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REACTION OF DIENAMINES WITH ALLYLIC HALIDES[1]. A CASE OF FACILE MULTIPLE AZA-COPE REARRANGEMENT.

P. Houdewind[2] and U.K. Pandit*

Organic Chemistry Laboratory, University of Amsterdam.
Nieuwe Achtergracht 129, Amsterdam. The Netherlands.

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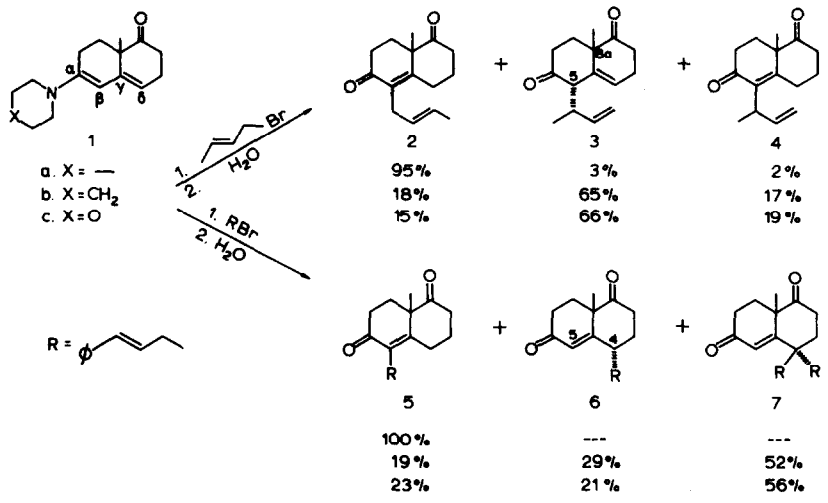
The course of the reaction of enamines with allylic halides is dominated by the nature of the base-component of the enamine system[3]. Since dienamines constitute nucleophiles with three potential sites of electrophilic attack, their reaction with allylic halides is of general mechanistic and synthetic interest.

The results of the reactions of dienamines 1a-c with crotyl and cinnamyl bromides (0°, CH_3CN, 65hr) are presented in Fig. 1. The ratio of the products 2,3 and 4 was determined by GLC and represents an average of two runs. The cinnamyl derivatives 5,6 and 7 were isolated by column chromatography. Isolated yields of the pro-products varied from 70-90% - crotyl derivatives - to 50-70% in the case of the cinnamyl substituted diketones. Unreacted dienamines - identified as the α,β-unsaturated ketone corresponding to 1a-c - accounted for the rest of the material balance. Structures of diketones 2-7 followed from their spectral (IR, UV, NMR) data. The stereochemistry of 3 was deduced from the solvent shifts of the C_5-H and C_{8a}-CH_3 signals. ($CDCl_3$ δ: C_5-H 3.06 d, J=8Hz, C_{8a}-CH_3 1.13 s. C_6D_6 δ: C_5-H < 2.86, falls under unresolved signal of methylene protons; C_{8a}-CH_3 0.97 s). The upfield shifts in going from $CDCl_3$ to C_6D_6 attest to axial configurations for C_5-H and C_{8a}-CH_3[4]. In view of the possible unpredictable influence of the crotyl substituent on the solvent shift of C_5-H, further evidence for the stereochemistry of 3 was developed by its conversion (Δ/xylene, quantitative) into 10 (Fig. 2) and examining the NMR spectrum of the latter compound. Bhacca and Williams[5] have shown that C_4-protons of C_6α-substituted Δ^4-3-keto steroids appear as a doublet (J=1.6-2.0 Hz) due to coupling with the pseudo-axial C_6β-proton. In 10, as well as in 6, the C_5-H appears as a doublet at δ 5.88 and 5.94, respectively, with a coupling of 1.5 Hz. This attests to a β-configuration for the C_4-H in both compounds. Since the formation of 10 from 3 represents a suprafacial [3,3] sigmatropic rearrange-

ment, proceeding via a chair-like transition state 9b[6], it follows that the configuration of the 1-methyl-2-propenyl substituent in 3 must be the same, namely α-, as in 10.

The ratios of 2/3+4 (4 represents the product of double bond migration in 3 or its precursor 11a during workup) in the reactions of 1a-c with crotyl bromide are similar to those observed with the same halide with simple enamines[3]. These results arise presumably due to operation of similar processes. Formation of 2, represents the direct C-alkylation reaction, being highly favoured by the pyrrolidine dienamine 1a, while dienamines 1b and 1c undergo an initial N-alkylation, which is followed by a suprafacial aza-Cope rearrangement (8, R = Me).

