Imine-Enamine Tautomerism – Nucleophilic Reactions of Imines

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A reinvestigation of the reactivity of N-isopropylidene cyclohexylamine to methyl acrylate by GC-MS analysis has shown that the major product is the β -aminoester (**9**) formed by the N-alkylation of cyclohexylamine which may be generated by a dimerisation-elimination sequence. A number of other products resulting from N- and C-alkylation of the ketimine have been identified.

Tertiary enamines (**1**) are versatile intermediates in organic synthesis [1, 2] and have also been invoked as key intermediates in alkaloid biosynthesis [3]. Secondary enamines predominantly exist as the imine (**2**) rather than the enamine (**3**) and a mobile tautomeric equilibrium exists between these two forms [4]. Our earlier studies on the naturally occurring ketimine harmaline (**4**) showed that ketimines are ambident nucleophiles and it was found possible to control the course of the reactions of harmaline (N- or C-alkylation) by adjusting the reaction conditions [5] (Scheme 1). A report in the

Scheme 1.

literature that exclusive C-alkylation of ketimines occurs in reaction with electrophilic olefins [6, 7] was therefore contrary to our experience on the behaviour of harmaline which afford both N- and C-alkylated products and led us to examine the behaviour of N-isopropylidene cyclohexylamine (**7**) with various electrophilic olefins. The major product isolated in each case was the N-alkylated cyclohexylamine which was thought to be formed by the N-alkylation of the ketimine, followed by hydrolysis during work up (Scheme 2).

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Scheme 2.

(Peak No. 6, Fig. 1)

Recently Pfau and co-workers have repeated our work and confirmed the formation of the N-alkylated cyclohexylamine though they obtained this in low yields, and they account for its formation by a dimerisation elimination sequence (Scheme 3), re-

Scheme 3.

sulting in the formation of cyclohexylamine which then undergoes alkylation with methyl acrylate to afford **9** [9]. These findings have led us to undertake a reinvestigation of the reaction products obtained in this reaction by a GC-MS analysis.

N-Isopropylidene cyclohexylamine was prepared by the method of Campbell [10] and was refluxed with equimolar quantity of methyl acrylate in dry benzene for 14.5 h. GC-MS analysis of the crude mixture revealed the presence of at least twenty compounds. Out of these the fifteen major compounds have been identified. The mass spectra of all twenty compounds are tabulated in Table I and the relative percentages of these compounds are apparent from the GC plot (Fig. 1).

In agreement with our previous observation the predominant product (peak No. 6 Fig. 1) obtained was the β -amino ester (Scheme 2) $\text{M}^+ = m/e$ 185 and not the C-alkylated product described by the French

group. The formation of each product is rationalised in Schemes 3 to 16.

Table I.

Peak Nos.	Com-pounds	Mass spectra
1	—	<i>m/e</i> 93 (M^+ , 10%), 92 (96%), 91 (98%), 85 (2%), 83 (14%), 78 (32%), 65 (4%), 63 (10%), 55 (8%)
2	—	<i>m/e</i> 98 (M^+ , 32%), 83 (68%), 78 (3%), 63 (2%), 55 (100%)
3	7	<i>m/e</i> 139 (M^+ , 28%), 138 (12%), 125 (10%), 111 (6%), 110 (26%), 98 (16%), 97 (24%), 96 (84%), 84 (38%), 83 (84%), 68 (48%), 58 (100%), 54 (91%)
4	—	<i>m/e</i> 152 (M^+ , 6%), 124 (4%), 112 (34%), 101 (12%), 96 (10%), 85 (36%), 74 (60%), 59 (88%), 55 (100%)
5	26	<i>m/e</i> 179 (M^+ , 32%), 164 (100%), 150 (4%), 136 (36%), 122 (20%), 108 (22%), 96 (39%), 82 (88%), 67 (36%), 55 (100%)
6	9	<i>m/e</i> 185 (M^+ , 43%), 156 (20%), 142 (100%), 141 (32%), 129 (12%), 112 (66%), 102 (22%), 82 (22%), 68 (68%), 56 (62%)
7	—	<i>m/e</i> 219 (M^+ , 6%), 204 (30%), 191 (2%), 176 (22%), 162 (4%), 122 (28%), 107 (12%), 95 (20%), 82 (100%), 67 (14%), 55 (60%)
8	14	<i>m/e</i> 225 (M^+ , 6%), 210 (4%), 194 (8%), 182 (6%), 166 (20%), 152 (40%), 139 (89%), 124 (64%), 112 (52%), 96 (38%), 83 (100%), 70 (30%), 55 (100%)
9	15	<i>m/e</i> 265 (M^+ , 12%), 250 (66%), 222 (16%), 206 (4%), 192 (35%), 178 (20%), 164 (30%), 152 (14%), 128 (34%), 110 (22%), 96 (34%), 82 (100%), 67 (14%), 55 (72%)
10	16	<i>m/e</i> 271 (M^+ , 15%), 228 (100%), 242 (4%), 212 (2%), 198 (96%), 156 (8%), 142 (14%), 116 (52%), 84 (52%)

