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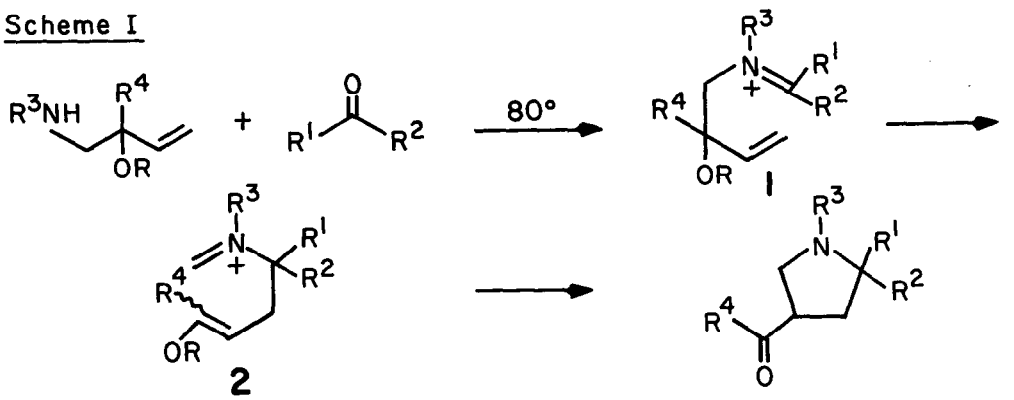
DIRECTED 2-AZONIA-[3,3]-SIGMATROPIC REARRANGEMENTS. A CONVENIENT PREPARATION OF SUBSTITUTED 1-AZASPIRO[4,5]DECANES

Larry E. Overman,*[1] Masa-aki Kakimoto, and Makoto Okawara
Department of Chemistry, University of California, Irvine, California, 92717; and Research Laboratory of Resources Utilization, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-Ku, Yokohama, Kanagawa, Japan

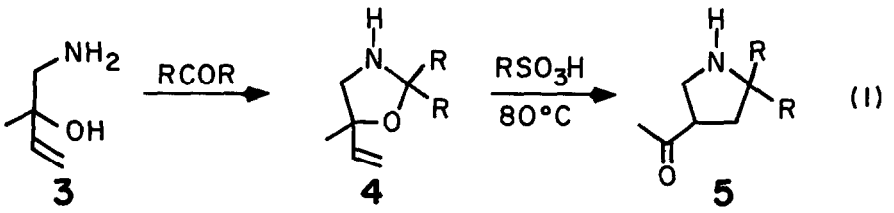
SUMMARY: 3-Acetylpyrrolidines are prepared from 5-methyl-5-vinyloxazolidines in a reaction which involves a directed 2-azonia-[3,3]-sigmatropic rearrangement.

We recently reported [2] that salts of 2-alkoxy-3-butenamines react with a variety of aldehydes to produce 3-acylpyrrolidines in a single step, and in excellent yield. This pyrrolidine synthesis exploited the ability of a properly placed oxygen substituent to direct the course of the low temperature 2-azonia-[3,3]-sigmatropic rearrangement [3] ($\underset{\sim}{1} \rightarrow \underset{\sim}{2}$) by capturing the rearranged sigmatropic isomer in an intramolecular Mannich fashion, (Scheme I, R^1=H). This reaction was not

Scheme I



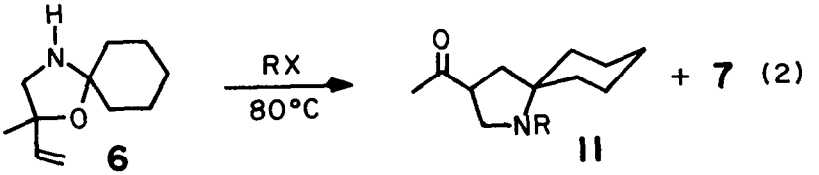
successfully extended to ketones, however, due to the inability to form the starting iminium ion $\underset{\sim}{1}$ in these cases.[2] We report in this letter that iminium ion $\underset{\sim}{1}$ may also be generated from an oxazolidine precursor. This approach (eq 1) allows cyclohexanones to be utilized as the carbonyl components in this pyrrolidine synthesis, and results in a convenient construction of substituted 1-azaspiro [4,5] decanes.



3 4 5

The required 5-vinyloxazolidines were prepared from readily available [4] 1-amino-2-methyl-3-buten-2-ol (3) by azetotropic dehydration in refluxing benzene, or alternatively at room temperature in THF in the presence of Na_2SO_4. The results obtained when oxazolidines 4 were treated with 1 equiv of anhydrous d-10-camphorsulfonic acid in refluxing benzene for 24 h are summarized in Table 1. Pyrrolidines 5 were formed in good yields from 5-vinyloxazolidines derived from cyclohexanones and aliphatic aldehydes. In this way the 1-azaspiro[4,5]decanes 7-9 were prepared in isolated yields of greater than 50% from their cyclohexanone precursors. It is significant that the 1-azaspirane formed from 4-t-butylcyclohexanone was predominantly a single isomer (92%)[5], and the stereochemical assignment for 8 follows from the expectation that sigmatropic rearrangement would occur preferentially [6] across the equatorial face of a cyclohexanone iminium ion intermediate. Azaspirane 7 was produced in lower yield (45%) from the direct [2] reaction of amino alcohol 3 and cyclohexanone, and was not formed to a significant extent when oxazolidine 6 was treated with 0.10 equiv of the acid catalyst. The imine prepared from cyclohexanone and 2-methoxy-2-methyl-3-butenamine also afforded azaspirane 7 (57% yield) when treated for 72 h in refluxing benzene with 1.0 equiv of p-toluenesulfonic acid monohydrate. Preliminary indications are that the use of ketones in the pyrrolidine synthesis of eq 1 may be limited to cyclohexanones, since 10 was formed in only low yield from 3-pentanone, and rearrangement of the 5-methyl-5-vinyloxazolidine derived from cyclopentanone afforded no recognizable 1-azaspiro [4,4]octane products.[7]

