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Expeditious Synthesis of Chiral Six and Seven Membered Nitrogen Heterocycles from Carbohydrate Amines by *N*-Allyl Carbohydrate Nitrone Cycloaddition : Tuning of Regioselectivity by *N*-Substitution

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Abstract : The cycloaddition of *N*-allyl carbohydrate nitrones leads to enantiomerically pure six and seven membered nitrogen heterocycles and the regioselectivity of the cycloaddition can be tuned by changing the substituent on the nitrogen atom.
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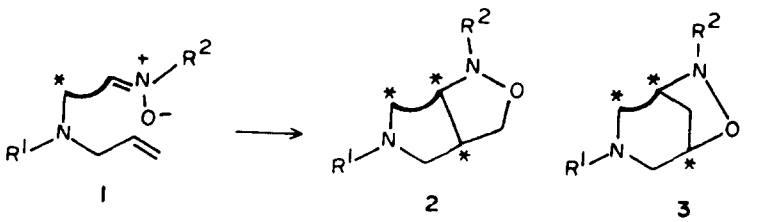
Chiral cyclic amines, particularly five, six and seven membered nitrogen heterocycles belong to the largest class of heterocyclic compounds with diverse biological activities.[1,2] Naturally intensive effort has been directed towards the development of efficient strategies for their synthesis.[1-3] The obvious requirement of expedient approaches to such systems has prompted us to disclose herein a strategy, which apart from being simple can enable the synthesis of different sizes of enantiomerically pure cyclic amines from carbohydrate derivatives.

The strategy as depicted in **Scheme 1** involves the cycloaddition of an *N*-allyl carbohydrate nitrone **1** giving rise to a fused isoxazolidine **2** or a bridged isoxazolidine **3** or both, which are essentially chiral cyclic amine derivatives incorporating two more chiral centres than **1**. The ring-size of **2** or **3** can be altered by changing the position of the *N* -allyl group on the carbohydrate template. Substituted cyclic amines



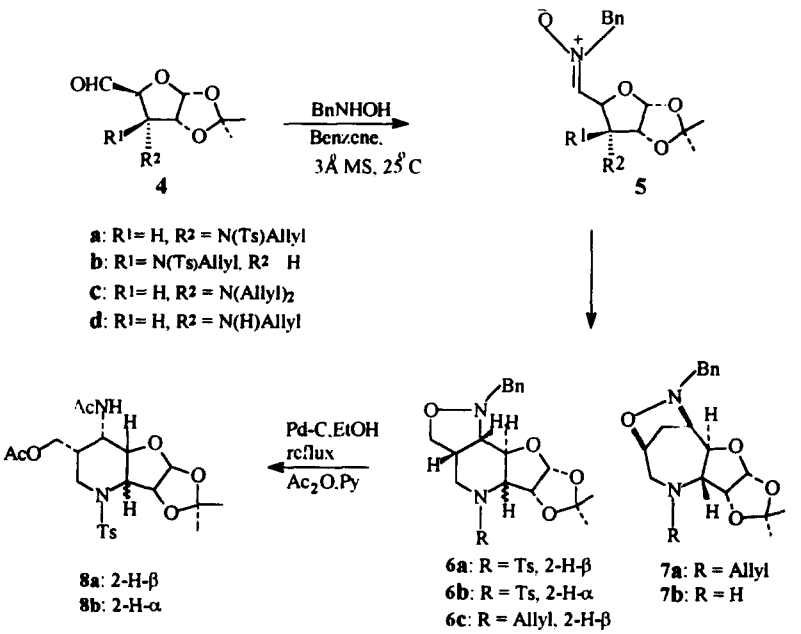
Scheme 1

can be obtained from **2** or **3** by cleavage of the isoxazolidine ring as well as by degradation of the carbohydrate framework. The strategy is demonstrated below by the synthesis of chiral piperidine and azepane derivatives via the cycloaddition of 3-*N*-allyl carbohydrate nitrones.

