MODIFIED AZA-CLAISEN REARRANGEMENT: GENERATION AND ISOMERIZATION
OF ALLYL ENAMMONIUM SALTS[1]

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SUMMARY: Base-promoted reaction of ketones and diethyl (diazomethyl)phosphonate in the presence
of allylic amines affords allylic enamines in good yields. These enamines undergo
[3,3]-sigmatropic rearrangement upon alkylation and heating at 80°C to iminium salts which can be
hydrolyzed to aldehydes. The procedure allows generation of quaternary carbon centers under mild
reaction conditions.

AZA-CLAISEN rearrangements, e.g., $RN(CH=CH_2)CH_2CH=CH_2 = RN=CHCH_2CH_2CH=CH_2$, have received
little attention in synthetic organic chemistry owing largely to the fact that the thermally
induced reaction requires temperatures some $100-150^\circ$C higher than the more familiar oxa-analog.[2]
Even the reports of Opitz, et al., that allyl enammonium salts (eq. 1, R = alkyl) undergo
[3,3]-sigmatropic rearrangements at 80°C failed to arouse substantial interest in the reaction
owing to the fact that the requisite salts were produced by allylation of N,N-dialkyl enamines[3]
and consequently were contaminated by C-allylated materials (eq. 1). Although this is of no
consequence with symmetrically substituted allylating agents, as both modes of reaction
eventually afford the same aldehyde upon hydrolysis, it is of considerable concern with
unsymmetrical materials, since mixtures of difficultly separable isomers result. A further
complication in the use of unsymmetrical allylating agents is the potential of their undergoing
both SN2 and SN2' attack by the enamine. A solution to the problems associated with C- vs.
N-allylation and application of the rearrangement of quaternary ammonium salts to the creation of
quaternary centers at carbon, an area of considerable current interest,[4] are reported herein.
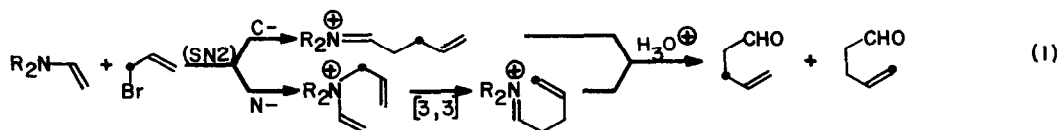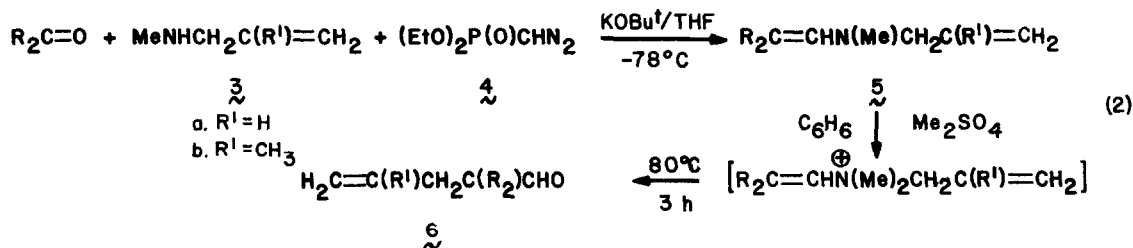

Brannock and Burpitt have noted that the allyl enamine, 1, undergoes N-methylation and

rearrangement when treated with methyl tosylate in refluxing acetonitrile to give 2 in 46% overall yield after hydrolysis.[5] With this result as a guideline, an approach to the synthesis of allyl enamines that promises to be of considerable generality has been developed, and it has been found that their <u>alkylation</u> and rearrangement can afford quaternary carbon centers in both acyclic and cyclic systems under relatively mild reaction conditions.
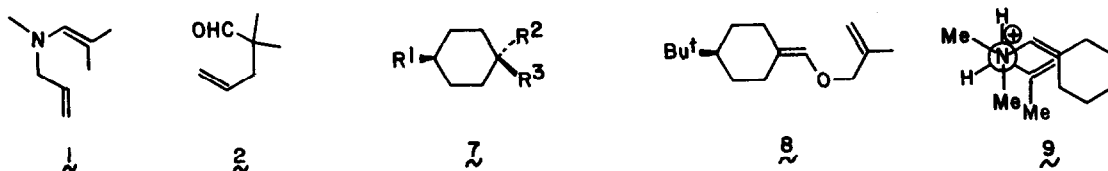
a. R^1 =Bu^t, R^2=CHO, R^3= allyl
b. R^1 =Bu^t, R^2=allyl, R^3= CHO
c. R^1 =H, R^2=CHO, R^3 = methallyl
d. R^1 =Bu^t, R^2,R^3=CHO, methallyl

Base-promoted reaction of diethyl (diazomethyl)phosphonate (DAMP)[6] and ketones at -78°C in the presence of a secondary allylic amine afforded the corresponding allyl enamines 5 (eq. 2) in good yields (Table), in analogy to the results obtained when saturated secondary amines were used in this reaction.[7] In runs 1-6, methylation of the enamine, heating at reflux in benzene, and hydrolysis afforded the expected 2-allyl aldehydes 6, again in uniformly good yields (Table). The selectivity for N- <u>vs.</u> C-alkylation was demonstrated in the case of run 2 by synthesis of an authentic sample of 1-methylcyclohexanecarbaldehyde (7, R^1 = H, R^2 = CH$_3$, R^3 = CHO), the product that would have been produced by C-methylation of the enamine, and showing by GC analysis that no more than 1% of it was present in the product obtained by the alkylation-rearrangement sequence.