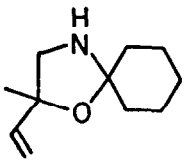
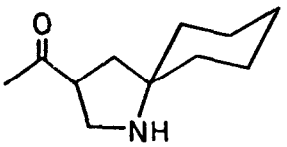
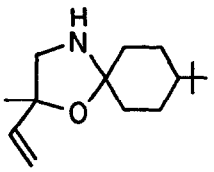
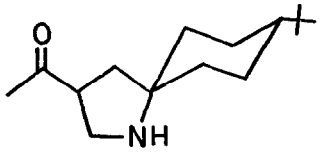
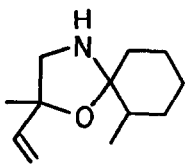
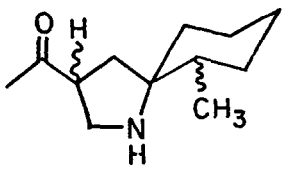
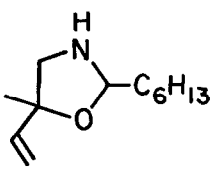
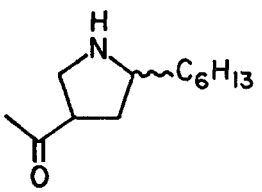
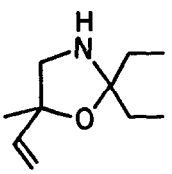
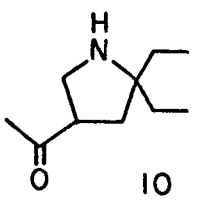
Treatment of oxazolidine 6 in refluxing benzene for 24 h with alkylating agents (1.0 equiv) afforded the 1-N-alkyl-1-azaspiro[4,5]decanes 11 in reasonable yield, together with smaller amounts of the nonalkylated azaspirane 7 (eq 2). Results are summarized in Table II.



6 11

The two-step procedure described here represents one of the most convenient constructions of the 1-azaspiro[4,5]decane ring system reported to date.[8] Moreover, the ability to utilize 5-vinyloxazolidines in directed 2-azonia-[3,3]-sigmatropic rearrangement synthetic strategies [2] further expands the potential of this mild carbon-carbon bond forming method.

TABLE I. Preparation of 3-Acetylpyrrolidines According to Eq. 1.

OXAZOLINE		ACETYLPYRROLIDINE	
 6	92% bp 75-5(3)[a]	 7	69%[b]
 8	91% bp 140-5(3)[a]	 8	70%[b]
 9	91%[c] bp 85(3)[a]	 9	55%[b,d]
 10	86%[c] bp 85(5)[a]	 10	65%[b]
	94%[c] bp 100-3(5)[a]	 10	9%[b]

[a]mm Hg. [b]Isolated bulb-to-bulb distillation: bath temperature: 80-120°C, 0.05 mm Hg. [c]A catalytic amount of p-toluenesulfonic acid was employed. [d]A mixture of four isomers.

TABLE II.

RX	Solvent	11,%	7,%
MeI	C_6H_6	54	17
MeOTs	C_6H_6	49	17
n-$C_8H_{16}I$	DMF	48	21
n-$C_6H_{12}I$	DMF	45	9

The following procedures are representative:

2-Methyl-2-vinyl-1-oxa-4-azaspiro[4,5]decane (6). A solution of cyclohexanone (2.95g, 30 mmol), 1-amino-2-methyl-3-buten-2-ol [4] (3.03g, 30 mmol), and 30 mL of benzene was heated at reflux for 2h with azeotropic removal of water. Concentration and distillation through a short Vigreaux column afforded 5.0g (92%) of 6: bp 73-75°C(3 mm); IR (film) 3300, 1450, 1080, 920 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ5.1-5.8 (m, CH=CH_2), 2.97 (d, J=1.7Hz, CH_2NH), 1.6 (m, NH), 1.29 (s, CH_3).

3-Acetyl-1-azaspiro[4,5]decane (7). A solution of 6 (543 mg, 3.00 mmol), d-10-camphorsulfonic acid (696 mg, 3.00 mmol), and 3 mL of anhydrous benzene was heated at reflux under N_2 for 3h. After the mixture cooled to room temperature, 3mL of 1 N NaOH was added and the amine product was isolated by ether extraction and dried (Na_2SO_4). Distillation (bulb-to-bulb; bath temperature 80-85°C; 0.05 mm) yielded 375 mg (69%) of pure 7: IR (film) 3370, 1710 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ2.17 (s, CH_3CO); ^{13}C-NMR ($CDCl_3$) δ209.1 (C=O), 62.9 (C-5), 52.6 (C-2), 47.8 (C-3), 39.7, 38.2, 37.3, 29.2 (CH_3CO), 25.9, 23.9, 23.6.

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References and Notes

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6. Cf. House, H.O.; Lubinkowski, J.; Good, J.J. J. Org. Chem. 1975, 40, 86.
7. In both of these cases low molecular weight, water soluble, products were produced.
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