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Synthesis of oxa-aza spirobicycles by intramolecular hydrogen abstraction promoted by *N*-radicals in carbohydrate systems

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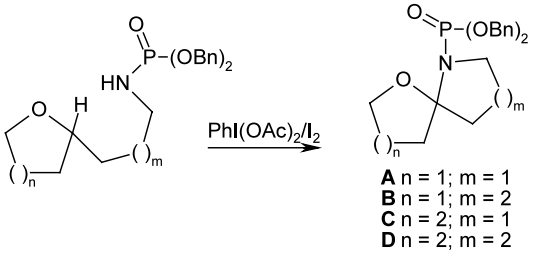
Abstract—The preparation of 1-oxa-6-azaspiro[4.4]nonane, 1-oxa-6-azaspiro[4.5]decane, 6-oxa-1-azaspiro[4.5]decane, and 1-oxa-7-azaspiro[5.5]undecane ring systems by 1,6- and 1,7-hydrogen atom transfer promoted by phosphoramidyl radicals in carbohydrate models is described. The *N*-radicals are generated by reaction of dibenzyl phosphoramidate derivatives of *C*-glycosides with (diacetoxyiodo)benzene and iodine through an homolytic fragmentation of iodoamide intermediates.

In previous papers, we have described the synthesis of pyrrolidines by an intramolecular hydrogen abstraction (IHA) reaction promoted by *N*-radicals generated in situ by reaction of an amide derivative with hypervalent iodine reagents in the presence of iodine.[1] The reaction, which resembles the Hofmann–Löffler–Freytag, proceeds on the contrary under very mild conditions compatible with the stability of the protecting groups most frequently used in carbohydrate chemistry.[2] The IHA triggered by amidyl radicals, generated from the photolysis of *N*-iodocarboxamides, is described as giving γ-butyrolactones.[3]

In this communication we describe the synthesis of dibenzyl phosphoramidate derivatives of 1-oxa-6-azaspiro[4.4]nonane (**A**), 1-oxa-6-azaspiro[4.5]decane (**B**), 6-oxa-1-azaspiro[4.5]decane (**C**) and 1-oxa-7-azaspiro[5.5]undecane (**D**) ring systems using this methodology (Scheme 1). These oxa-aza spirobicycles are a widespread substructure common to a number of natural products such as: hydantocidin[4] (**A**), solanum alkaloids[5] and azaspiracid[6] (**B**), and sanglifehrin A[7] (**D**). Some radical-based approaches have been developed for the synthesis of related anomeric spironucleosides.[8] A few examples of carbohydrate derivatives containing the 6-oxa-1-azaspiro[4.5]decane (**C**) ring system in their skeleton have been described.[9]



Scheme 1.

The preparation of the starting amines proceeded according to the following: The amines **1**, **6** and **10** were synthesised from the corresponding alcohols[10] by Mitsunobu azidation[11] ($ZnN_6 \cdot 2Py$, DIAD, Ph_3P, toluene, 75–77%) and reduction (H_2, Pd/C 10%, EtOAc). Amine **3** from 3,6-anhydro-7,8-dideoxy-1,2:4,5-di-*O*-isopropylidene-D-*glycero*-D-*manno*-nonitol[10] by cyanation (I_2, Ph_3P, imidazole, PhH then NaCN, DMSO, 77%) and reduction ($LiAlH_4$, Et_2O). Amine **8** from methyl 6,7,8,9-tetradeoxy-2,3,4-tri-*O*-methyl-β-D-*gluco*-non-8-enopyranoside[10] by ozonolysis (O_3, CH_2Cl_2/MeOH then $NaBH_4$, 90%), Mitsunobu azidation[11] ($ZnN_6 \cdot 2Py$, DIAD, Ph_3P, toluene, 76%), and reduction (H_2, Pd/C 10%, EtOAc). The reaction of the crude free amines with dibenzyl chlorophosphate in the presence of TEA gave the required dibenzyl phosphoramidates (51–58%, overall yield).[12]

The phosphoramidyl radicals were generated by reaction of the corresponding phosphoramidates with (diacetoxyiodo) benzene (DIB) and iodine under the reaction conditions mentioned in Table 1. The [4.4]bicycle **2**[13] was synthesised starting with a *C*-glycoside **1** derived from D-mannose with the amide attached to a trimethylene α-thether extended from C1