$$R_2C\!=\!O \; + \; MeNHCH_2C(R^1)\!=\!CH_2 \; + \; (EtO)_2P(O)CHN_2 \xrightarrow[-78^\circ C]{KOBu^t/THF} R_2C\!=\!CHN(Me)CH_2C(R^1)\!=\!CH_2$$

3
a. R^1=H
b. R^1=CH$_3$

4

5

$$H_2C\!=\!C(R^1)CH_2C(R_2)CHO \xleftarrow[3\,h]{80^\circ C} \left[R_2C\!=\!CHN(Me)_2CH_2C(R^1)\!=\!CH_2\right]$$

6

C_6H_6 | Me$_2$SO$_4$

(2)

Interestingly, the stereochemical requirements of the rearrangement when an unsubstituted allyl moiety is present appear to be identical to those of the oxa-Claisen rearrangement itself. This conclusion is based on the fact that the mixture of aldehydes obtained in run 3 consists of 7a and 7b in the ratio of 77·23, which is the same value as that obtained by House, <u>et al.</u> from the isomerization of the corresponding allyl vinyl ether.[9] Stereochemical differences between the two varieties of [3,3]-sigmatropic rearrangement become evident, however, when there is

substitution at the 2-position of the allylic component of the 1,5-dienic system. As indicated in run 7, preparation of the allyl enamine 5 (R^1 = CH_3) using N-methyl (2-methyl)-2-propen-1-amine (3a) is successful, but its alkylation-rearrangement fails to produce the expected aldehyde 7c; only cyclohexanecarbaldehyde (7, R^1 = R^2 = H, R^3 = CHO) is obtained upon hydrolysis of the reaction mixture. In contrast, the thermal isomerization of the ether 8 is unexceptional, giving a mixture of the aldehydes 7d.[10] The source of this difference undoubtedly resides in the fact that rearrangement of the ammonium salt 9 by way of a chair-like transition state requires development of a 1,3-diaxial interaction, as shown in the Newman projection, and this raises the energy of the transition state substantially. No such problem attends the comparable transition state in the case of the ether 8, of course. Clearly, application of the modified aza-Claisen rearrangement to problems in synthesis must take into account the added steric considerations associated with the presence of the tetrahedrally substituted nitrogen atom in the 1,5-dienic system.

This type of rearrangement has potential advantages in cases where the conditions for the oxa-Claisen process are too demanding for molecules containing functional groups that are thermally labile.[11] Moreover, this approach to the aza-Claisen rearrangement has important advantages over that of Opitz, et al.[3] Unsymmetrically substituted allyl moieties can be incorporated without the problems associated with allylation of enamines; C-alkylation, if it were to occur at all, would eventually produce an aldehyde which is not isomeric with that derived from N-alkylation and therefore would be more readily separable from it.

The following procedure for the preparation of allylic enamines and for their subsequent alkylation, rearrangement and hydrolysis is representative. A dispersion of 1.3 mmol of potassium t-butoxide in 1 mL of dry THF and 10 mmol of freshly distilled amine 3 contained in a round-bottomed flask were cooled to -78 °C, and a solution of 1.2 mmol of DAMP (4) in 1 mL of dry THF was added dropwise. The mixture was stirred for five min and 1 mmol of the ketone dissolved in 1 mL of dry THF was then introduced in a dropwise fashion during two min. After being stirred at -78 °C for 3 h, the reaction mixture was allowed to warm to RT. Solvent was removed under reduced pressure, and the residue was extracted thoroughly with anhydrous ether. The combined extracts were concentrated under reduced pressure to give crude allyl enamine 5.

A solution of 2.6 mmol of crude product in 10 mL of anhydrous benzene was combined with 3 mmol of freshly distilled dimethyl sulfate, and the solution was heated at reflux under an atmosphere of nitrogen for 2.5-3 h. The resulting mixture was then stirred at RT for 6 h with 25 mL of 0.5 $\underline{M}$ hydrochloric acid, after which it was extracted with three 25-mL portions of ether. The combined extracts were washed sequentially with 25-mL portions of 10% aqueous $NaHCO_3$ and of brine and dried ($MgSO_4$). Removal of solvent afforded the desired aldehyde 6.

TABLE. DATA FOR PREPARATION OF ALLYL ENAMINES AND ALDEHYDES.

RUN	KETONE	AMINE[a]	ALLYL ENAMINE (%)[b,c]	ALDEHYDE (%)[b-d]
1	Cyclopentanone	3a	63	78
2	Cyclohexanone	3a	66	77
3	4-Bu^t-Cyclohexanone	3a	79	72
4	2-Adamantanone	3a	68	68[e]
5	5-Nonanone	3a	70	84 (75)[f]
6	Cyclooctanone	3a	82	76 (72)[f]
7	Cyclohexanone	3b	60	--

[a] Amines 3a and 3b were prepared according to the methods of Raphael, R.A.; Parker, W. J. Chem. Soc. 1955, 1723, and of Weston, A.W.; Ruddy, W.A.; Suter, C.M. J. Am. Chem. Soc. 1943, 65, 674, respectively.

[b] Yields based on analysis of ^{1}H-NMR spectra of the allyl enamines and aldehydes using benzene as the internal standard.

[c] Characterized by ^{1}H-NMR, IR, and high resolution mass spectral data.

[d] Satisfactory combustion analyses were obtained on the 2,4-dinitrophenylhydrazones of all new aldehydes.

[e] Obtained after hydrolysis with 10% aqueous HCl at reflux for 3 h.

[f] Isolated yield.

FOOTNOTES AND REFERENCES

1. The support of this research by the National Institutes of Health (GM 29972) is gratefully acknowledged.

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