Tetrahedron. Vol. 31, pp. 2427 to 2429. Pergamon Press 1975. Printed in Great Britain

ENAMINES—XXXIX[1]
ENAMINES FROM CYCLOPROPYLKETONES

D. POCAR*, R. STRADI and P. TRIMARCO
Istituto di Chimica Organica della Facoltà di Farmacia, Università di Milano, Viale Abruzzi 42, 20131 Milano, Italy

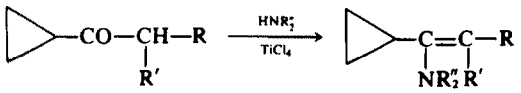
(*Received in the UK 22 April 1975; Accepted for publication 7 May 1975*)

Abstract—The enamines from cyclopropyl-methyl-, -ethyl- and -cyclopentylketone have been prepared by reaction of the ketone with a secondary amine and $TiCl_4$. Their vinylcyclopropane structure has been demonstrated by NMR. The reaction of dicyclopropylketone, cyclopropylphenylketone or cyclopropyl-α-thienylketone with secondary amines and $TiCl_4$ afforded homoallylic rearrangement products, namely 1-cyclopropyl-, 1-phenyl- and 1-(α-thienyl)-1,4-diamino-1-butene, respectively.

AS A part of our continuing interest in the chemistry of enamines, several enamines of cyclopropylketones have been prepared, to study the behaviour of the cyclopropyl group in view of possible occurrence of homoallylic rearrangement reactions. Moreover, the influence of the cyclopropyl group on the tautomerism of the corresponding enamines was of interest.

The enamines derived from cyclopropylketones have received some attention, but an extensive investigation of this particular class of compounds has never been performed, several problems being still open. Cook *et al.*[2] prepared in low yield the pyrrolidino-enamine of cyclopropylmethylketone by reacting the ketone with pyrrolidine in the presence of an acidic catalyst. The product was identified as 1 - pyrrolidino - 1 - cyclopropylethene, and the presence of the corresponding tautomeric 1 - pyrrolidino - 1 - cyclopropylidene - ethane could not be positively demonstrated. Higher yields can be obtained by the synthesis of White and Weingarten[3] which has been used for the preparation of all the enamines described hereafter.

Cyclopropylmethyl-, -ethyl- and -cyclopentylketone easily afforded the corresponding enamines **1**–**3**:

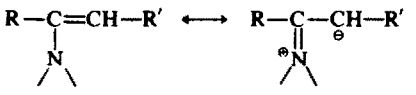


1: R = R' = H; NR'_2 = morpholino
2: R = H; R' = Me; NR'_2 = diethylamino
3: R—R' = $(CH_2)_4$; NR'_2 = morpholino
4: R = H; R' = —C(=CH_2)—; NR'_2 = morpholino

The NMR spectrum of **1**, in accordance with the proposed structure, does not show signals associated with the tautomeric 1 - cyclopropylidene - 1 - morpholinoethane. From the reaction mixture of **1** no other products were generally isolated. Only if the crude reaction mixture was left standing for a long time before working up was a substantial amount of the enamine **4** obtained together with **1**. **4** is clearly formed through selfcondensation of **1** under the influence of the acidic amine hydrochloride, as has been reported for other enamines of methylketones.[4–6]

The enamines **2** and **3** are also formed free from the corresponding cyclopropylidene tautomers. This fact shows that the formation of an exocyclic double bond is not the preferred process.

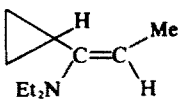
The enamine **2** is an equilibrium mixture of the *E* and *Z* isomers, as frequently occurs. In the NMR spectrum (C_6D_6) of **2** two signals are found at 4·58 δ and 4·97 δ (ratio 7:3) which can be associated with enaminic hydrogens. The *E*–*Z* isomerism of the enamines of ketones has been extensively investigated[1,7–10] and the relationships between the structure and the chemical shift of the olefinic protons are known. For enamines of the general formula **5** the NMR signal associated with the proton of the *E* isomer is always shifted to higher field, because the less steric interaction of the amine residue with the bulky R' group bonded to the β carbon atom allows better conjugation:



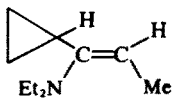
5

R = alkyl or aryl
R' = alkyl

Accordingly, the *E* isomer is generally present in greater amount in the equilibrium mixture. According to the above facts, the signal at 4·58 δ was associated with **2**–*E*. The above assignment is also confirmed by the observed values of the homoallylic coupling constants. For **2**–*E* ^5J = 0·9 cps and for **2**–*Z* ^5J = 1·2 cps. It is known that generally $J_{transoid}$ is greater than J_{cisoid}.[11] The conformational situation of **2**–*E* and **2**–*Z* can be inferred from the NMR data and examination of molecular models; the allylic coupling constant for **2**–*E* is about 1·4 cps and for **2**–*Z* about 1·0 cps.



