Tetrahedron Letters,Vol.26,No.21,pp 2577-2580,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

REGIOSELECTIVITY OF ENAMINE REACTIONS. PREFERENTIAL 2,2-DISUBSTITUTION OF 2-METHYLCYCLOHEXANONE IMINES

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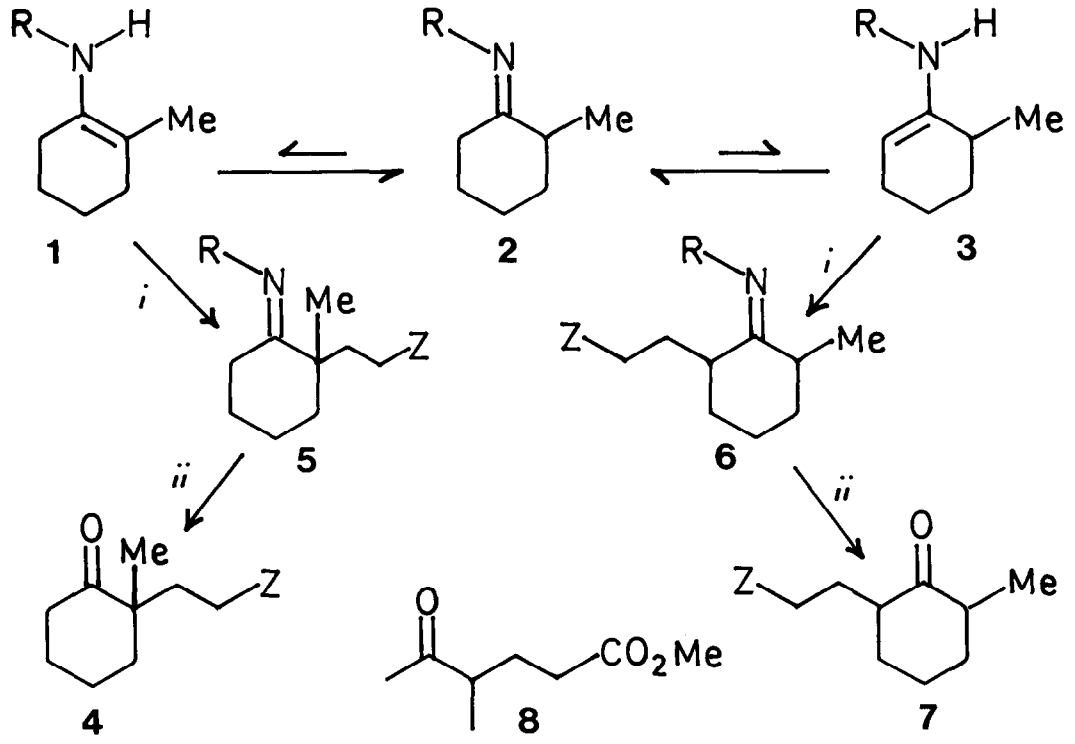
Summary: *Secondary enamines, derived from imines of unsymmetrical α-substituted ketones, react with electrophilic alkenes at the more substituted position to give α,α-disubstituted ketones on hydrolysis.*

Spectroscopic studies[1,2] of imine-enamine tautomerism have shown that, unless the secondary enamine is stabilised by further conjugation with an unsaturated system[1,3,4,5], the equilibrium is usually almost completely in favour of the imine form. With a few exceptions, such as the t-butylamine imine of cyclohexanone ($\delta_{=CH}$ 4.6),[6] signals due to the enamine tautomer cannot be observed in the ^{1}H n.m.r. spectra of imines. Nevertheless imine-enamine tautomerism has been clearly demonstrated in reactions which involve the enamine form reacting with a variety of electrophilic reagents at the α-position to the original carbonyl function (C-β of the enamine)[2,7,8,9,10] and, despite their thermodynamic instability, methods have been developed for the isolation of secondary enamines[11].

The object of the present study was to investigate the regioselectivity of the reaction between electrophilic alkenes and imines of unsymmetrical ketones. The underlying hypothesis was that the imine of 2-methylcyclohexanone **2** would be in equilibrium mainly with the more substituted secondary enamine **1** rather than the less substituted double bond isomer **3**. The reason for this is that enamine **1** is stabilised over enamine **3** by the hyperconjugative interaction of the methyl group without incurring the allylic destabilization [i.e. $A^{(1,3)}$ strain[12]] normally associated with a tertiary enamine,[13,14] since a bulky N-alkyl substituent or ring residue in the latter has been replaced by a hydrogen atom (in **1** and **3**). Furthermore since there is no $A^{(1,3)}$ strain present in the imine (**5**) produced by alkylation of enamine **1**, and minimal $A^{(1,3)}$ strain in the transition state leading to it, we predicted that alkylation would give mainly the 2,2-disubstituted cyclohexanone **4** on hydrolysis, rather than the 2,6-



Reagents: (i) CH_2=CH-Z (-H^+); (ii) H_2O, Δ; Z = CO_2Me, CN, SO_2Ph

disubstituted cyclohexanone **7**[15,16]. We now report that these predictions have been fully verified.