The 3-*N*(Ts)-allyl carbohydrate aldehyde derivative **4a**, which was readily available from 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-allofuranoside[4] through tosylation and allylation, following a known[5,6] sequence of reactions. Treatment of **4a** with *N*-benzylhydroxylamine in benzene led to the formation of the nitrone **5a**, which underwent cycloaddition to furnish the piperidine derivative **6a**[10,11] in 85% yield (**Scheme 2**). The stereochemistry of ring fusion in **6a** was established from the relevant $^1H,^1H$ coupling constants *viz.* $J_{3,4}$, $J_{4,5}$ and $J_{5,6B}$ in **8a**[10], which could be easily prepared in 44% yield by the cleavage of the isoxazolidine ring in **6a** by transfer hydrogenation[7] using cyclohexene and Pd-C followed by acetylation. Similarly the chiral piperidine derivative **6b**[10,11] was obtained in 78% yield from the nitrone **5b** prepared from 3-amino-3-deoxy- 1,2:5,6-di-*O*-isopropylidene-α-glucofuranoside[8] via **4b** and could be cleaved to **8b**[10] in 61% yield. It is noteworthy that no bridged isoxazolidine could be detected in the cycloaddition of **5a** or **5b**.

The formation of the fused isoxazolidines **6a** or **6b** from the respective nitrones **5a** and **5b** was conspicuous, because the corresponding *O*-allyl-*N*-benzyl nitrones[5,6] or the *O*-allyl- *N*-methyl nitrones[9] were reported to give bridged isoxazolidines as exclusive or preponderant products. Specifically, in contrast to the *N*-allyl nitrone **5a**, the corresponding *O*-allyl nitrone has been reported[6] to give the bridged isoxazolidine exclusively. An interesting and useful aspect of the regioselectivity of this cycloaddition was subsequently discovered when the substitution on the nitrogen atom was changed. Unlike the *N*-tosyl nitrones **5a** and **5b**, the corresponding *N,N*-diallyl nitrone **5c** afforded a mixture (78%) of the piperidine derivative **6c**[10] and the azepane derivative **7a**[10] in the ratio of 2:1. A more dramatic change in the regioselectivity was observed when the azepane derivative **7b**[10] was formed as the exclusive product in 80% yield from the *HN*-allyl nitrone **5d**. The structure of **7b** was easily established by its conversion to **7a** by allylation. Thus it is evident that the cycloaddition of the 3-*N*-allyl nitrone with the nitrogen atom bearing no substituent was observed to show the same regioselectivity as found in the corresponding *O*-allyl nitrone cycloaddition. The regioselectivity gradually shifted to the other end by substitution of the nitrogen atom by allyl and tosyl groups.

We believe that the transition state for the formation of the bridged isoxazolidine, which is more probable for the earlier reported *O*-allyl nitrone[6] and *HN*-allyl nitrone **5d**, becomes less so for the nitrones **5a** and **5c** because of a destabilising steric interaction between the *N*-substituent *viz.* tosyl or allyl group and the developing isoxazolidine ring in the latter nitrones. It is of much practical significance that the regioselectivityin the *N*-allyl carbohydrate nitrone cycloaddition can be effectively tuned by changing the substitution on the nitrogen atom, and accordingly the above methodology will be potentially useful for preparing six- or seven membered chiral nitrogen heterocycles by using suitably substituted *N*-allyl carbohydrate derivatives as starting



Scheme 2

materials. Application of the general strategy to the synthesis of other ring-sizes of nitrogen heterocycles is in progress.

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REFERENCES AND NOTES

1. Casiraghi, G.; Zanardi, F. *Chem. Rev.* **1995**, *95*,1677.
2. Koide, K.; Bunnage, M. E.; Paloma, L. G.; Kanter, J. R.; Taylor, S. S.; Brunton, L. L.; Nicolaou, K. C. *Chemistry and Biology.* **1995**, *2*, 601.
3. Vissor, M. S.; Heron, N. M.; Didiuk, M. T. ; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291.
4. Onodera, K.; Hirano, S.; Kashimara, N. *Carbohydr. Res.* **1968**, 276.

