INFLUENCE OF THE HETEROCYCLIC BASE-COMPONENT ON THE REACTION OF ENAMINES WITH ALLYLIC HALIDES

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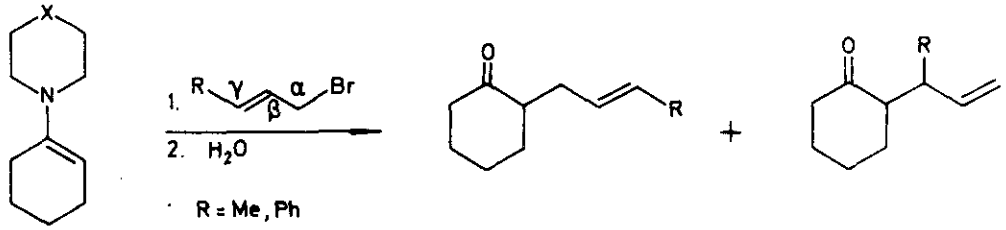
Pyrrolidine, piperidine and morpholine enamines of cyclohexanone (1a-c) react with allylic halides to give *mixtures of isomeric alkylated products in which the* isomer-ratio can be correlated with the chemical shifts (^{1}H and ^{13}C) of the β-carbon of the enamines.

Enamine reagents are frequently prepared from carbonyl compounds and (hetero)-cyclic secondary amines. Recent work from this laboratory has drawn attention to the important role of the base-component in the reaction of enamines[2,3]. We now present results which show that the reactivity pattern of enamines with allylic halides is profoundly influenced by the nature of the heterocyclic base-component.

Enamines are known to react with allylic (and propargylic) halides to give two types of substituted products; those in which the integrity of the starting electrophilic substituent is conserved and those in which the substituent is present in its rearranged form[4a-g]. The formation of the latter products has been shown to proceed via an initial N-alkylation reaction, followed by an Aza-Cope rearrangement of the resulting ammonium salt[4c,d].

When enamines 1a-c were allowed to react with crotyl and cinnamyl bromides (0°, CH_3CN, 65h), the reaction mixture, after hydrolysis, yielded isomeric ketones 2 (R = Me,Ph) and 3 (R = Me,Ph) in good yield. The ratio of 2:3 was determined by GLC; the results are presented in Fig. I.



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	2 (%)		3 (%)	
	R = Me	R = Ph	R = Me	R = Ph
a. X = —	71	87	29	13
b. X = CH_2	15	11	85	89
c. X = O	10	20	90	80

Total yield: R = Me, 48-59%; R = Ph, 78-85%. Unreacted enamine, identified as cyclohexanone, accounted for the rest of the reaction mixture.

Fig. I

In the light of the known mechanism of the reaction of enamines and allylic halides, allylated cyclohexanones 2 and 3 may be regarded as the products of C- and N-electrophilic attack of the enamines, respectively (Fig. II).

That formation of 3 (R = Me,Ph) involved intermediates 4 and 5 was strongly supported by the observation that reaction of enamine 6 with methyl iodide, under conditions of alkylation of 1a-c, yielded 3 (R = Ph) as the major (>80%) product. Since 6 is stable under the reaction conditions, these results imply that ammonium salt 7 undergoes an extremely facile Aza-Cope rearrangement[5].

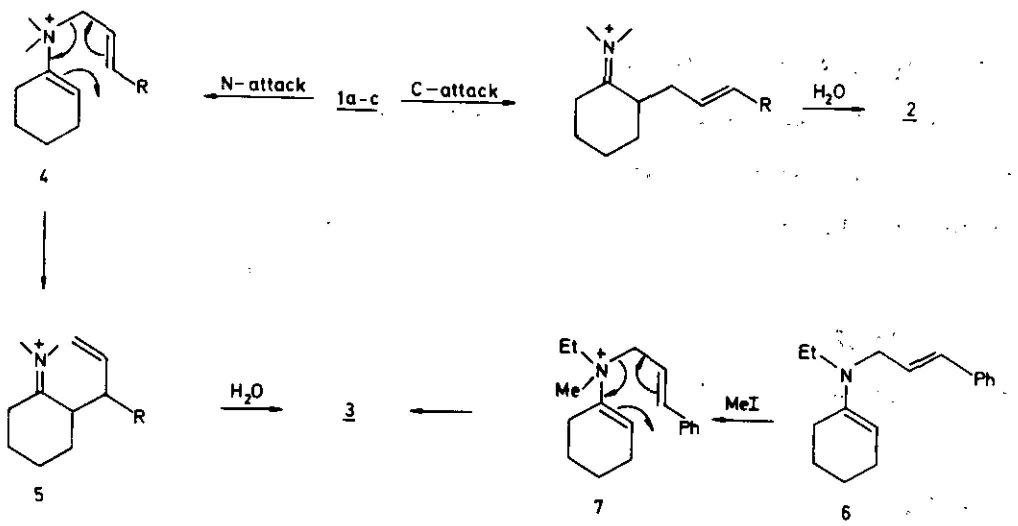

Fig. II

It is apparent from the results in Fig. I that while the pyrrolidine enamine (1a) undergoes predominant C-alkylation, piperidine and morpholine enamines (1b,c) both (initially) undergo N-alkylation as the major process. The difference between the reactivity patterns of 1a and 1b, enamines whose base-components possess similar basicities (Table I) and environment around the nitrogen, can be best rationalized in terms of the ease of formation of an exo-cyclic double bond to the 5-membered pyrrolidine ring[6a,b]. While such a factor would be undoubtedly involved in the transition state of the enamine reaction (at C_β), chemical shifts of H_β and C_β (Table I) suggest that - assuming these values reflect electron densities at that centre[7a,b] - the dipolar resonance *structure of the enamine contributes more significantly to the ground state* of 1a than to that of 1b. It is noteworthy that the C/N ratios of alkylation of enamines *1a-c*, with allylic halides, parrallel the chemical shifts of the β-carbons and β-protons of the enamines rather than the basicity constants of the corresponding base-components.

Enamine	pK_a(Base)	H_β^a	C_β^a	C/N Allylation	
				R = Me	R = Ph
1a	11.32	4.29	93.4	2.45	6.7
1b	11.20	4.64	100.1	0.17	0.12
1c	8.4	4.67	100.5	0.11	0.25

^{a}ppm from TMS

Table I

These results emphasize the importance of the selection of the base-component in preparing an enamine-reagent for synthetic objectives.

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