Table I (continued).

Peak Nos.	Com-pounds	Mass spectra
11	—	<i>m/e</i> 305 (M^+ , 6%), 290 (8%), 262 (10%), 232 (10%), 204 (18%), 176 (18%), 136 (16%), 108 (10%), 82 (100%)
12	17	<i>m/e</i> 311 (M^+ , 2%), 280 (12%), 252 (4%), 242 (50%), 225 (72%), 198 (20%), 182 (8%), 152 (82%), 124 (74%), 96 (16%), 83 (100%)
13	18*	<i>m/e</i> 311 (M^+ , 7%), 275 (13%), 268 (2%), 252 (8%), 238 (47%), 225 (30%), 215 (16%), 198 (14%), 145 (41%), 138 (82%), 128 (100%), 96 (90%), 83 (55%), 52 (82%)
14	19	<i>m/e</i> 351 (M^+ , 8%), 336 (32%), 320 (10%), 310 (8%), 278 (30%), 265 (12%), 250 (11%), 237 (5%), 214 (6%), 192 (10%), 182 (15%), 164 (28%), 148 (10%), 108 (8%), 82 (100%), 52 (65%)
15	20*	<i>m/e</i> 351 (M^+ , 2%), 320 (5%), 278 (6%), 265 (10%), 250 (3%), 194 (2%), 152 (3%), 124 (32%), 83 (100%)
16	21	<i>m/e</i> 351 (M^+ , 13%), 320 (12%), 278 (28%), 250 (53%), 222 (10%), 192 (6%), 164 (8%), 137 (25%), 128 (100%), 96 (46%), 83 (32%), 52 (59%)
17	22*	<i>m/e</i> 351 (M^+ , 11%), 320 (8%), 278 (45%), 265 (98%), 238 (6%), 196 (12%), 192 (94%), 164 (32%), 176 (8%), 136 (12%), 110 (8%), 83 (18%), 52 (44%)
18	23	<i>m/e</i> 366 (M^+ , 9%), 338 (2%), 325 (17%), 311 (16%), 284 (5%), 252 (5%), 237 (18%), 225 (20%), 210 (15%), 182 (16%), 150 (12%), 128 (100%), 96 (44%), 83 (28%), 52 (45%)
19	24	<i>m/e</i> 366 (M^+ , 5%), 325 (30%), 311 (17%), 284 (3%), 263 (2%), 238 (42%), 204 (2%), 182 (3%), 156 (3%), 124 (30%), 83 (100%), 52 (48%)
20	25	<i>m/e</i> 436 (M^+ , 8%), 423 (2%), 406 (16%), 364 (32%), 350 (14%), 336 (31%), 278 (10%), 250 (28%), 214 (32%), 182 (51%), 168 (49%), 149 (23%), 136 (94%), 108 (42%), 81 (45%)

* The structural assignment of compounds have been made on the basis of mass spectral fragmentation.

It was observed that inspite of careful distillation the ketimine (**7**) contained significant quantities of cyclohexylamine, which may be formed by an intramolecular dimerization reaction to afford **11** followed by an intramolecular deamination to give the ketimine (**12**) and cyclohexylamine (**13**). The form-

ation of the N-alkylated cyclohexylamine (9) on reaction of the ketimine (7) with methyl acrylate may therefore be attributed to the direct attack of the cyclohexylamine present in the ketimine mixture with methyl acrylate.

In another experiment N-isopropylidene cyclohexylamine was refluxed in benzene for 14.5 h. The crude mixture on GC-MS analysis showed three products exhibiting parent ions at *m/e* 99, 139 and 179 which were identified as cyclohexylamine (13), ketimine (7) and the dimerized product (12) respectively.

