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[3,3]-SIGMATROPIC REARRANGEMENT OF 2-AZA-4-OXY-1,5-HEXADIENE SYSTEM
A NOVEL PYRROLIDINE SYNTHESIS

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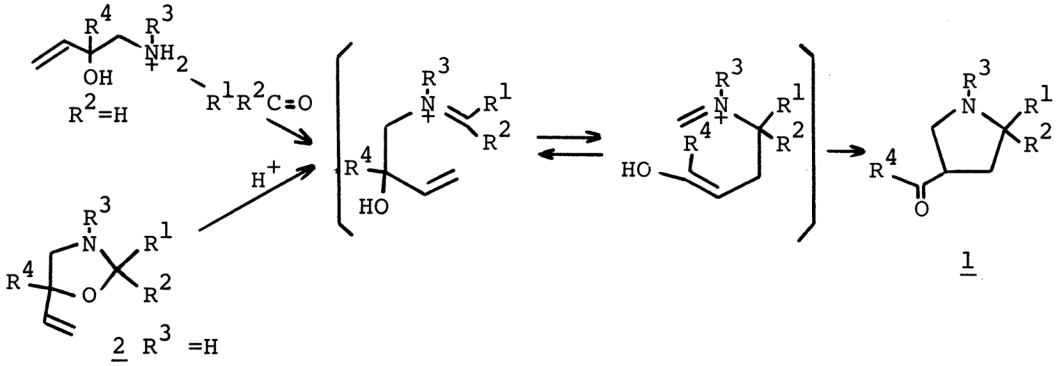
3-Acetylpyrrolidines were prepared in high yield when 5-vinyloxazolidines were treated with potassium hydride and 18-Crown-6. The base catalyzed oxy-2-aza-Cope rearrangement features this reaction.

It is a major objective of synthetic chemistry to develope synthetic methods which proceed under mild conditions. Sigmatropic rearrangements have been particularly useful in this request.[1] Overman and coworkers recently reported the new pyrrolidine synthesis by the intramolecular trapping of the intermediate produced via 2-azonia-[3,3]-sigmatropic rearrangement (eq.1).[2] In the present communication we report that the reaction from 5-vinyloxazolidines 2 to 3-acetylpyrrolidines 1 is dramatically catalyzed by base. The overall transformation features a base catalyzed 4-oxy-2-aza-[3,3]-sigmatropic rearrangement and is carried out under remarkably mild conditions.

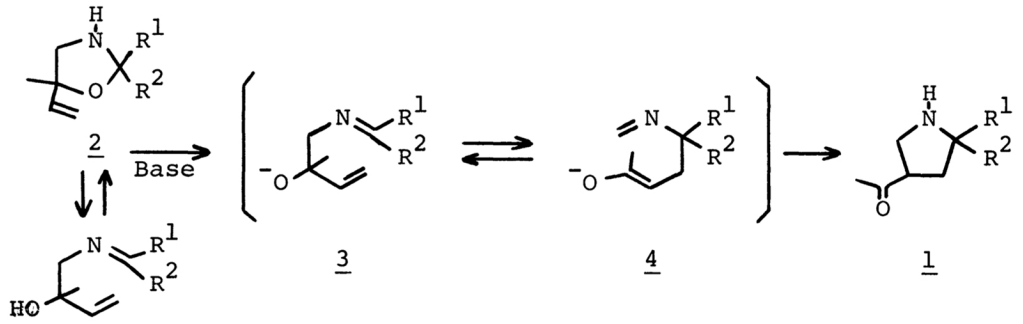


(1)

The oxy-Cope rearrangement has been well studied[3] and strongly developed by Evans as the base accelerated oxy-Cope rearrangement.[4] The strategy to incorporated this reaction into the 2-aza-Cope rearrangement system is depicted in Scheme I. Readily available 5-vinyloxazolidines 2,[2b,5] derived from 1-amino-2-methyl-3-buten-

2-ol[6] and various carbonyl compounds, react with potassium hydride to produce the base accelerated oxy-Cope type intermediates 3.[4] The following intramolecular ring closure[7] to 3-acetylpyrrolidines 1 is induced by the attack of the rearranged enolate anions 4 on the imine function endocyclically.