2-*E*

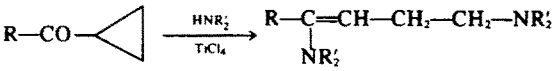


2-*Z*

The value for **2**–*Z* appears to be in the normal range, as already observed in the case of the *Z*-enamines of diethylketone which show a typical value of 1·2 cps, whereas for the corresponding *E*-isomers $J_{allylic}$ is remarkably small and not very different from 0 cps.[7] This discrepancy is likely to be due to the different preferred

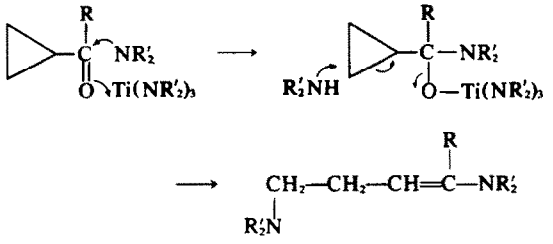
conformation of the cyclopropyl group in the two isomers, owing to the interaction with the methyl group in **2**-*E*.[12,13]

Another series of enamines was obtained from dicyclopropylketone and cyclopropylarylketones. In this case the cyclopropyl groups becomes involved in the enamine formation and homoallylic rearrangement products were isolated:



6: R = Ph; NR'_2 = morpholino
7: α-thienyl; NR'_2 = morpholino
8: R = cyclopropyl; NR'_2 = dimethylamino
9: R = cyclopropyl; NR'_2 = diethylamino
10: R = cyclopropyl; NR'_2 = pyrrolidino
11: R = cyclopropyl; NR'_2 = morpholino

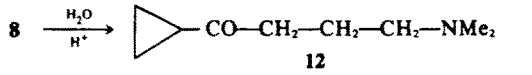
According to the accepted mechanism of the enamine formation from ketones, amines and $TiCl_4$[14] and by analogy with the already-observed homoallylic rearrangements in the reaction of dicyclopropylketone with Grignard reagents,[15–17] the course of the above reaction can be formulated as follows†:



In all the above enamines, with the exception of **9**, a single isomer is present, as demonstrated by NMR.

The chemical shifts associated with the enamine protons are in the range of 4·50 δ, showing that this is the *E*-isomer. Only **9** contains a detectable amount of both **9**–*E* and **9**–*Z*. As expected the signal associated with the enaminic hydrogen of **9**–*Z* is about 0·4 δ at lower field with respect to **9**–*E*.

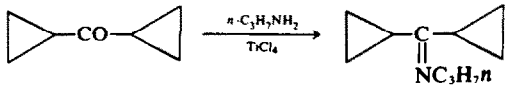
The enamines **8–11** represent a useful source of the corresponding cyclopropyl - (γ - aminopropyl)ketones which are readily obtained by acidic hydrolysis:



12

The above results show that the allylic rearrangement occurs only when the starting ketone is structurally prevented from giving an enamine leading the α,β double bond (with respect to the cyclopropyl ring).

The fact that the reaction of dicyclopropylketone with propylamine in the presence of $TiCl_4$ readily affords the corresponding imine **13**, free from rearrangement products



13

†The exact stereochemistry of this rearrangement deserves further investigation, since it is difficult to obtain data from the reaction products as in the case of other homoallylic rearrangements[18] owing to the easy *cis-trans* isomerization of enamines.[8]

is an indication that the homoallylic rearrangement involves the ketone-titanium complex rather than the ketone itself.

EXPERIMENTAL

NMR spectra were recorded with a Varian A-60 spectrometer operating at 60 MHz in C_6D_6 with TMS as internal standard.

Ketones. Cyclopropylmethylketone, dicyclopropylketone, cyclopropylphenylketone and cyclopropyl - α - thienylketone were commercial products. Cyclopropylethylketone was prepared according to the literature.[19] Cyclopentylcyclopropylketone was obtained by reacting cyclopropylcyanide with cyclopentylmagnesium bromide in ether following the method employed for cyclopropylethylketone. Yield 35%. Colourless liquid, bp 98–100°C (35 torr).

