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[2+2] CYCLOADDITIONS OF KETENIMINIUM IONS AND ALKENES: A STEREOSELECTIVE SYNTHESIS OF SUBSTITUTED CYCLOBUTYLAMINES

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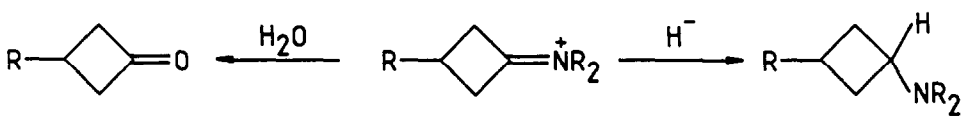
Summary: The [2+2] cycloaddition of keteniminium ions and alkenes followed by in situ reduction of the resultant iminium ions gives cyclobutylamines in good yields.

The [2+2] cycloaddition of keteniminium ions to alkenes has been shown to be a convenient and practical route to cyclobutanones (1) by Ghosez[1-5], Snider[6,7] and Brady[8]. We were attracted to the reaction as a source of the reactive intermediate iminium ions (2) which could undergo reduction to give cyclobutylamines (3).



(1) (2) (3)

We describe here a convenient and stereoselective one-pot synthesis of substituted cyclobutylamines from alkenes based on this reaction. The keteniminium ion (4) was generated and trapped in situ with an alkene by the general method of Ghosez[5]. The resulting iminium ion (2) was reduced in situ with either tetrabutylammonium cyanoborohydride (method A) or sodium cyanoborohydride in the presence of Aliquat 336 (method B)[9] to afford the corresponding cyclobutylamine (3).

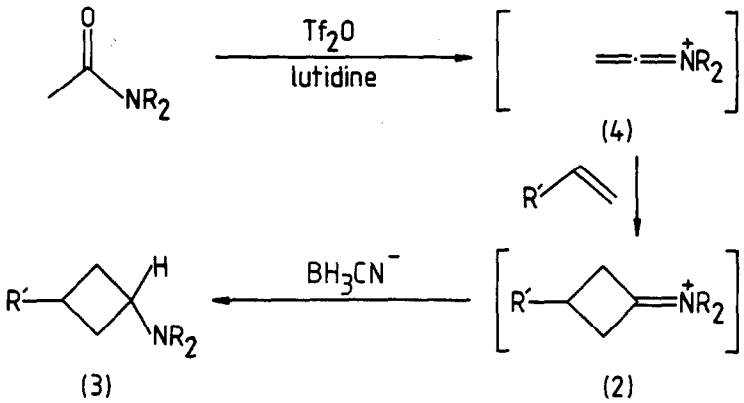


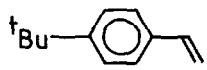
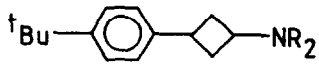
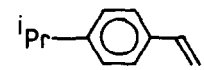
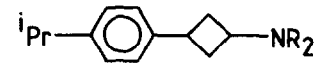
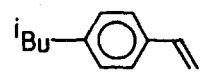
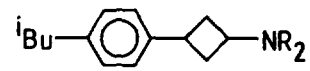
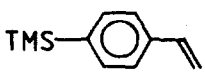
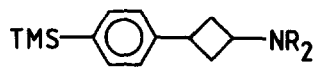
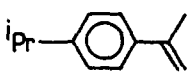
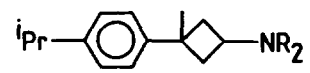
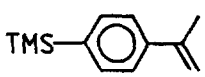
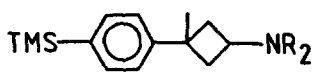
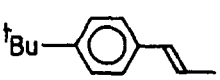
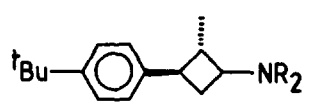
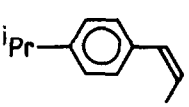
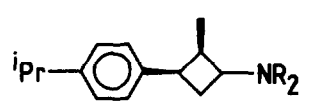
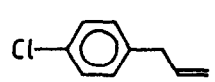
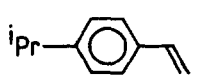
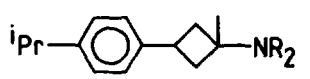
Table 1 shows the results achieved with a range of alkenes; NR_2 represents cis 2,6-dimethylmorpholino in all cases.

The regiochemistry of the cycloaddition was as found by Ghosez[5], with the more electron-donating substituent in the 3-position of the cyclobutylamine. For monosubstituted alkenes and acetamides the method gave a mixture of cis and trans 3-substituted cyclobutylamines with the cis isomer predominant. The isomer ratio varied according to the precise reaction conditions, but this effect was not investigated further. The stereochemistry of the major isomer of the first product in Table 1 was confirmed by x-ray diffraction.[10] For 1,2-disubstituted alkenes there was a similar trend for the amine to be cis to any substituent in the 2-position of the cyclobutylamine (see Entries 7 and 8 of Table 1). Both these results are a natural consequence of the reducing agent attacking the iminium ion (2) from the sterically less hindered side.

The final example in Table 1 shows that in addition to reduction with hydride it was lso possible to react the iminium ion (2) with a carbon nucleophile to produce 1-substituted cyclobutylamines, albeit in low yield.

A typical experimental procedure is as follows (Entry 6, Table 1):
Trifluoromethanesulphonic anhydride (0.9ml, 5.4mmol) in dry chloroform (37ml) was added over a period of 7 hours to a stirred solution of 2-(4-trimethylsilylphenyl)prop-1-ene (2.80g, 14.7mmol), N-acetyl cis 2,6-dimethylmorpholine (0.75g, 4.8mmol) and lutidine (0.59g, 5.5mmol) in dry chloroform (20ml) heated under reflux. The mixture was cooled to room temperature and tetrabutylammonium cyanoborohydride (2.02g, 7.2mmol) was added. After a further 16 hours the mixture was washed with 2M sodium hydroxide solution, dried ($MgSO_4$) and evaporated in vacuo. Chromatography [SiO_2, hexane-ethyl acetate (100:0) to (50:50)] gave Z 3-(4-trimethylsilylphenyl)-3-methyl-1-[4-(cis 2,6-dimethylmorpholino)]cyclobutane (0.733g, 46%) and E 3-(4-trimethylsilylphenyl)-3-methyl-1-[4-(cis 2,6-dimethylmorpholino)]cyclobutane (0.348g, 22%).

TABLE 1

No.	Alkene	Method[1]	Product[2]	Yield	Ar/N cis:trans
1.		A		67%	3:2
2.		B		50%	>4:1
3.		B		80%	>4:1
4.		B		66%	2:1
5.		B		45%	2:1
6.		A		68%	2:1
7.		A		61%	1:5
8.		A		12%	>10:1
9.		B		21%	2:1
10.		MeMgBr		19%	2:1

1. Method A: Bu_4NBH_3CN; Method B: $NaBH_3CN$/Aliquat 336

2. All new products were fully characterised by NMR, IR and MS.

Conclusion

Clearly the methodology described herein represents a powerful new regio- and stereoselective synthesis of cyclobutylamines from readily available starting materials in generally good yields.

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10. Performed by Dr. D. Williams, Department of Chemistry, Imperial College of Science and Technology, London, SW7 2AY.

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