Scheme I.



The results obtained, when 5-vinyloxazolidines 2 were treated with 1.5 equiv. of potassium hydride and 0.1 equiv. of 18-Crown-6[8] in tetrahydrofuran (THF) for 24 hr at 25°C, are summarized in Table 1. The pyrrolidines syntheses succeed with a variety of aliphatic and alicyclic ketones and even with hindered aldehydes. It is significant that 4-acetyl-2,2-diethylpyrrolidine 8 and 3-acetyl-1-azaspiro[4.4]nonane 9 were prepared in good yield by this procedure. These pyrrolidines were, however, obtained in very poor yield by 2-azonia-[3,3]-sigmatropic rearrangement.[2b] While the 1-azaspiro[4.5]decanes were also prepared in high isolated yields, 7 derived from 4-t-butylcyclohexanone was a mixture of two stereoisomers in a ratio of 3:2.[9]

If sodium hydride or n-butyllithium was used as the base with 18-Crown-6, 5-vinyloxazolidine 5 was recovered quantitatively even in refluxing THF, and thus, these bases were found ineffective.

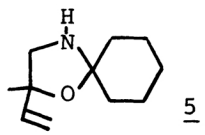
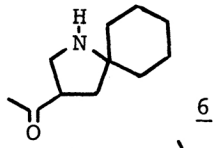
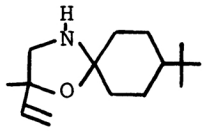
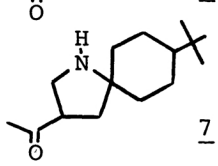
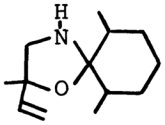
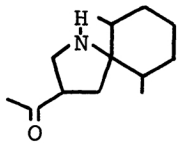
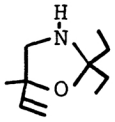
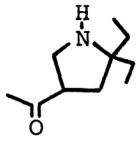
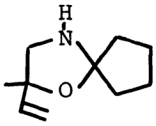
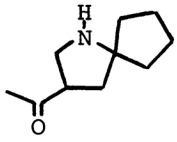
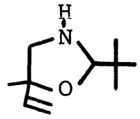
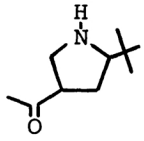
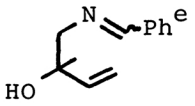
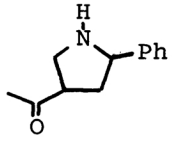
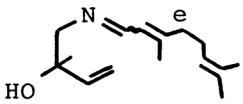
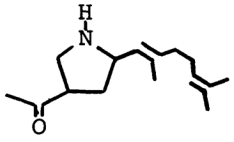
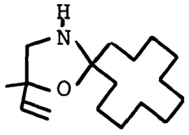
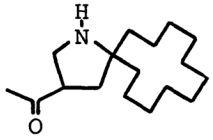
The method reported here is a mild procedure for pyrrolidine synthesis and the first publication of the base catalyzed oxy-2-aza-Cope rearrangement. With the success of this reaction, the pyrrolidine ring system can be constructed from 5-vinyloxazolidines under basic conditions as well as acidic conditions. It clearly seems that these methods should have wide applications especially in the natural products area.

The following procedure is representative:

3-Acetyl-1-azaspiro[4.5]decane, 6[11]

Two mmol of 2-methyl-2-vinyl-1-oxa-4-azaspiro[4.5]decane 5 was added dropwise to 3-mmol of prewashed potassium hydride suspended in 5-ml of THF at 0°C. After

