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A NEW SYNTHESIS OF NITROGEN-CONTAINING HETEROCYCLES BY MEANS OF ORGANOALUMINUM REAGENTS

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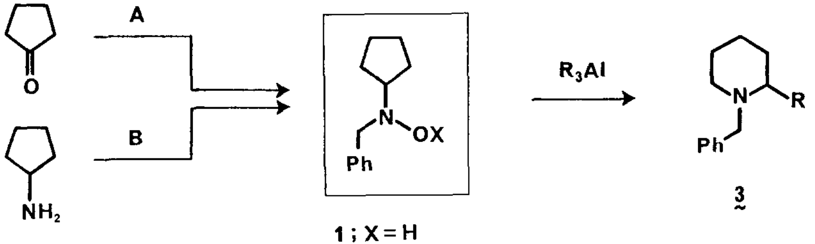
Summary: Nitrogen-containing heterocycles can be derived in synthetically good yields from a variety of carbocyclic frameworks via the successive rearrangement-alkylation sequence of hydroxylamine carbonates with trialkylaluminums.

Nitrogen-containing heterocycles such as pyrrolidines, piperidines, and perhydroazepines constitute basic skeletons of many naturally occurring alkaloids.[1] The development of procedures for efficiently constructing these ring systems from carbocyclic frameworks with simultaneous functionalization α to the nitrogen of amines is of crucial importance in alkaloid synthesis.[2] Disclosed herein is a general procedure which effects such transformation under mild conditions.

This method is based on the successive rearrangement-alkylation sequence of hydroxylamine derivatives with organoaluminum reagents.[3-5] The hydroxylamines as key intermediates were conveniently prepared from a variety of carbocyclic ketones, amines, or their synthetic equivalents as exemplified by the synthesis of benzylcyclopentylhydroxylamine 1 according to Method A or B (eq. 1):

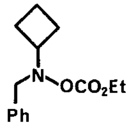
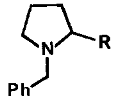
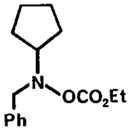
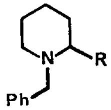
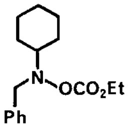
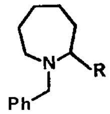
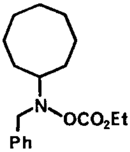
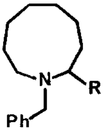
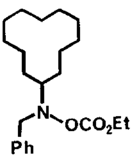
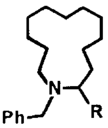


1; X = H
2; X = CO₂Et
3

(1)

Method A: Amination of cyclopentanone with benzylhydroxylamine in the presence of $NaBH_3CN$ (85%)[6]; Method B: Benzylation of cyclopentylamine ($PhCH_2Cl$, K_2CO_3, MeOH; 74%), Michael addition of the resulting amine (CH_2=CHCOOMe, p-TsOH, MeOH; 94%), and oxidation (MCPBA, CH_2Cl_2) with concurrent elimination (56%). The hydroxylamine 1, thus obtained, was converted to the corresponding

Table I. Rearrangement of Hydroxylamine Carbonates by Trialkylalumimums. [a]

entry	substrate	R_3Al [b]	product	yield (%) [c]
1		R = Me		71
2		= $Me_3SiC{\equiv}C$		98
3		R = Me		74
4		= n-BuC≡C		89
5		= $Me_3SiC{\equiv}C$		71
6		R = Me		79
7		= n-BuC≡C		70
8		R = Me		62
9		R = Me		59

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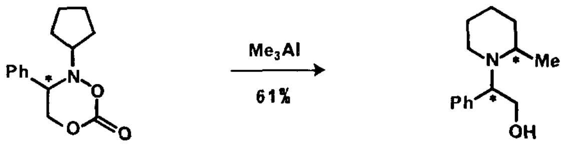
[a] Reaction was carried out under argon atmosphere using 4 equiv of R_3Al.

[b] Trialkynylaluminums were prepared by treatment of the corresponding alkynyllithium with $AlBr_3$ in CH_2Cl_2 at 0°C for 30 min. See ref. 4. [c] Isolated yield after column chromatography on silica gel.

carbonate 2 by treatment with ethyl chloroformate and triethylamine in CH_2Cl_2 (95% yield). When the hydroxylamine carbonate 2 was treated with 4 equiv of trialkylaluminum in CH_2Cl_2 at 0-25°C for several hours, α-alkylated piperidine 3 was obtained after ordinary aqueous workup in a high yield.[7] Other examples are listed in Table I.

