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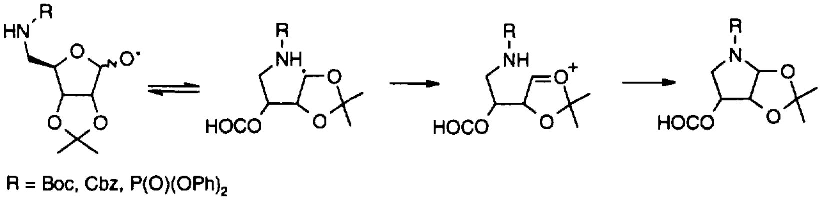
Fragmentation of carbohydrate anomeric alkoxy radicals. Synthesis of azasugars

Cosme G. Francisco, Raimundo Freire, Concepción C. González and Ernesto Suárez *
Instituto de Productos Naturales y Agrobiología del C.S.I.C., Carretera de La Esperanza 3, 38206-La Laguna, Tenerife, Spain

Abstract: The reaction of conveniently protected 5-amino-5-deoxy pentoses and 6-amino-6-deoxy hexoses with iodosylbenzene and iodine is an efficient method, via β-fragmentation of the anomeric alkoxy radicals, for the synthesis of azasugars of the tetrose and pentose series, respectively. © 1997 Elsevier Science Ltd

Polyhydroxylated pyrrolidines and piperidines structurally related to cyclic carbohydrates in which the ring oxygen is substituted by a nitrogen atom, the so-called *azasugars*, have received recently considerable attention from synthetic organic chemists.[1] These substances are inhibitors of glycosidases since they are thought to mimic the transition state of these enzymatic reactions and have a promising therapeutic value as antiviral and anticancer agents.[2] In recent years we have been engaged in a program directed towards the study of the β-fragmentation reaction of anomeric alkoxy radicals of carbohydrates using hypervalent iodine reagents.[3] Using this methodology, carbohydrates with one carbon less can be obtained and it is therefore useful for descending the aldose series as well as for the preparation of chiral building blocks.[3a] This reaction can also be applied to the synthesis of cyclic aldoses and ketoses in furanose and pyranose form.[3b]

In this context we report here on an extension of this methodology which is particularly effective for the synthesis of five- and six-membered azasugars. As shown in Scheme 1, a conveniently protected 5-amino-5-deoxy-pentose, as a carbamate or phosphoramidate group, was treated with iodosylbenzene in the presence of iodine in order to generate the anomeric alkoxy radical. β-Fragmentation and oxidation of the formed C-radical with an excess of reagent gave an oxonium ion which was intramolecularly trapped by the amide group to give the corresponding azasugar.



Scheme 1.

To this end *N*-Boc derivative **1** was prepared starting from the readily available benzyl 2,3-*O*-isopropylidene-D-ribofuranoside.[4] Zinc azide-mediated Mitsunobu substitution of the primary alcohol,[5] followed by reduction of the azide group with tri-*n*-butylstannane, treatment of the crude amine with $(Boc)_2O$, and deprotection of the benzyl ether by catalytic hydrogenation (Pd/C 10%) afforded compound **1** in 76% overall yield. Reaction of this compound **1** with iodosylbenzene and iodine under the conditions shown in Table 1 (entry 1) gave the erythrofuranose derivative **3**.[6] The ^1H and ^{13}C NMR spectra of this *N*-Boc derivative **3** appear at room temperature as a mixture of two

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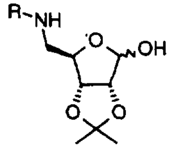
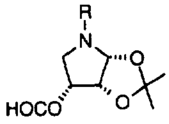
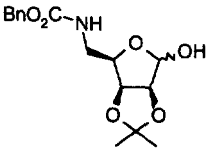
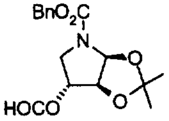
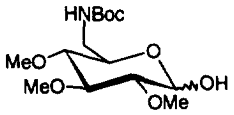
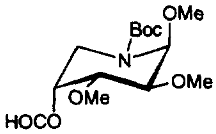
* Corresponding author.

Table 1. Synthesis of azasugars by β-fragmentation of anomeric alkoxy radicals

Entry	Substrate	Conditions[a]			Products	Yield (%)
		PhIO (mmol)	I_2 (mmol)	time (h)		
						
1	**1** R = Boc	2.5	1	21	**3** R = Boc	73
2	**2** R = $PO(OPh)_2$	2.5	1.2	2	**4** R = $PO(OPh)_2$	72
						
3	**5**	2.2	1.2	2	**6**	70
						
4	**7**	2.2	1.2	2	**8**	68

a) All reactions were performed in dry dichloromethane at rt; mmol of iodosylbenzene and I_2 per mmol of substrate.

conformers due to the restricted rotation of the nitrogen–carbon bond of the amide group. To overcome this situation NMR spectra were run at 75°C. At this temperature the spectra are consistent with the proposed structure.