The nature and the formation of products of the reaction of 1a-c with cinnamyl bromide deserve comment. Alkylation at the β-carbon of 1a is consistent with the reactivity pattern observed thus far with the pyrrolidine (di)enamines. The formation of 6 may be explained by an initial N-alkylation and rearrangement, as observed with crotyl bromide, followed by a fast second aza-Cope rearrangement (9a, R = ϕ) of the intermediate iminium salt 11b. It will be noted that two factors affect the second rearrangement step: (a) conjugative stabilization of the iminium function and (b) restoration of the cinnamyl chromophore, in the resulting product. The significance of factor (b) may be assessed from the fact that while intermediate 11a can be quenched to yield 3 and 4, all attempts to isolate the hydrolytic product of 11b were unsuccessful. Additional evidence supporting the proposed mechanism for the formation of 6 was derived from the following experiment. Treatment of dienamine 14 with ∿ 2 eq. of CH_3I (CH_3CN, 0^0, 85hr) yielded exclusively 6 upon hydrolysis. Furthermore, addition of N-(1-cyclohexenyl)pyrrolidine, under appropriate conditions, to the reaction mixture in the last-mentioned experiment, did not result in the formation of detectible (GLC) amounts of 2-cinnamylcyclohexanone. These experiments indicate that the cinnamyl group in the ammonium salt 15 migrates readily from N- to the δ-carbon of the dienamine chromophore without becoming accessible (free) to interception by the reactive pyrrolidine enamine of cyclohexanone. Combined with the results of the reaction of 1b,c with crotyl bromide, a double aza-Cope rearrangement explains the origin of 6 most satisfactorily.


a
β
γ
δ
X
1
a. X = —
b. X = CH2
c. X = O
1. Br
2. H2O
1. RBr
2. H2O
R = ϕ
2
95%
18%
15%
3
3%
65%
66%
4
2%
17%
19%
5
100%
19%
23%
6

29%
21%
7

52%
56%

Fig. 1

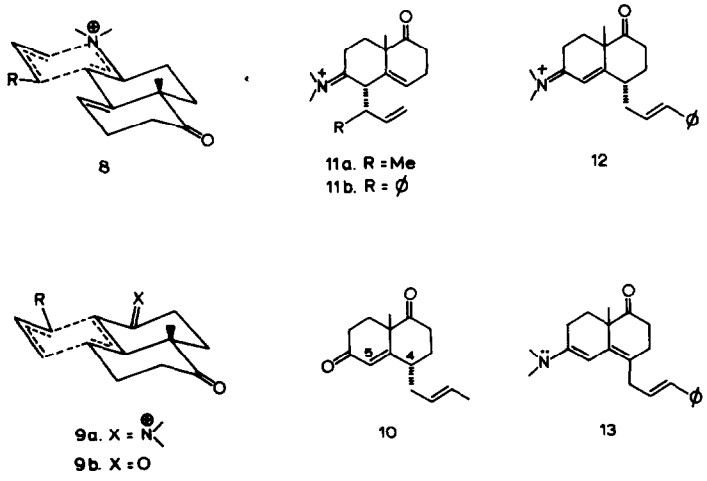
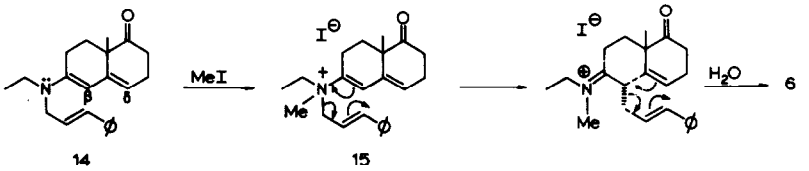

8
11a. R = Me
11b. R = ϕ
12
9a. X = N
9b. X = O
10
13

Fig. 2



The formation of 7 may be rationally explained by considering a loss of proton by intermediate 12 to yield 13, presumably to an unreacted dienamine system, followed by N-alkylation and two aza-Cope rearrangements. It is significant that dialkylation, which, due to steric factors is seldom observed with enamines, becomes the predominant process when the site of the initial reaction is remote from the first substituent. Obviously, steric effects to the introduction of the second substituent would be minimum for an intramolecular process.

The control of reactivity patterns by the appropriate choice of conditions, the enamine and the halide reagent, is of synthetic interest. The facile aza-Cope rearrangement appears to be specific to systems containing a charged N-atom. This aspect of the rearrangement and its implications in the general theory of electrocyclic processes is being further examined.

Correct spectral and/or analytical data have been obtained for all compounds described in this communication.

References.

*To whom all correspondence should be addressed.

1. Functionalized Enamines Part XIX. For Part XVIII see P. Houdewind, J.C. Lapierre Armande and U.K. Pandit, Tetrahedron Letters 591 (1974).

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