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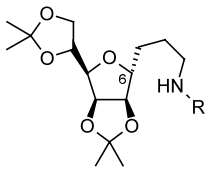
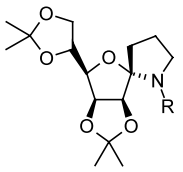
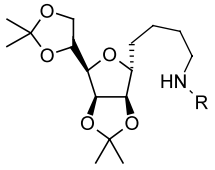
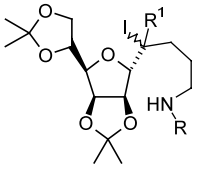
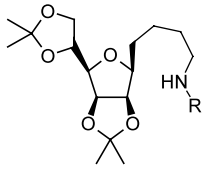
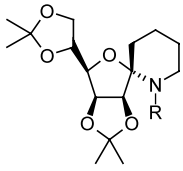
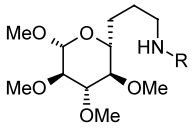
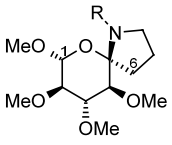
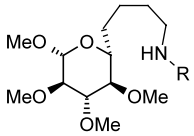
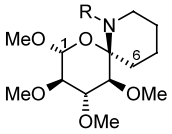
Table 1. Synthesis of oxa-aza spirobicycles[a]

Entry	Substrate	Time h	Product	Yield % (dr)
1	 **1**	4.5	 **2**	74
2	 **3**	5.5	 **4** R^1 = H **5** R^1 = I	14 28
3	 **6**	5	 **7**	45[b]
4	 **8**	1	 **9**	74[c] (2:1)
5	 **10**	6.5	 **11**	41[c,d] (3:1)

[a] All reactions were performed in dry CH_2Cl_2 (80 ml) at reflux temperature containing (diacetoxyiodo)benzene (2.5 mmol), iodine (1.4 mmol) and solid $NaHCO_3$ (25 mmol%) per mmol of substrate. Ratios were determined by isolation of pure compounds and the major isomer is illustrated. R = $P(O)(OBn)_2$.

[b] Compound **12** (31%) was also obtained.

[c] Solid $NaHCO_3$ was omitted.

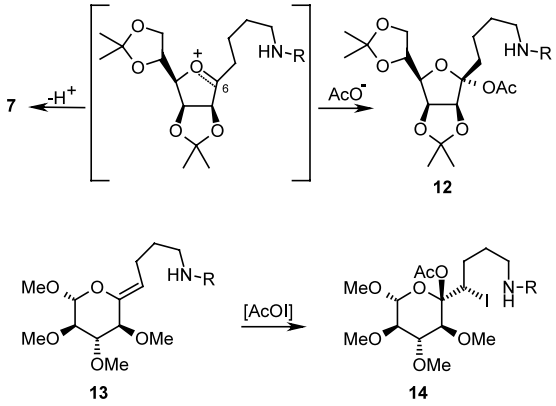
[d] Compound **14** (29%) was also obtained.

of the furanose ring. The 1,6-hydrogen atom transfer (HAT) reaction proceeded smoothly in good yield on the sterically crowded β-side of the furanose ring (entry 1). Unfortunately, **3** failed to undergo the desired 1,7-HAT on this side of the molecule and hence the formation of the [4.5]bicycle, a more steric demanding 1,7-transition state was postulated as responsible for the failure. In this case only monoiodine **4** and diiodine **5** which are both produced by 1,6-HAT reactions were isolated in low yields (entry 2). The structures of **4** and **5** were confirmed spectroscopically and by reduction to the starting amine **3** with the *n*-Bu_3SnH/AIBN system.

The bicycle 1-oxa-6-azaspiro[4.5]decane **7**[13] was formed from the 6*S*-isomeric phosphoramidate **6** where the 1,7-HAT proceeded on the less hindered side of the molecule. Although, the hydrogen abstraction occurred with a 76% global yield, the formation of the side product **12** in a substantial amount decreased the spirocycle **7** yield (Scheme 2). The acetyl derivative **12** may arise from external nucleophilic attack of the acetate anion to the oxycarbenium ion intermediate in competition with the intramolecular reaction (Scheme 2). The proposed stereochemistry, where the acetate adds to the less hindered side of the molecule, is consistent with the deshielding experimented for the ring protons in its ^1H NMR spectrum according to similar products found in the literature.[14] The strong hindrance of the β-side of the molecule may also be responsible for the formation of only one isomer of the spirocycles **2** and **7**.

The synthesis of spirobicycles **9** and **11**[13] was accomplished from D-glucose derivatives **8** and **10** and in general exhibited a similar behaviour as the spirocyclisations shown before (entries 1 and 3); analogous yields, smooth formation of the pyrrolidine ring and external nucleophilic competition during the cyclisation to the piperidine ring (entries 4 and 5). The formation of β-iodo ester **14**, as a side product of the IHA reaction of phosphoramidate **10**, can be explained by a *trans* electrophilic addition of acetyl hypoiodite[15] to the hypothetical *Z*-olefin **13**, resembling Prévost reaction (Scheme 2).[16] Plausibly, the olefin **13** can be formed from the oxycarbenium ion intermediate or by acid–catalysed ring opening of the O–N-spirocycle **11**.[17] The assignment of the stereochemistry of **14** was based on the strong deshielding of the axial protons at C1 and C3 in comparison with those of the amine **10** which suggest an axial acetyl group at C5.