Table 1. Preparation of 5-vinyloxazolidines 2 and 3-acetylpyrrolidines 1

Oxazolidines 2	B.p. of 2 °C/mmHg	Y% of 2[a]	Pyrrolidines 1	B.p. of 1 °C/mmHg	Y% of 1[a,f]
 5	73-75/3	92[b]	 6	80-85/0.05	79
	140-145/3	91[b]	 7	100/0.05	91
	120/3	58[c]		75-80/0.03	82[g]
	100-103/5	94[c]	 8	80-85/0.05	82[g]
	100-105/6	83[d]	 9	80/0.1	66
	110/250	93[d]		130-140/2	72
	120-125/6	99[d]		130-135/0.07	91
	105-110/0.05	56[d]		135-140/0.03	49
	120-130/0.05	92[c]		130-140/0.02	84

a) The yields were isolated yields. b) 1-Amino-2-methyl-3-buten-2-ol and carbonyl compounds were refluxed for 2-3 hr in benzene with azeotropic removal of water. c) Catalytic amount of TosOH was used under the condition of b). d) 1-Amino-2-methyl-3-buten-2-ol and carbonyl compounds were stirred in THF in the presence of excess Na_2SO_4 at 25°C. e) Spectral data supported the imine structure. f) The reaction time was 24 hr in the described conditions unless otherwise noted. g) The reaction time was 36 hr.

0.2 mmol of 18-Crown-6 was added, the solution was stirred for 24 hr at 25°C under N_2. Work-up[10] by adding 4 mmol of crystalline ammonium chloride and 2g of crystalline sodium sulfate hydrate ($Na_2SO_4 10H_2O$) gave the crude amine product. Distillation (bulb to bulb; bath temparature, 80-85°C/0.05 mmHg) yielded 79% of pure 3-acetyl-1-azaspiro[4.5]decane 6. IR (film) 3370, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$ δ) 2.17 (s, CH_3CO); ^{13}C-NMR ($CDCl_3$ δ) 209.1(C=O), 63.9(C-5), 52.6(C-2), 47.5(C-3), 39.7, 38.2, 37.3, 29.2($\underline{C}H_3CO$), 25.9, 23.9, 23.6.

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References and Notes

1. For recent reviews of sigmatropic rearrangement: F.E.Ziegler, Acc. Chem. Res., 10, 227 (1977) and G. B. Bennett, Synthesis, 1977, 589.
2. a) L. E. Overman and M. Kakimoto, J. Am. Chem. Soc., 101, 1310 (1979), b) L. E. Overman, M. Kakimoto, and M. Okawara, Tetrahedron Lett., in press.
3. S. J. Rhoads and N. R. Raulins, "Organic Reaction," John Wiley & Sons Inc., Vol.22, (1975), P.61, and for further examples, see 4a.
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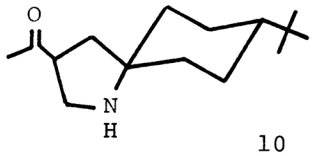
5. The required 5-vinyloxazolidines were prepared from 1-amino-2-methyl-3-buten-1-ol and carbonyl compounds by azeotropic dehydration in refluxing benzene or dehydration in THF in the presence of Na_2SO_4 at 25°C.
6. 1-Amino-2-methyl-3-buten-2-ol was prepared by the reaction between 1-bromo-2-methyl-3-buten-2-ol and 28% aqueous ammonium hydroxide solution at 60°C for 24 hr (yield, 70%) in the manner described by A. Mishra, S. N. Rice and W. Lwowski, J. Org. Chem., 33, 481 (1968).
7. J. H. Manson and R. F. J. Ingleby, J. Chem. Soc., 1958, 3639.
8. It is well known that 18-Crown-6 catalyzes the oxy-Cope rearrangement when KH is used as the base.[4] The present reaction was very slow at 25°C without 18-Crown-6 in THF. Although details of the effect of 18-Crown-6 on the rate of the rearrangement will be the subject of a future report, 0.1 equiv. of 18-Crown-6 seems to be enough for this reaction.
9. The ratio was confirmed by ^{1}H-NMR analysis in the presence of $Eu(FOD)_3$. The major isomer is expected 10: See reference 2b.



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10. Work-up with water or saturated aqueous ammonium chloride solution gave lower (65%) yield of 6. Work-up described here was convenient for this procedure, because the inorganic crystals could be separated very easily from the organic layer.
11. All new compounds were characterized by ^{1}H and ^{13}C-NMR, IR and Mass spectra.

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