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Samarium (II) Iodide Mediated Transformations of Carbohydrate Derived Iodo Oxime Ethers into Stereodefined Alkoxy Aminocyclopentanes

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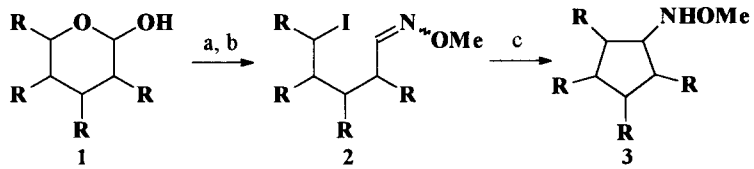
Abstract: Carbohydrate derivatives were employed as precursors in the synthesis of stereodefined alkoxy aminocyclopentanes. This rapid samarium diiodide promoted conversion involves intramolecular trapping of a radical by an oxime ether.

The evolution of SmI_2 as reagent in synthesis has been one of the exciting recent developments in organic chemistry.[1] The construction of highly functionalised carbocycles from carbohydrates promoted by SmI_2 is currently receiving significant interest and a series of carbocyclisation strategies have been described in the literature.[2]

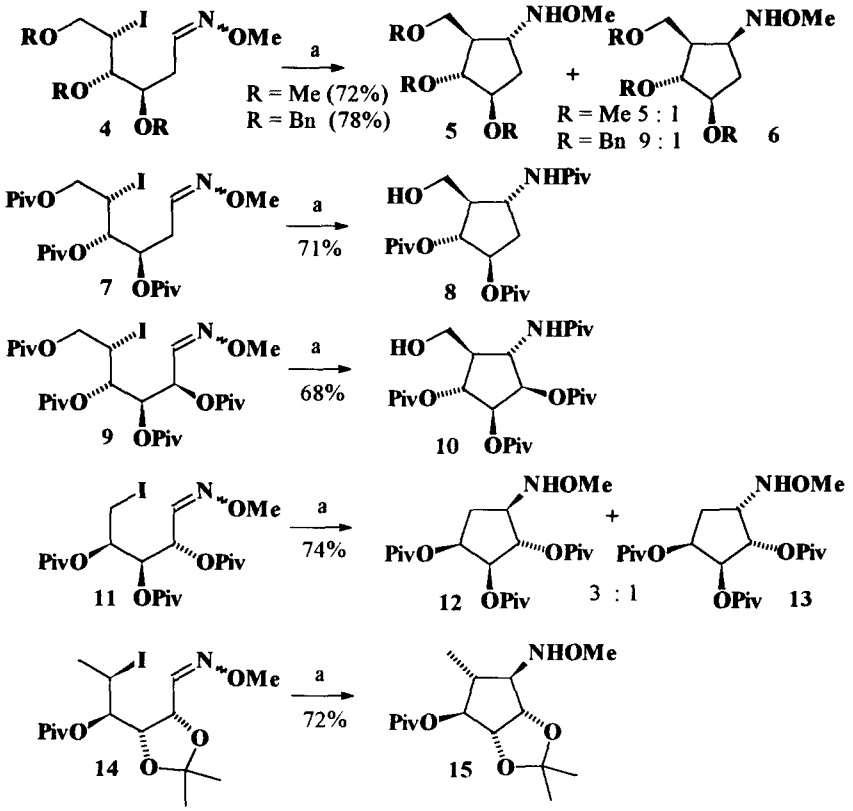
We herein report an efficient method for the preparation of highly functionalised aminocyclopentanes from readily available carbohydrate templates by a stereoselective intramolecular trapping of a radical by an oxime ether promoted by samarium diiodide (Scheme1).



a) $H_2NOMe.HCl$, Py b) PPh_3, Im, I_2 c) SmI_2

Scheme 1

The substrates for the cyclisation reactions were easily prepared from the corresponding protected carbohydrate hemiacetals in good overall yields. These sugar hemiacetals were converted into the corresponding oxime-ether by condensation with *O*-methylhydroxylamine followed by iodination[3] of the released hydroxyl group. The reductive cyclisation took place smoothly in a THF solution containing HMPA to furnish the alkoxy or acyl aminocyclopentanes in good overall yields after extractive workup and chromatography over silica gel (Scheme 2).[4]



a. SmI_2, HMPA, THF

Scheme 2

The efficiency of these reactions can be rationalised in terms of the stabilisation of the intermediate aminyl radical (Fig 1) by the lone pair electrons on the adjacent oxygen atom.[5] Although the reaction proceeds in the absence of HMPA the yields are generally low. The stereochemistry at the two newly introduced asymmetric centers was confirmed by nOe data using the existing stereochemistry as a reference. In all cases the major isomer showed a *trans*-relationship between the *O*-methylhydroxylamino group and the substituents on C-2 and C-5. The sense of diastereoselection probably results from reaction of the alkyl radical through a chairlike transition structure with the substituents at the existing stereocenters preferentially occupying pseudoequatorial positions.[6] The structure leading to the major isomer suffers the least steric interactions between the ring substituents and the functional groups on C-1 and C-5 in the transition state (Fig. 1).