To investigate the influence of the amine protecting group in the cyclization reaction the phosphoramidate **2** was synthesised starting with the same ribofuranoside and following a similar procedure. In this case the reaction proceeded analogously and compound **4**[7] was obtained in similar yield (entry 2). The NMR spectral properties of this substance showed a complex pattern because they reflected the presence of long-range coupling between the phosphorous atom and the carbons and hydrogens of the molecule. The reaction does not seem to be dependent on the stereochemistry at C2 since the D-lyxose derivative **5** prepared from the known[8] benzoyl 5-azido-5-deoxy-2,3-*O*-isopropylidene-D-lyxofuranoside, gave rise to the threofuranose derivative **6**,[9] also in good yield (entry 3).

The reaction was also extended to the synthesis of azasugars of the pentose series in pyranose form via a 1,6-cyclization coupling, as shown in Table 1 (entry 4). Compound **7** prepared from D-glucose afforded exclusively the 5-amino-5-deoxy-D-arabinose derivative **8**.[10] The stereochemistry at C1 and the proposed conformation (${}^1C_4$) was determined by comparing the observed coupling constants with those calculated over a minimised structure using the MMX force field.[11]

In conclusion, we describe a one-pot procedure suitable to obtain, under mild reaction conditions, azasugars through a tandem β-fragmentation–cyclization process.

Representative experimental procedure

A solution of 5-[(*tert*-butoxycarbonyl)amino]-5-deoxy-2,3-*O*-isopropylidene-D-ribofuranose (**1**) (50 mg, 0.17 mmol) in dry dichloromethane (10 ml) containing freshly prepared iodosylbenzene[12] (93.5 mg, 0.425 mmol) and iodine (40 mg, 0.17 mmol) was stirred at room temperature (20°C) for 21 h. The reaction mixture was then poured into aqueous solution of sodium thiosulphate, extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated. The residue was purified by chromatotron chromatography over silica gel (*n*-hexane–EtOAc, 80:20) to give 4-[(*tert*-butoxycarbonyl)amino]-4-deoxy-3-formyl-1,2-*O*-isopropylidene-α-D-erythrofuranose **4** (36.1 mg, 0.125 mmol, 73%).

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References

1. For recent references see, *inter alia*: Hansen, A.; Tagmose, T. M.; Bols, M. *Tetrahedron* **1997**, *53*, 697–706; Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340–347; Cipolla, L.; Lay, L.; Nicostra, F.; Pangrazio, C.; Panza, L. *Tetrahedron* **1995**, *51*, 4679–4690; Poitout, L.; Lemerrer, Y.; Depezay, J. C. *Tetrahedron Lett.* **1996**, *37*, 1609–1612; Henderson, I.; Laslo, K.; Wong, C.-H. *Tetrahedron Lett.* **1994**, *35*, 359–362; Takaoka, Y.; Kajimoto, T.; Wong, C.-H. *J. Org. Chem.* **1993**, *58*, 4809–4812; Dondoni, A.; Merino, P.; Perrone, D. *Tetrahedron* **1993**, *49*, 2939–2958; Furneaux, R. H.; Tyler, P. C.; Whitehouse, L. A. *Tetrahedron Lett.* **1993**, *34*, 3613–3616; Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W. J.; Ramsden, N. G.; Cenci de Bello, I.; Winchester, B. G.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron.* **1992**, *48*, 3365–3376; Straub, A.; Effenberger, F.; Fischer, P. *J. Org. Chem.* **1990**, *55*, 3926–3932; Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron Lett.* **1988**, *29*, 2871–2874.
2. Winchester, B.; Fleet, G. W. J. *Glycobiology* **1992**, *2*, 199–210; Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182–190; Hughes, A. B.; Rudge, A. J. *Nat. Prod. Rep.* **1994**, *11*, 135–162.
3. (a) Armas, P.; Francisco, C. G.; Suarez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772–774; (b) Armas, P.; Francisco, C. G.; Suarez, E. *J. Am. Chem. Soc.* **1993**, *115*, 8865–8866; Armas, P.; Francisco, C. G.; Suarez, E. *Tetrahedron Lett.* **1993**, *34*, 7331–7334; Francisco, C. G.; González, C. C.; Suarez, E. *Tetrahedron Lett.* **1996**, *37*, 1687–1690.
4. Duvoid, T.; Francis, G. W.; Papaioannou, D. *Tetrahedron Lett.* **1995**, *36*, 3153–3156.
5. Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130–132.
6. Compound **3**: mp 71–73°C (from CH_2Cl_2); $[\alpha]_D$ −73.3 (*c*=0.514, $CHCl_3$); IR 1736, 1714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 75°C) 1.36 (3H, s), 1.48 (9H, s), 1.50 (3H, s), 3.38 (1H, dd, *J*=10.1, 10.1 Hz), 3.97 (1H, dd, *J*=10.3, 7.7 Hz), 4.75 (1H, dd, *J*=4.7, 4.7 Hz), 4.95 (1H, ddd, *J*=4.7, 7.7, 10 Hz), 5.85 (1H, brs), 8.04 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$, 75°C) 26.30 (q), 26.81 (q), 28.31 (3×q), 46.04 (t), 69.87 (d), 81.01 (d), 88.52 (d), 112.98 (s), 153.51 (s), 159.67 (s); MS *m/z* (rel intensity) 288 (M^++1, 2), 272 (3), 241 (8), 232 (28), 185 (19), 172(11), 141 (25), 112 (19), 84 (66), 57 (100); HRMS calcd for $C_{12}H_{18}O_6N$ 272.113413, found 272.111816. Anal. Calcd for $C_{13}H_{21}O_6N$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.25; H, 7.37; N, 4.89.
7. Compound **4**: amorphous; $[\alpha]_D$ −25.9 (*c*=0.328, $CHCl_3$); IR 1737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 1.32 (3H, s), 1.38 (3H, s), 3.34 (1H, m), 3.82 (1H, m), 4.73 (2H, m), 5.85 (1H, m), 7.15 (2H, m), 7.29 (8H, m), 8.01 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$)25.82 (q), 26.12 (q), 46.38 (t, ^2J_P=3.8 Hz), 70.99 (d, ^3J_P=11.4 Hz), 76.80 (d, ^3J_P=9.5 Hz), 90.50 (d, ^2J_P=3.8 Hz), 112.86 (s), 120.04 (d, J_P=3.8 Hz), 120.11 (d, J_P=5.7 Hz), 124.91 (d, J_P=5.7 Hz), 129.46 (d, J_P=7.6 Hz), 150.59 (s, J_P=5.7 Hz), 159.26 (s); MS *m/z* (rel intensity) 419 (M^+, 0.6), 404 (8), 373 (36), 344

