps at room temperature.
[b] $NaHCO_3$ was added.
[c] PhIO was used as an oxidant.
[d] The hemiaminal is in equilibrium with its open form.
[e] $T = 40$ °C.
[f] Reflux temperature.

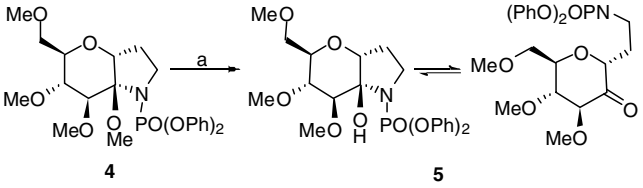
TS, it was not surprising that compound **2** was formed exclusively. The product was obtained as a mixture of two diastereoisomers 4*S*/4*R* (2:1). A NOE enhancement observed between the axial hydrogen at C-6 and the methoxyl group at C-4 revealed that the major isomer has a 4*S* stereochemistry. Apparently, a lower nucleophilicity of the carbamate group is responsible for the competitive intermolecular attack of the acetate anion coming from the reagent.

On the contrary, with phenyl phosphonate as the amine protecting group (entry 2), the cyclic product **4** was exclusively obtained in good yield. Curiously, the absence or presence of solid $NaHCO_3$ in the reaction medium may either lead to methyl ether **4** or to the hydroxylated alcohol **5** (entries 2 and 3).

The slightly acidic condition of the reaction in entry 3 seems to be sufficient to catalyse hydrolysis of the ketal group at C-4. Indeed, compound **5**, which is at room temperature in equilibrium with its open form, can be obtained in quantitative yield by acid-catalysed hydrolysis of **4** under mild conditions (Scheme 2).

This behaviour concerning $NaHCO_3$ was reproduced in other models in good yields as can be observed with the L-rhamnose derivative **6** in entries 4 and 5. Analogously, hemiaminal **8** was also quantitatively obtained from **7** after treatment with citric acid. Similar or even better results were obtained using iodosyl benzene instead of DIB as the oxidant (compare entries 2 vs 3 and 4 vs 5).

This IHAT-cyclisation sequence was further extended to furanose models (entries 6, 7 and 8). The D-mannofuranosyl derivatives **9** and **11** gave the expected cyclic product in moderate yield. In both cases, it was necessary to neutralise the medium with solid $NaHCO_3$ to prevent undesirable hydrolysis of the acid-sensitive 7,8-isopropylidene group.

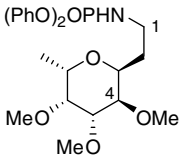
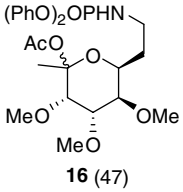
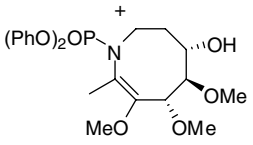
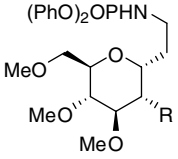


Scheme 2. Reagents and conditions: (a) citric acid, DCM, rt, 33 h.

Phosphoramidate **13**, derived from D-ribose, yielded smoothly the acetate-derivative **14** showing that the 1,5-HAT reaction had occurred but no cyclisation product was formed because of the competitive acetate nucleophilic addition.

Alkoxyl radicals are able to undergo 1,6-HAT reactions on pyranose and furanose systems to obtain bicyclic compounds in good yields.[13] However, 1,6-HAT promoted by nitrogen centred radicals is not a general process and only a few examples are known.[6c,f,14] With the aim to direct the IHAT reaction to form products derived from the 1,6-abstraction, we prepared some precursors where the hydrogen atom at C-4 is deactivated towards the 1,5-HAT (Table 2). In most cases, no reaction was observed (entries 2 and 3), but surprisingly with the L-fucose model **15**, three 1,6-HAT products were generated (entry 1).

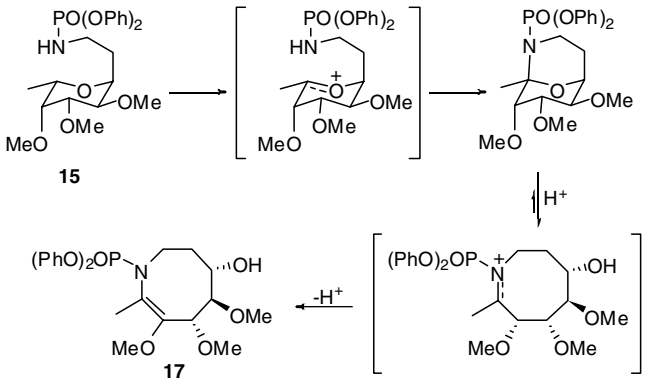
Table 2. 1,6-HAT reaction promoted by N-radicals[a]

Entry	Substrate	Reagent (mmol)	Time (h)	Products yield (%)
1	 **15**	2.4	3.5	 **16** (47) +  **17** (20)
2	 **18**R = OMe	3.1	9	No reaction
3	**19**R = H	2.0	6	No reaction

[a] A solution of the amide (1 mmol) in dry CH_3CN (20 mL) containing (diacetoxyiodo)benzene (DIB), iodine (1 mmol) and $NaHCO_3$ was irradiated with two 80 W tungsten-filament lamps at room temperature.

Product **16** is an inseparable mixture of epimers, by conventional column chromatography, resulting from the 1,6-HAT and consecutive nucleophilic addition of acetate. However, compound **17** to which an eight-membered enamine structure was tentatively assigned may proceed from the nucleophilic addition of the phosphoramidate group and subsequent opening of the pyranose ring under acid conditions (Scheme 3).[15] The high complexity observed in the NMR spectra may be indicative of the existence of a sluggish conformational equilibrium, feasible in this sort of eight-membered rings. Nevertheless, it was impossible to carry out variable temperature NMR experiments due to the instability of the product.

In summary, we have now demonstrated that 1,5-HAT reactions can be useful to synthesise hexahydro-2*H*-furo[3,2-*b*]pyrrole and octahydropyrano[3,2-*b*]pyrrole structures, which are not readily accessible by other methodologies. The virtues of hypervalent iodine reagents are the mildness of the conditions and the observed high protecting group tolerance. The achieved yields are comparable to those previously obtained from the O-centred radical studies. We are conscious that the 1,6-HAT reaction promoted by N-radicals is not easy to accomplish, probably due to the bulkiness of the *N*-protecting group but the results obtained from L-fucose model are encouraging.



Scheme 3.

Acknowledgments

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Supplementary data

Full characterisation of compounds and experimental details. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.152.

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