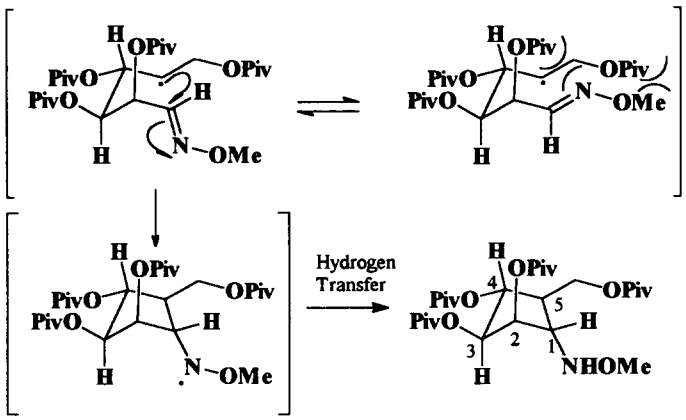


Fig 1

Increasing the steric bulk of the alkoxy substituents on the carbon skeleton resulted in an increase in diastereoselection, in support of the proposed conformation of the transition states.

The resultant cyclic hydroxylamine ethers can be efficiently converted *in situ* into the corresponding aminocyclopentane derivatives by reductive N-O cleavage promoted by excess samarium diiodide and water.[7] With *O*-pivaloyl substituents on C-6, the isolated compounds were the corresponding *N*-acyl derivatives where the N-O bond had been cleaved, probably after acyl migration to the nitrogen atom from C-6. These results are in accordance with published results which showed that N-O bonds of *N*-acyl derivatives were reduced under milder conditions by SmI_2 than the corresponding alkylated hydroxylamine derivatives.[8]

In conclusion we have discovered a facile and rapid means of converting appropriately functionalised carbohydrates into the corresponding stereodefined aminocyclopentanes. Our protocol nicely complements Chiara's[9] reductive coupling of carbonyl tethered oxime ethers for the construction of highly functionalised aminocyclopentitols as key intermediates for the preparation of carbocyclic glycosidase inhibitors,[10] carbocyclic nucleosides,[11] and analogues.

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4. General procedure for the cyclisation reactions with SmI_2: a solution of the oxime-ether (0.3 mmol) in THF (10 ml) containing HMPA (1 ml) was cooled to 0°C, after which a solution of SmI_2 in THF (9 ml of a 0.1 M solution, 0.9 mmol) was added dropwise over a period of 5 min. The reaction mixture was allowed to warm to ambient temperature for *ca.* 30 min, quenched by addition of a saturated aq. solution of NH_4Cl (5 ml) and worked up as follows: The mixture was diluted with H_2O (5 ml) and extracted with EtOAc (3 x 10 ml). The combined extracts were washed with H_2O (3 x 10 ml), saturated aq. $Na_2S_2O_3$ (10 ml) and brine (10 ml). The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and the crude products were purified by flash chromatography over silica gel using a mixture of EtOAc and hexane. All products afforded satisfactory ^1H NMR, ^{13}C NMR and low-and high resolution mass spectra. For example, compound **15**: ^1H NMR ($CDCl_3$, Varian Gemini 2000, 300 MHz): δ 1.10 (3H, d, J 6.9), 1.18 (9H, s), 1.26 (3H, s), 1.48 (3H, s), 2.01-2.08 (1H, m), 3.04 (1H, dd, J 8.4 and J 3.9), 3.53 (3H, s), 4.40 (1H, dd, J 7.5 and J 3.6), 4.59 (1H, dd, J 7.5 and J 3.9), 4.79 (1H, dd, J 7.8 and J 3.6), 5.59 (1H, s); ^{13}C NMR: δ 15.8, 24.5, 26.7, 27.0, 38.6, 41.1, 62.4, 70.9, 81.1, 82.5, 83.6, 112.5, 177.7; m/z (EI-MS, Finnigan-Matt 8200) 301 (M^+, 16%), 286 (M^+ - CH_3, 22%), 243 (M^+ - CH_3 and C_2H_3O), 57 (C_4H_9, 100%); HRMS found 301.1884, calculated for 301.1889
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