It was of interest to examine the gradual change in relative concentrations of the products when N-isopropylidene cyclohexylamine was refluxed for prolonged periods. N-Isopropylidene cyclohexylamine was refluxed directly (not benzene solution) for about 14.5 h and the aliquots drawn after every 2 h were subjected to gas chromatography. It was found that concentration of cyclohexylamine increased with time of reflux while that of ketimine decreased. The concentration of the dimerized increased at first but on prolonged reflux it started decreasing, possibly due to decomposition.

Table II.

Time [h]	A Cyclohexyl- amine (13) [%]	B Ketimine (7) [%]	C Deaminated product (12) [%]
2	21.415	61.448	17.136
4	20.602	62.693	16.704
6	22.73	55.03	22.22
8	28.72	51.30	19.75
10	30.80	53.21	15.98
12	28.66	54.88	16.50

It is apparent that the reaction of ketimines with electrophilic olefins is of rather limited utility as it does not result in the *exclusive* formation of a C-alkylated product as originally claimed by Pfau *et al.* [6, 7] but rather in a very complex mixture of reaction products as demonstrated by us earlier [5]. Our previous observations [8] that the major product of the reaction mixture was the β -amino ester (9) stands confirmed by the GC-MS analysis although the mechanism for its formation appears to be a dimerization-deamination sequence followed by N-

alkylation (Scheme 3) [9] rather than the N-alkylation-hydrolysis sequence earlier proposed by us (Scheme 2).

Experimental

Note: GC-MS analysis of all the compounds reported in this paper were carried out on a Varian model 3700 capillary gas chromatograph attached with mass spectrometer MAT 112 S. 0.5 μ l of sample was injected each time, the column temperature was set at 40 °C during injection and raised by 8 °C/min to 240 °C.

Gas chromatography of all the compounds was done on Dani model 6800 equipped with programmer for temp. control, and connected to FID detector. The spiral glass column packed with 5% OV-101 chromosorb WAW was used for separation whereas nitrogen gas was used as carrier. The column temp. (using programme control) was set at 50 °C during all injections and was increased by 5 °C/mt to 180 °C. The recorder speed was adjusted at 0.1 mm/s.

I. Preparation of N-isopropylidene cyclohexylamine (7)

Cyclohexylamine (160 ml) and acetone (96 ml) were mixed at room temperature and a catalytic amount of HCl (1 ml) was added. The reaction mixture was kept for 24 h and was shaken exhaustively with potassium hydroxide pellets (500 g). The water which separated out on shaking was removed. The organic layer was distilled off at atmospheric pressure. The fraction distilling at 178 to 180 °C was carefully collected. The ketimine (50 ml) so obtained was stored under molecular sieve (Linde 10 Å) and in a nitrogen atmosphere to prevent hydrolysis and oxidation.

II. Reaction of N-isopropylidene cyclohexyl amine with methyl acrylate

Equimolar amount of N-isopropylidene cyclohexylamine (0.2 mole) and methyl acrylate (0.2 mole) were refluxed in dry benzene (20 ml) for 14.5 h in strictly anhydrous conditions. The mixture was cooled down to room temperature and then submitted for GC-MS analysis.

The GC plot showed twenty peaks (Fig. 1). The mass spectrum of each compound was recorded and is tabulated in Table I. Out of twenty compounds fifteen major compounds could be identified and their formation is rationalized in Schemes 3 to 16.

The GC plot (Fig. 1) shows the relative abundance of each product. Peak No. 6, which is the major peak in the plot, shows M^+ at 185 and was identified as the β -amino ester formed due to N-alkylation by cyclohexylamine.

III. *N*-isopropylidene cyclohexylamine (blank reflux in benzene)

N-Isopropylidene cyclohexylamine (5 ml) was refluxed in dry benzene (10 ml) for 14.5 h. The reaction mixture was subjected to GC-MS analysis. The gas chromatograms showed three peaks exhibiting M^+ ions at m/e 99, 139 and 179 for cyclohexylamine, ketimine and deaminated product respectively. The major peak of the plot was of ketimine showing that ketimine predominates in the mixture.

IV. *N*-Isopropylidene cyclohexylamine (blank reflux without benzene)

N-Isopropylidene cyclohexylamine was refluxed directly (without benzene) for 12 h. The aliquots were drawn after every 2 h during reflux so that six aliquots were collected each aliquot was subjected to gas chromatography under the same parameter. The percentage of each peak was calculated and are tabulated in Table II.

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