In summary, the virtues of this reagent are the mildness of the conditions and the high protective group tolerance observed. With the synthesis of four different types of oxa-aza spirobicycles we have shown the scope and usefulness of this new methodology for the construction of building blocks for complex organic molecules.



Scheme 2. Minor products from entries 3 and 5. R = $P(O)(OBn)_2$.

Acknowledgements

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13. All new compounds gave correct elemental analysis. Compound **2**: syrup; $[\alpha]_D$ +22 ($CHCl_3$, $c=1.03$); ^1H NMR ($CDCl_3$, 500 MHz) 1.34 (3H, s), 1.36 (3H, s), 1.44 (3H, s), 1.46 (3H, s), 1.73 (1H, m), 1.88 (1H, m), 2.00 (1H, m), 2.09 (1H, m), 3.08 (1H, ddd, $J=8.8$, 8.8, 8.8 Hz), 3.20 (1H, ddd, $J=8.8$, 8.8, 0.0 Hz), 3.97 (1H, dd, $J=4.6$, 8.5 Hz), 4.04 (1H, dd, $J=6.2$, 8.5 Hz), 4.33 (1H, ddd, $J=5.0$, 6.4, 6.4 Hz), 4.52 (1H, dd, $J=3.8$, 7.1 Hz), 4.97 (1H, dd, $J=7.3$, 11.9 Hz), 5.00–5.06 (4H, m), 5.16 (1H, d, $J=5.9$ Hz), 7.30–7.38 (10H, m); ^{13}C NMR ($CDCl_3$, 125.7 MHz) 22.6 ($J_P=9.1$ Hz), 24.4, 25.4, 25.9, 26.9, 36.6 ($J_P=9.1$ Hz), 48.4, 66.6, 67.3, 67.7, 73.8, 79.9, 81.7, 86.5, 104.8, 108.8, 112.0, 127.7 (4×), 128.1, 128.2, 128.4 (4×), 136.2 (2×). Compound **7**: syrup; $[\alpha]_D$ −5.2 ($CHCl_3$, $c=0.65$); ^1H NMR ($CDCl_3$, 500 MHz) 1.21–1.75 (4H, m), 1.24 (3H, s), 1.35 (6H, s), 1.44 (3H, s), 2.01 (2H, m), 3.14 (1H, m), 3.49 (1H, m), 3.86 (1H, dd, $J=7.9$, 3.6 Hz), 3.97 (1H, dd, $J=4.3$, 8.6 Hz), 4.06 (1H, dd, $J=6.2$, 8.6 Hz), 4.33 (1H, ddd, $J=5.0$, 6.9, 6.9 Hz), 4.57 (1H, dd, $J=3.8$, 5.7 Hz), 4.94–5.08 (4H, m), 5.32 (1H, d, $J=5.7$ Hz), 7.32–7.38 (10H, m); ^{13}C NMR ($CDCl_3$, 125.7 MHz) 20.8, 24.4, 25.3, 25.8, 26.9, 29.7, 30.8, 43.1, 67.0, 68.2, 68.3, 73.2, 78.9, 80.5, 83.9, 95.9, 109.0, 111.9, 127.9 (4×), 128.3 (2×), 128.6 (4×), 136.0 (2×). Compound **9**-β: syrup; $[\alpha]_D$ −27 ($CHCl_3$, $c=0.87$); ^1H NMR ($CDCl_3$, 500 MHz) 1.75 (1H, m), 1.99 (1H, m), 2.04 (1H, m), 2.11 (1H, ddd, $J=12.0$, 7.3, 0.0 Hz), 3.01 (1H, dd, $J=8.2$, 8.2 Hz), 3.26 (1H, m), 3.37 (1H, d, $J=9.3$), 3.39 (3H, s), 3.43 (1H, ddd, $J=9.6$, 8.7, 0.0 Hz), 3.56 (3H, s), 3.59 (3H, s), 3.66 (3H, s), 4.79 (1H, dd, $J=8.7$, 8.7 Hz), 4.83 (1H, d, $J=8.0$ Hz), 5.02 (2H, dd, $J=6.3$, 4.0 Hz), 5.12 (2H, d, $J=7.0$ Hz), 7.29–7.40 (10H, m); ^{13}C NMR ($CDCl_3$, 125.7 MHz) 21.5 ($J_P=6.1$ Hz), 42.0 ($J_P=9.2$ Hz), 50.5, 56.4, 59.6, 60.2, 61.5, 67.3, 67.9, 83.4, 83.6, 84.5, 95.4 ($J_P=6.1$ Hz), 99.5, 127.6 (2×), 127.7 (2×), 128.0, 128.1, 128.4 (2×), 128.4 (2×), 136.6 ($J_P=6.1$ Hz), 137.2 ($J_P=6.1$ Hz). Compound **9**-α: syrup; $[\alpha]_D$ −8.4 ($CHCl_3$, $c=0.24$); ^1H NMR ($CDCl_3$, 500 MHz) 1.81–1.90 (3H, m), 2.14 (1H, ddd, $J=12.2$, 8.7, 7.3 Hz), 3.07 (1H, dd, $J=9.4$, 9.4 Hz), 3.14 (1H, dd, $J=8.5$, 8.5 Hz), 3.16 (1H, ddd, $J=7.0$, 7.0, 7.0 Hz), 3.38 (1H, m), 3.41 (3H, s), 3.57 (3H, s), 3.59 (3H, s), 3.63 (3H, s), 4.20 (1H, d, $J=8.0$ Hz), 4.36 (1H, d, $J=9.8$ Hz), 5.06 (2H, dd, $J=7.0$, 7.0 Hz), 5.11 (2H, dd, $J=6.8$, 2.6 Hz), 7.27–7.38 (10H, m); ^{13}C NMR ($CDCl_3$, 125.7 MHz) 23.3 ($J_P=9.2$ Hz), 30.5 ($J_P=9.2$ Hz), 47.9, 56.3, 60.4 (2×), 60.7, 67.3, 67.4, 80.4, 83.0, 84.6, 95.8, 100.7, 127.5 (2×), 127.7 (2×), 127.9 (2×), 128.1, 128.3, 128.4 (2×), 136.5 ($J_P=9.2$ Hz), 137.1 ($J_P=9.2$ Hz). Compound **11**-β: syrup; $[\alpha]_D$ −3.5 ($CHCl_3$, $c=0.20$); ^1H NMR ($CDCl_3$, 500 MHz) 1.41 (1H, m), 1.49–1.63 (2H, m), 1.84–1.97 (1H, m), 2.12–2.18 (2H, m), 3.01 (1H, dd, $J=8.2$, 8.2 Hz), 3.09–3.18 (1H, m), 3.15 (1H, d, $J=8.9$ Hz), 3.43 (1H, m), 3.44 (3H, s), 3.54 (3H, s), 3.56 (3H, s), 3.61 (3H, s), 4.41 (1H, d, $J=8.4$ Hz), 4.46 (1H, dd, $J=8.7$, 8.7 Hz), 4.99–5.10 (4H, m), 7.29–7.38 (10H, m); ^{13}C NMR ($CDCl_3$, 125.7 MHz) 20.2, 24.2, 35.5, 43.6, 57.0, 59.9, 60.0, 61.8, 68.0 ($J_P=6.1$ Hz), 68.1 ($J_P=6.1$ Hz), 81.5, 84.5, 87.3, 88.4, 98.9, 127.5 (2×), 127.8, 128.0 (2×), 128.1, 128.3 (2×), 128.5 (2×), 136.6 ($J_P=6.1$ Hz), 137.1 ($J_P=6.1$ Hz). Compound **11**-α: syrup; $[\alpha]_D$ −3.7 ($CHCl_3$, $c=0.16$); ^1H NMR ($CDCl_3$, 500 MHz) 1.44 (1H, m), 1.52–1.68 (3H, m), 1.76 (1H, m), 2.00 (1H, m), 3.12 (1H, dd, $J=8.0$, 9.4 Hz), 3.17–3.29 (2H, m), 3.25 (1H, dd, $J=9.4$, 9.4 Hz), 3.49 (3H, s), 3.57 (3H, s), 3.58 (3H, s), 3.67 (3H, s), 4.24 (1H, d, $J=4.2$ Hz), 4.71 (1H, d, $J=4.7$ Hz), 4.99–5.14 (4H, m), 7.28–7.39 (10H, m); ^{13}C NMR ($CDCl_3$, 125.7 MHz) 16.2, 23.2, 24.5 ($J_P=6.1$ Hz), 41.4, 56.4, 60.3, 60.4 (2×), 67.4, 67.5, 81.3, 83.8, 84.6, 88.8, 99.8, 127.5, 127.9 (4×), 128.1, 128.4 (2×), 128.4 (2×), 136.6 (2×).

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