General procedure for the preparation of enamines. The ketone (0·1 mole) was dissolved in anhydrous n-pentane (*ca.* 100 ml). The secondary amine (0·6 mole) was then added, followed dropwise, with stirring under nitrogen, by a solution of titanium tetrachloride (0·055 mole) in anhydrous n-pentane (*ca.* 30 ml). After complete reaction (GLC), the reaction mixture was filtered and the filtrate was evaporated. The crude enamine was distilled at reduced pressure. The purity of all products was confirmed by GLC. The properties of the enamines are shown in Table 1.

Table 1.

Compound	Yield%	bp (torr)	δ–CH=
1	31	85 (3)	3·87 (s) and 3·91 (s)
2	40	70 (3)	4·58 (q) (*E*) and 4·97 (q) (*Z*)
3	71	150 (3)	—
4	60	210 (3)	4·47 (m) and 5·70 (m) (=CH_2)
6	56	170 (0·5)	4·59 (m) (*E*)
7	45	205 (35)	4·70 (m) (*E*)
8	59	102 (35)	4·55 (m) (*E*)
9	44	165 (35)	4·55 (m) (*E*) and 4·93 (m) (*Z*)
10	41	170 (4)	4·35 (m) (*E*)
11	41	165 (3)	4·50 (m) (*E*)

4 - *Dimethylamino* - 1 - *cyclopropyl* - 1 - *butanone* **12**. The enamine **8** (1 g) was stirred with 8 ml of 5% HCl for 20 h, the solution was basified, and extracted with ether. The ethereal solution was distilled under reduced pressure. The aminoketone **12** was isolated in 20% yield as a colourless liquid. bp 65°C (2 torr). Found: C, 69·70; H, 11·35; N, 9·21. $C_9H_{17}NO$ requires: C, 69·63; H, 11·04; N, 9·02%.

N - *Dicyclopropylmethylydene* - *n* - *propylamine* **13**. This compound was prepared following the general procedure employed for the preparation of the enamines. **13** was isolated as a pure liquid (GLC), bp 130–140°C (35 torr). Found: C, 79·66; H, 11·57; N, 8·99. $C_{10}H_{17}N$ requires C, 79·40; H, 11·34; N, 9·26%.

Acknowledgement—We are indebted to the Italian C.N.R. for financial aid.

REFERENCES

[1]Part XXXVIII. R. Stradi, D. Pocar and C. Cassio, *J. Chem. Soc., Perkin IX* 2671 (1974).
[2]A. G. Cook, S. B. Herscher, D. J. Schultz and J. A. Burke, *J. Org. Chem.* **35**, 1550 (1970).
[3]W. H. White and H. Weingarten, *Ibid.* **32**, 213 (1967).
[4]G. Bianchetti, P. Dalla Croce and D. Pocar, *Tetrahedron Letters* 2039 (1965); *Rend. Ist. Lomb. Acc. Sci. Lett.* **A99**, 259 (1965).
[5]G. Bianchetti, P. Ferruti and D. Pocar, *Gazz. Chim. Ital.* **97**, 579 (1967).
[6]D. Pocar, G. Bianchetti and P. Dalla Croce, *Ibid.* **95**, 1220 (1965).
[7]R. Stradi and D. Pocar, *Chim. e Ind.* **53**, 265 (1971).
[8]M. E. Munk and Y. K. Kim, *J. Org. Chem.* **30**, 3705 (1965).
[9]G. Bianchetti, R. Stradi and D. Pocar, *J. Chem. Soc. Perkin I* 997 (1972).
[10]M. Rivière and A. Lattes, *Bull. Soc. Chim. Fr.* 2559 (1967).

[11]S. Sternhell, *Rev. Pure and Appl. Chem.* **14**, 25 (1964); *Anal. Rev.* **23**, 236 (1969).
[12]H. Günther and H. Klose, *Chem. Ber.* **104**, 3898 (1971).
[13]L. Ernst and T. Schaefer, *Ibid.* **105**, 2368 (1972).
[14]H. Weingarten and W. H. White, *J. Org. Chem.* **31**, 4041 (1966).
[15]J. Yovell, *Dissertation*, The Hebrew University of Jerusalem (1967).
[16]S. Sarel, J. Yovell and M. Sarel-Imber, *Israel J. Chem.* **4**, 21p (1966).
[17]M. S. Newman and G. Kangars, *J. Org. Chem.* **31**, 1379 (1966).
[18]S. Sarel, J. Yovell and M. Sarel-Imber, *Angew. Chem.* **80**, 592 (1968).
[19]P. Bruylants, *Bull. Soc. Chim. Belg.* **36**, 519 (1927).