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Intramolecular Nucleophilic Substitution on Nitrogen. A New Heterocyclic Synthesis

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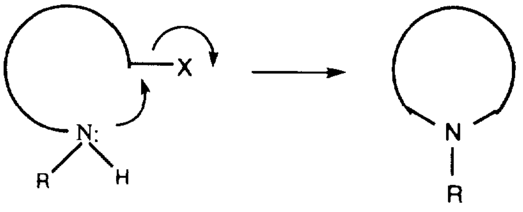
Abstract: *A series of 5-(diphenylphosphinyloxyamino)valeric acid esters has been prepared. Their treatment with appropriate bases led to cyclization to proline derivatives. The reaction constitutes the first reported case of intramolecular nucleophilic substitution on nitrogen.*

The displacement of leaving groups on nitrogen atoms by carbanions presents a method of making carbon-nitrogen bonds in which the roles of the atoms are reversed to the usual ones. Although numerous examples of the reversed reaction were described in the literature by us and by others,[1] the intramolecular version which would lead to nitrogen heterocycles (depicted below) has not yet been demonstrated experimentally.



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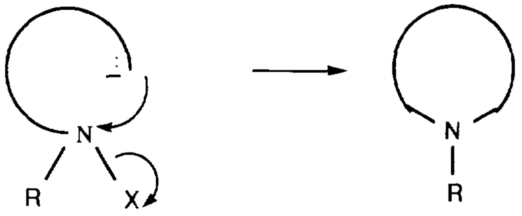
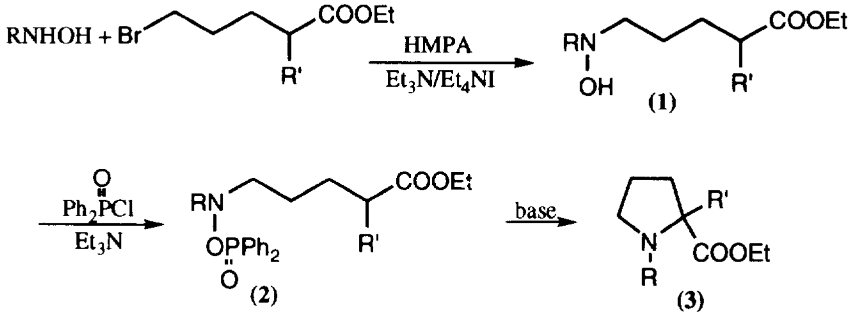


(reversed)

We now report the first examples of such reactions, which involved the cyclization of 5-aminovaleric acid derivatives to proline derivatives. The leaving group employed here was the diphenylphosphinyloxy[2,3]. The substrates **2** were prepared by the reaction of N-substituted hydroxylamines with 5-bromovalerate esters to give 5(N-hydroxyamino) esters **(1)**[4] (80-90% yields), and subsequent reaction with diphenylphosphinyl chloride (70-90%). Treatment of compounds **2** with base effected the desired cyclization to the pyrrolidines **3**[5].

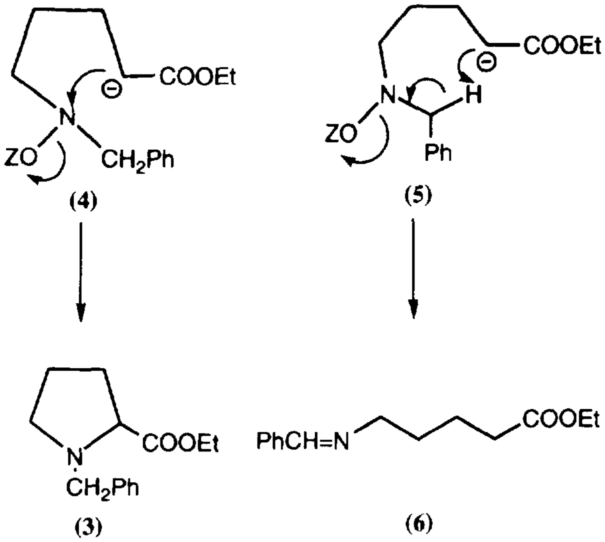


Results: The transformation **2**-->**3**

No	R	R'	Base	Yield(%)
a	$-CH_3$	COOEt	t-BuOK	95
b	$-CH_3$	H	LDA	75
c	$-CH_2Ph$	COOEt	t-BuOK	81
d	$-CH_2Ph$	H	LDA	47
e	$-CH(CH_3)Ph$	H	LDA	10
f	$-CH_2CH{=}CH_2$	H	LDA	20
g	$-C(CH_3)_2Ph$	H	LDA	0