5. Datta, S.; Chattopadhyay, P.; Mukhopadhyay, R. ; Bhattacharjya, A. *Tetrahedron Lett.* **1993**, *34*, 3585.

6. Bhattacharjc . A. ; Bhattacharjya, A.; Patra, A. *Tetrahedron Lett.* **1995**, *36*, 4677.

7. Collins, P. M.; Ashwood, M. S.; Eder, H.; Wright, S. H. B.; Kennedy, D. J. *Tetrahedron Lett.* **1990**, *31*, 2055.

8. Brimacombe, J. S.; Bryan, J. G. H.; Husain, A.; Stacey, M.; Tolley, M. S. *Carbohydr. Res.* **1966 - 67**, 318.

9. Shing, T. K. M.; Fung, W. C.; Wong, C. H. *J. Chem. Soc. Chem. Commun.* **1994**, 449.

10. All new compounds had satisfactory ^{1}H NMR, ^{13}C NMR and mass spectral data. In addition, satisfactory microanalytical data were obtained for crystalline compounds and HRMS data were available for **6b**. Compound **7b** was correlated with **7a** as described in the text. *Selected physical and spectral data*: NMR and optical rotations were taken in $CDCl_3$ and $CHCl_3$ respectively. **6a**: m.p 110^0-111^0 C; $[\alpha]_D^{30}$ $+21.1^0$ (c 0.66); δ 2.47 (m, 1H, 5-H); 41.8 (d, 5-C). **6b**: sticky solid; $[\alpha]_D^{30}$ -102.5^0 (c 0.40); δ 2.78 (m, 1H, 5-H); 39.9 (d, 5-C). **6c**: syrupy liquid; $[\alpha]_D^{27}$ $+37.6^0$ (c 0.51); δ 3.04 (m, 1H, 5-H); 40.3 (d,5-C). **8a**: m.p 120^0-123^0C; $[\alpha]_D^{30}$ $+80.8^0$ (c 0.50); δ 2.54 (dd, $J_{6A,6B}$ = 12.5 Hz, $J_{6B,5}$ = 2.7 Hz, 1H, 6-H_B); 2.62 (m, 1H, 5-H); 3.80 (dd, $J_{6B,6A}$ = 12.5 Hz, $J_{6B,5}$ = 2.3 Hz, 1H, 6-H_A), 3.90 (dt, $J_{4,3}$ = $J_{4,5}$ = 8.5 Hz, $J_{4,NH}$ = 5.1 Hz, 1H,4-H); δ 36.4 (d,5-C). **8b**: m.p. 83^0-85^0C; $[\alpha]_D^{28}$- 9.8^0 (c 0.45); δ 2.54 (m, 1H, 5-H), 3.13 (dd, $J_{6B,6A}$ = 13.4 Hz, $J_{6B,5}$ = 6.2 Hz, 1H, 6-H_B), 3.19 (dd, $J_{6A,6B}$ = 13.4 Hz, $J_{6A,5}$ = 6.2 Hz, 1H, 6-H_B), 4.62 (dt, $J_{4,5}$ = $J_{4,NH}$ = 9.6 Hz, $J_{4,3}$ = 5.2 Hz, 1H, 4-H); δ 32.3 (d, 5-C). **7a**: m.p. 118^0-119^0C; $[\alpha]_D^{27}$ $+144.8^0$ (c 0.54); δ 2.15 (d, $J_{5A,5B}$ = 12.4 Hz, 1H, 5-H_A) and 2.30 (m, 1H, 5-H_B) ; δ 28.9 (t, 5-C).

11. Indian patent filed.

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