Acid-catalysed Rearrangement of Cyclobutylimines. A New Synthesis of Tetrahydropyridines

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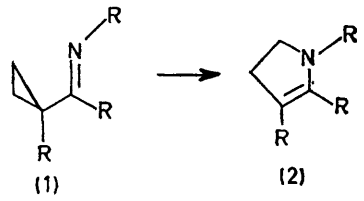
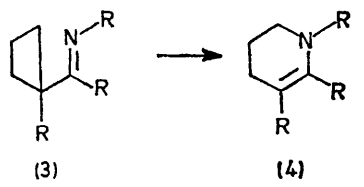
Summary The scope and limitations of the thermally induced acid-catalysed rearrangement of cyclobutylimines to tetrahydropyridines are discussed.

IN connection with research to develop new methods of alkaloid synthesis, we have found that the acid-catalysed rearrangement of the cyclopropylimines (**1**) is an effective method for generating various Δ^2-pyrrolines (**2**).[1] We have now investigated the analogous rearrangement of the cyclobutylimines (**3**) as a synthetic route to tetrahydropyridines (**4**), which are important intermediates in alkaloid synthesis.[2]



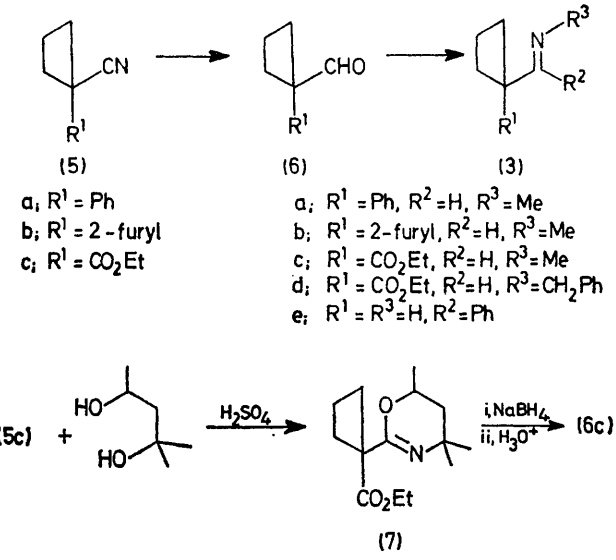


With one exception the cyclobutylimines† used were prepared from the corresponding aldehydes which, in turn, were obtained by selective reduction of the appropriate nitrile. The scope and limitations of the reaction are indicated by the results in the Table. Reduction of the carbonitriles (**5a**) or (**5b**) with Bu^t_2AlH provided the corresponding aldehydes (**6a**) and (**6b**) in >80% yields. Treatment of (**6a**) and (**6b**) with Me_2NH in the presence of 4A molecular sieves provided the desired imines (**3a**) and (**3b**) (*ca.* 90%).

TABLE. Rearrangement of cyclobutylimines to tetrahydropyridines at 170 °C

Cyclobutylimine	Tetrahydropyridine	Catalyst	Yield (%)
(**3a**)	(**4a**)	NH_4I	30
(**3b**)	(**4b**)	NH_4I	31
(**3c**)	(**4c**)	NH_4Br	66
(**3d**)	(**4d**)	NH_4Br	61
(**3e**)	(**4e**)	NH_4I	0

The selective reduction of the carbonitrile (**5c**) required an indirect procedure we had devised previously in the cyclopropane series.[3] Thus, conversion of (**5c**) into the dihydrooxazine (**7**)[4] and reduction ($NaBH_4$) of this intermediate followed by hydrolysis of the resultant tetrahydro-oxazine gave the desired aldehyde (**6c**). Conversion of (**6e**) into the aldimines (**3c**) and (**3d**) proceeded in high yield. Finally, the ketimine (**3e**) was prepared (96%) by addition of phenyl-lithium to cyclobutanecarbonitrile, followed by careful hydrolysis with $Na_2SO_4 \cdot 10H_2O$.



In contrast to vinylcyclopropanes, cyclopropylimine rearrangement is not a purely thermal process since, in this case, acid catalysis is required. Furthermore, it has been observed that the gegenion must be nucleophilic, and qualitatively the order of reactivity is $I^- > Br^- > Cl^-$; BF_4^- or ClO_4 salts fail to rearrange. Based on these observations, less strained cyclobutylimines might be expected to require higher temperatures and better nucleophiles. Furthermore, any substituent capable of facilitating nucleophilic opening should also facilitate the rearrangement.

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† The structure of all new compounds reported were confirmed by i.r., ^1H n.m.r., and mass spectral analysis.

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[2] E. Wenkert, *Accounts Chem. Res.*, 1968, **1**, 78.
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[4] A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, 1973, **38**, 36.