Clearly in the case of N-methyl (formation of **3a** and **3b**), which represents simple alkyl groups, the intramolecular substitution on nitrogen is a quite smooth and efficient reaction. The benzyl derivatives **3c** and **3d** were prepared as precursors of N-unsubstituted pyrrolidines. Although the benzylic protecting group could not be used in the intermolecular version as it undergoes a very easy elimination[6], its use was attempted here, as we hoped that the 5-

membered cyclic transition state (**4**) required for substitution will be preferred over the 7-membered (**5**) required for elimination and formation of **6**.



(4) (5) (3) (6)

This expectation (preference of **4** over **5**) materialized in full in the case of **3c** and in part in **3d**. In order to prevent the elimination (formation of **6d**, 40%) which accompanies the cyclization to **3d**, we tried to replace the benzylic protons by methyls and prepared **2g**^{7}. The dimethylbenzyl group is however probably too bulky and **2g** did not react with bases. The use of the allyl protecting group (**2f**, removable with palladium(0) complexes^8) also proved to be unsatisfactory, and this problem remains partially open. The result with optically active α-methylbenzyl(**2e**) was particularly disappointing, as it was intended to use the cyclization of **2e** as a tool for the study of asymmetry induction in the reaction. The elimination product **6e** was formed almost exclusively.

Work in progress on this new heterocyclic synthesis includes a study of the stereochemical aspects and of extension to the formation of other types and sizes of nitrogen heterocycles.

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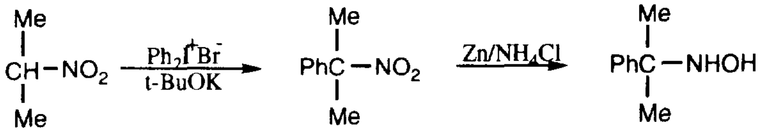
References and notes

1. Review: Erdik E.; Ay M. *Chem. Reviews*, **1989**, 89 1947.
2. Colvin E.W.; Kirby G.W.; Wilson A.C. *Tetrahedron Lett.* **1982**, 23, 3835.
3. Boche G.; Bernheim M.; Schrott W.C. *Tetrahedron Lett.* **1982**, 23, 5399.
4. The alkylation conditions employed (solvent: HMPA, base: Et_3N, additive: Et_4NI) are according to: Mukaiyama T.; Tsuji T.; Watanabe Y. *Chemistry Lett.* **1978**,1057.
   The hydroxylamines **1** were prepared also by H_2O_2 oxidation of the corresponding δ-aminovalerate esters, but the yields were considerably lower.
5. All the new compounds of types **1**, **2** and **3** displayed the right spectral properties (IR and NMR) and elemental analyses (C,H,N).
6. Sheradsky T.; Itzhak N. *J. Chem. Soc. Perkin Trans. I* **1986**, 13.
7. (α,α–Dimethyl)benzylhydroxylamine, required for the preparation of **2g**, was made as outlined below, m.p. 40-42° C.



$$\mathrm{Me_2CH{-}NO_2} \xrightarrow[\text{t-BuOK}]{\mathrm{Ph_2I^+Br^-}} \mathrm{PhC(Me)_2{-}NO_2} \xrightarrow{\mathrm{Zn/NH_4Cl}} \mathrm{PhC(Me)_2{-}NHOH}$$

8. Lemaire-Audoire S.; Savignac M.; Genet J.P. *Tetrahedron Lett.* **1995**, 36, 1267.

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