(18), 316 (100); HRMS calcd for $C_{20}H_{22}O_7NP$ 419.113391, found 419.114592. Anal. Calcd for $C_{20}H_{22}O_7NP$: C, 57.28; H, 5.29; N, 3.34. Found: C, 57.44; H, 5.46; N, 3.25.

8. Ichikawa, Y.; Igarashi, Y. *Tetrahedron Lett.* **1995**, *36*, 4585–4586.
9. Compound **6**: mp 74–76°C (from *n*-hexane-diethyl ether); $[\alpha]_D$ +68.2 (*c*=0.54, $CHCl_3$); IR 1736, 1723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 75°C) 1.34 (3H, s), 1.45 (3H, s), 3.75 (1H, dd, *J*=13.0, 4.0 Hz), 3.82 (1H, d, *J*=13.0 Hz), 4.56 (1H, d, *J*=4.5 Hz), 5.17 (1H, d, *J*=12.4 Hz), 5.21 (1H, d, *J*=12.4 Hz), 5.24 (1H, d, *J*=4.0 Hz), 6.03 (1H, brs), 7.32 (5H, m), 7.95 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$, 75°C) 25.79 (q), 26.78 (q), 49.56 (t), 67.22 (t), 74.31 (brd), 82.27 (brd), 88.83 (d), 112.25 (s), 127.65 (d), 127.83 (d), 128.25 (d), 154.20 (s), 159.00 (s); MS *m/z* (rel intensity) 321 (M^+, 13), 306 (6), 263 (7), 219 (11), 214 (8), 174 (12), 156 (10), 107 (20), 91 (100); HRMS calcd for $C_{16}H_{19}O_6N$ 321.121238, found 321.121613. Anal. Calcd for $C_{16}H_{19}O_6N$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.74; H, 6.05; N, 4.30.
10. Compound **8**: amorphous; $[\alpha]_D$ −92.1 (*c*=0.34, $CHCl_3$); IR 1732, 1703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 75°C) 1.46 (9H, s), 3.06 (1H, d, *J*=14.7 Hz), 3.32 (3H, s), 3.43 (3H, s), 3.46 (1H, dd, *J*=9.7, 3.7 Hz), 3.52 (3H, s), 3.59 (1H, dd, *J*=10.1, 3.3 Hz), 4.11 (1H, brs), 5.33 (1H brs), 5.53 (1H, brs), 8.06 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$, 75°C) 28.46 (3×q), 40.77 (t), 55.48 (q), 58.27 (q), 58.68 (q), 78.11 (2×d), 78.50 (2×d), 80.99 (s), 154.76 (s), 160.03 (s); MS m/z (rel intensity) 319 (<1%), 287 (2), 241 (2), 231 (3) 218 (4), 204 (29), 141 (100); HRMS calcd for $C_{14}H_{25}O_7N$ 319.163120, found 319.163483. Anal. Calcd for $C_{14}H_{25}O_7N$: C, 52.65; H, 7.89; N, 4.39. Found: C, 52.56; H, 7.84; N. 4.01.
11. MMX force field as implemented in PCMODEL (v. 4.0), Serena Software, Bloomington IN, 47402–3076.
12. Saltzman, H.; Sharefkin, J. G. *Org. Synth., Coll. Vol. V*, **1973**, pp. 658–659.

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