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

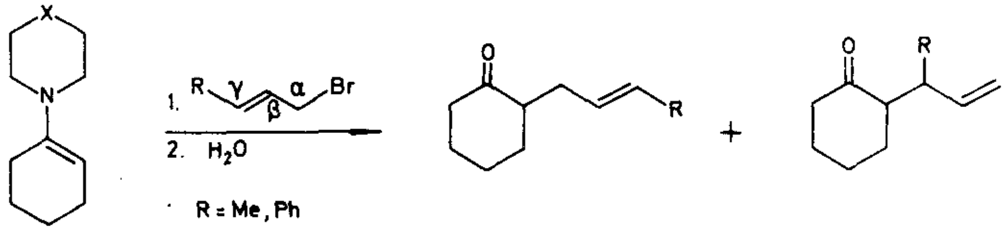
Pieter Houdewind[1] and Upendra K. Pandit*
Organic Chemistry Laboratory, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.
and
Ajay K. Bose, Raymond J. Brambilla and George L. Trainor
Stevens Institute of Technology, Hoboken, N.J., U.S.A.

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 (^1H 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.



1

	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].

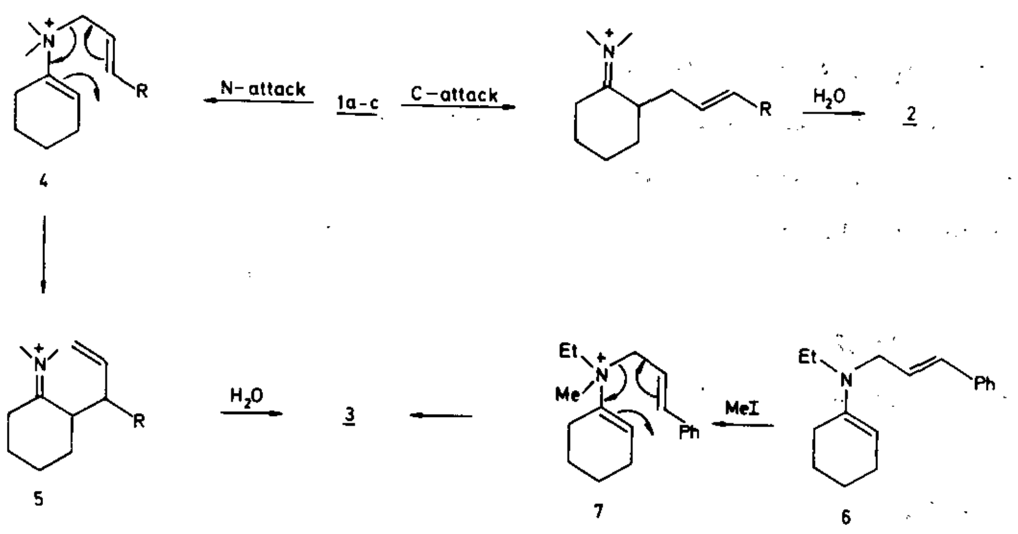


Fig. II

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.

ACKNOWLEDGEMENT. The work was carried out in part under auspices of the Netherlands Foundation for Chemical Research (SON) and with financial support from the Netherlands Organization for Advancement of Pure Research (ZWO).

REFERENCES

1 Taken in part from the doctorate thesis of P. Houdewind.

2 U.K. Pandit and S.A.G. de Graaf, Chem.Comm., 1970, 381.

3 U.K. Pandit, S.A.G. de Graaf, C.T. Braams and J.S.T. Raaphorst, Rec.Trav.Chim., 1972, 91, 799.

4 (a) G. Opitz, H. Hellmann, H. Mildenberger and H. Suhr, Ann., 1961, 649, 36;
  (b) G. Opitz and H. Suhr, ibid., 1961, 649, 47;
  (c) G. Opitz, ibid., 1961, 650, 122;
  (d) K.C. Brannock and R.D. Burpitt, J.Org.Chem., 1961, 26, 3576;
  (e) G.F. Hennion and F.X. Quinn, ibid., 1970, 35, 3054;
  (f) P. Cresson and J. Corbier, C.R. Acad.Sci., Ser C, 1969, 268, 1614;
  (g) J. Corbier and P. Cresson, ibid., 1970, 270, 2077.

5 E. Winterfeldt and W. Franzischka, Chem.Ber., 1967, 100, 3801.

6 (a) H.C. Brown, J.H. Brewster and H. Schechter, *J.Amer.Chem.Soc.*, 1954, **76**, 467;

(b) H.C. Brown, *J.Chem.Soc.*, 1956, 1248.

7 (a) T. Tokuhiro and G. Fraenkel, *J.Amer.Chem.Soc.*, 1969, **91**, 5005;

(b) J.E. Bloor and E.L. Breen, *J. Phys.Chem.*, 1968, **72** 716;

(c) O. Kajimoto and T. Fueno, *Tetrahedron Lett.*, 1972, 3329.

Received, 7th August, 1973