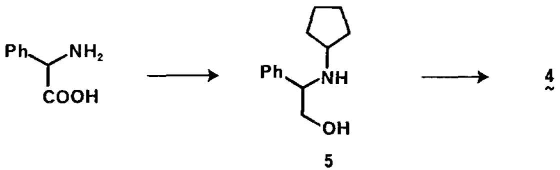
The reaction is applicable to a variety of carbocyclic hydroxylamine carbonates except cyclopropylhydroxylamine derivatives.[8,9] Notable is the marked regiospecificity of the reaction, and no trace of the N-alkylation products were detected. In contrast to the previously reported Beckmann rearrangement of oxime sulfonates,[2] the present method is characterized by the ultimate potentiality of introducing a new carbon-carbon bond in a diastereoselective manner at the α position of amines, thus allowing the asymmetric synthesis of α-alkylated amines.[10]

A simple illustration of the potential utility of the reaction for the asymmetric synthesis can be envisioned by the rearrangement-alkylation sequence of cyclic carbonates of type 4, which would be an interesting substrate to reduce the conformational mobility and to increase the free energy difference of diastereomeric transition states in the reaction. Accordingly, phenylglycine was converted to its methyl ester ($SOCl_2$, MeOH; 100%)[11] which was alkylated (cyclopentanone, $NaBH_3CN$, methanolic HCl; 88%)[6] and reduced with $LiAlH_4$ in ether to give N-cyclopentylphenylglycinol (5) (67%). Transformation of 5 into hydroxylamine (37%) according to the Method B, followed by treatment with p-nitrophenyl chloroformate and triethylamine in CH_2Cl_2 furnished the cyclic carbonate 4 (51%). Exposure of 4 to excess trimethylaluminum (6 equiv) in CH_2Cl_2 at 0°C for 10 h afforded the desired amine 6 (61% yield) in 22% diastereomeric excess.[12]



4

6



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(1) Glasby, J. S. "Encyclopedia of the Alkaloids"; Plenum Press: New York, 1975; Vol. 1, 2; 1977; Vol. 3.

(2) For relevant reactions, see: Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. J. Am. Chem. Soc. **1983**, 105, 2831.

(3) General reviews on rearrangements of hydroxylamines: de Mayo, P. "Molecular Rearrangements"; John Wiley & Sons: New York, 1963; Vol. 1; Thyagarajan, B. S. "Mechanisms of Molecular Migrations"; Interscience: New York, 1968; Vol. 1.

(4) Nucleophilic aromatic substitution of arylhydroxylamines: Fujiwara, J.; Fukutani, Y.; Sano, H.; Maruoka, K.; Yamamoto, H. J. Am. Chem. Soc. **1983**, 105, 7177, and references cited therein.

(5) The reduction of oximes with diisobutylaluminum hydride producing isomeric secondary amines might proceed via the rearrangement of the intermediary hydroxylamines: Girault, Y.; Decouzon, M.; Azzaro, M. Bull. Soc. Chim. France **1975**, 385; Sasatani, S.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. Tetrahedron Lett. **1983**, 24, 4711.

(6) Borch, R. F.; Bernstein, M. D.; Durst, H. D. J. Am. Chem. Soc. **1971**, 93, 2897.

(7) The use of other hydroxylamine derivatives (e.g. X = $COCH_3$, $Si(CH_3)_3$) gave less satisfactory results.

(8) Attempted reaction of benzylcyclopropylhydroxylamine derivatives with trialkylaluminums resulted in the formation of deteriorated reaction mixtures.

(9) In case of benzyl(2-methylcyclopentyl)hydroxylamines, the rearrangement is highly dependent on the stereochemistry of the cyclopentyl moiety. Thus, reaction of benzyl(trans-2-methylcyclopentyl)-hydroxylamine carbonate with trimethylaluminum proceeded smoothly with loss of regioselectivity for rearrangement-alkylation site to furnish several amine products in 60% yield. On the other hand, rearrangement of the cis isomer was significantly retarded and most of the starting carbonate was recovered under the same reaction conditions.

(10) For recent asymmetric synthesis of α-alkylated amines, see: Meyers, A. I.; Fuentes, L. M. J. Am. Chem. Soc. **1983**, 105, 117.

(11) Brenner, M.; Huber, W. Helv. Chim. Acta **1953**, 36, 1109.

(12) Diastereomeric ratio was determined by the capillary GLC comparison (25-m PEG-HT, 190°C) with the authentic sample: t_r = 8.97 and 10.71 min. The authentic **6** was prepared according to the literature procedure: Overman, L. E.; Flippin, L. A. Tetrahedron Lett. **1981**, 22, 195.

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