The reaction of methyl acrylate with imines of 2-methylcyclohexanone, under various conditions, is summarised in the Table. Under all conditions the 2,2-disubstituted ketone **4** (Z = CO_2Me) was the main product. The benzylamine and cyclohexylamine imines gave comparable yields of 2,2-disubstituted product, but the amount of 2,6-disubstitution appeared to be greater for the latter (Table 1; Nos. 2 and 5). The aniline imine gave very little product (Table 1; No. 6), presumably due to stabilisation of the imine tautomer and/or low reactivity of the enamine tautomer. The benzylamine imine has therefore been used in our preliminary investigations into the optimisation of the experimental conditions. Best yields have so far been obtained in methanol as solvent using a large excess of alkylating agent (Table 1; No. 4) for reasons which have not yet been ascertained. The use of aprotic solvents of low dielectric constant (benzene, toluene) gave very low yields even on prolonged reaction (Nos. 7 and 8). However these yields were significantly improved by the use of a solvent of high dielectric constant (acetonitrile; No. 9) or by the addition of weakly acid (No. 10) or base (Nos. 11-14) catalysts, presumably due to catalysis of the imine-enamine equilibrium.

Table: Reaction of imines of 2-methylcyclohexanone with methyl acrylate[a]

No.	Imine	Equivalents of methyl acrylate	Solvent	Reaction time (h)	Other additives	% Yield[b] 2,2-	% Yield[b] 2,6-[c]
1	Benzylamine	1	MeOH	4	-	13	2
2	Benzylamine	2	MeOH	4	-	46	4
3	Benzylamine	2	MeOH	24[d]	-	45	3
4	Benzylamine	5	MeOH	4	-	64	4
5	Cyclohexylamine	2	MeOH	4	-	42	9
6	Aniline[e]	2	MeOH	4	-	3	Trace
7	Benzylamine	2	Benzene	68	-	3	0
8	Benzylamine	2	Toluene	68	-	33	0
9	Benzylamine	2	CH_3CN	95	-	50	2
10	Benzylamine	2	Benzene	68	Me_2NH, HCl[f]	32	0
11	Benzylamine	2	Benzene	68	Et_3N[f]	32	0
12	Benzylamine	2	Benzene	24	4-DAP[f,g]	40	1
13	Benzylamine	2	Benzene	24	4-DAP[g,h]	49	1
14	Benzylamine	2	MeOH	4	4-DAP[f,g]	59	5

[a] At boiling point of dry solvent unless stated otherwise. [b] Analysed by GLC. [c] Mixture of stereoisomers. [d] At room temperature. [e] Mostly unreacted 2-methylcyclohexanone recovered. [f] One equivalent. [g] 4-Dimethylaminopyridine. [h] 0.1 Equivalents.

In preliminary investigations into the reaction of N-(2-methylcyclohexylidene) benzylamine (**2**, R = $PhCH_2$) with acrylonitrile and phenyl vinyl sulphone in methanol, the spectroscopic evidence again shows quite definitely that reaction has occurred at the more substituted position to give the 2,2-disubstituted ketone **4** (Z = CN or SO_2Ph, respectively) on hydrolysis. The reaction of methyl acrylate with N-(2-butylidene)benzylamine, in methanol, gave methyl 4-methyl-5-oxohexanoate (**8**) on hydrolysis, and indicates that this methodology can be used to direct reaction to the more substituted position of acyclic as well as cyclic ketones.

Acknowledgements

Financial assistance from the Council for Scientific and Industrial Research and the University Research Fund is gratefully acknowledged. We also thank Mrs. C.M.J. Day-Lewis (Sugar Milling Research Institute) for some of the GLC determinations, Mr. G.J. Davison for participating in the early stages of this work, and Mangosuthu Technikon for leave of absence (for B.R.).

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15. The step **3** → **6** has been shown to be irreversible by exposure of **6** (prepared from **7**) to the same reaction conditions [i.e. methanol (4 h, Δ) or benzene (68 h, Δ) with or without alkylating agent]. No 2,2-product (**4**) was formed (GLC). Consequently there is no question of **6** being formed preferentially and then rearranging into **5**.

16. It is difficult to envisage **1** reacting appreciably more rapidly than **3**, whether by reactant-like or product-like transition state. The preference for the formation of **5** over **6** can therefore most probably be attributed to the extremely small amount of **3** present at equilibrium.

(Received in UK 28 January 1985)