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NUCLEOPHILIC BEHAVIOUR OF 1-SUBSTITUTED MORPHOLINO ETHENES[1]

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Abstract—Morpholinoenamines derived from cyclohexyl-, cyclohexen-1-yl-, and phenyl methyl ketone react with diethyl azodicarboxylate (DAD) and phenylisocyanate (PIC) in a similar manner. Some difference in behaviour is observed in their reactions with mesyl chloride (MsCl), whereas a completely different reactivity is shown with β-nitrostyrene (βNS). An example of catalysed reversible transformation thietane 1,1-dioxide—enamino sulfone is reported.

This paper deals with the reactivity of some substituted amino-ethenes with a number of electrophiles. Compounds **1a, b, c**[2] (Scheme 1) were prepared by White-Weingarten condensation.[3] Enamine **1a** has been shown to be a 25:75 mixture of the more and less substituted forms.[4]

Reactions of **1a, b, c** with DAD always led to mixtures of adducts **2a, b, c,** and **4a, b, c** respectively, even if the ratio enamine: DAD was 2:1, owing to the well-known high reactivity of the electrophile with enaminic systems. Enamines **2a, b, c** could not be isolated but the NMR spectra of the crude reaction mixtures showed the signals for the vinylic protons. Enamine **2a** in fact consisted of a 1:1 mixture of configurational isomers, as two vinylic proton signals appeared at 5.0 and 5.18 δ, while **2b** and **2c** were single products, with the respective vinylic protons resonating at 4.7 and 5.8 δ respectively. All these enamines could not undergo equilibration by acidic treatment under refluxing benzene, thus indicating that their formation was under thermodynamic control. Although the E-isomers are considered the more stable, we did not make any configurational assignments, neither did it seem possible on the basis of NMR analysis. It is our opinion that too many unknown factors affect the chemical shift of the vinylic protons to permit separation and correct evaluation of our trisubstituted ethenes, though several cases are reported in the literature.[5–7]

When the same reactions were carried out with DAD in excess, enamines **4a, b, c** were obtained, which are unusual for the presence of two (diethoxycarbonyl) hydrazino groups on the same C atom. It seems also of interest to point out that the yield of **4a** is approximately equal to the percentage of the less substituted form in the parent enamine mixture. This would indicate that the equilibrium between the two isomeric forms is absent or very slow under the reaction conditions used. This conclusion is supported as follows: (i) During the synthesis of **1a**, the less substituted isomer was obtained as a single product which was converted into its isomer only by acid catalyst or by distillation.[8] (ii) When the reaction between **1a** and DAD in ratio 1:2 was performed at 80°, the yield of **4a** was quantitative. The analogies with the enamines derived from 2-methylcyclohexanone are evident.[9]

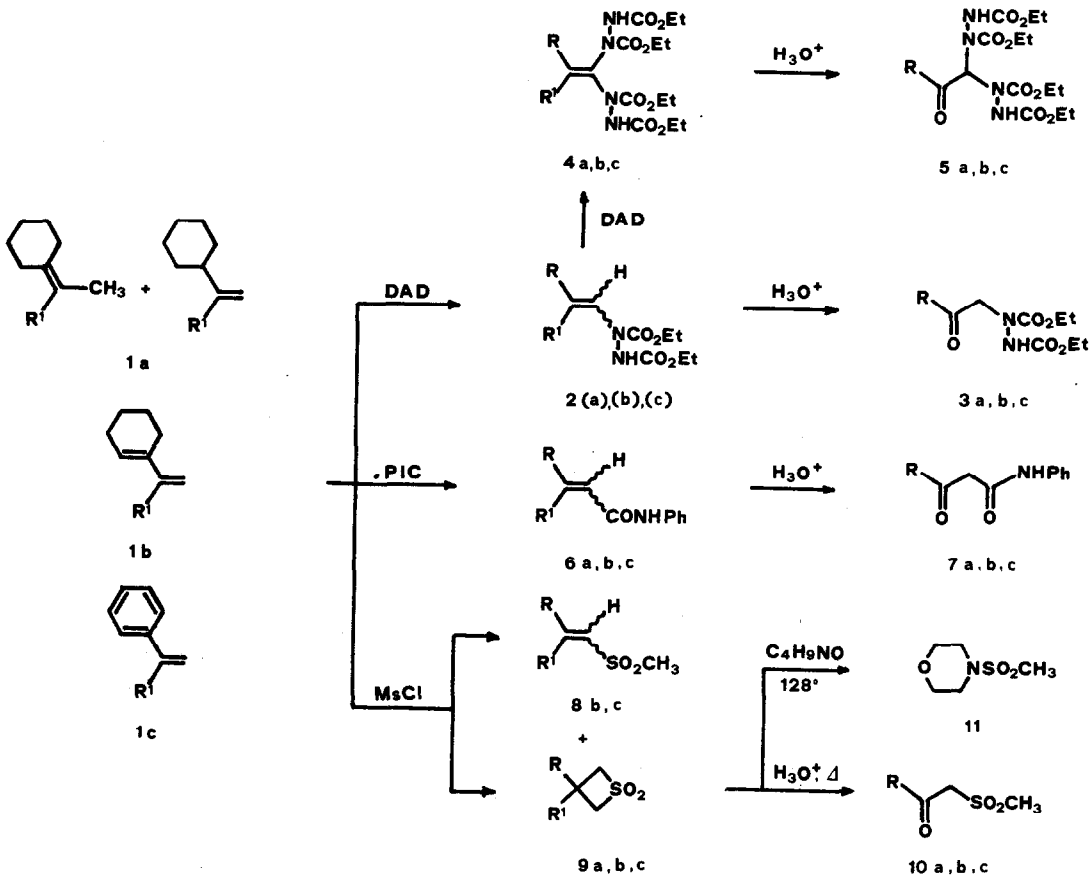
Acidic hydrolyses under mild conditions of enamines **2a, b, c** and **4a, b, c** gave the corresponding ketones **3a, b, c** and **5a, b, c** respectively. The increasing δ values for the protons geminal to the (diethoxycarbonyl) hydrazino groups are in agreement with the increasing deshielding effect of the R substituent (cyclohexyl < cyclohexenyl < phenyl) (Table 1). The same effect will operate also in enamines and in the other ketones obtained in the other reactions.

Reactions of **1a, b, c** with PIC led to the enamine adducts **6a, b, c** respectively. As in the above reaction, **6a** proved to be a 1:1 mixture of E and Z isomers, which did not undergo equilibration in acidic medium. The corresponding ketones **7a, b, c** were obtained by acidic hydrolyses of the respective enamines.

The substrates **1a, b, c** showed a different behaviour when they reacted with mesyl chloride. While **1a** gave the cyclic adduct **9a** as a single product, **1b** and **1c** led to mixtures of enamine adducts **8b** and **8c** together with the thietane 1,1-dioxides **9b** and **9c** respectively, the latter being the major products. The thietane 1,1-dioxide **9a** was very stable as it could not be converted to the open-chain enamine, unlike analogous compounds,[10] by basic treatment under reflux.

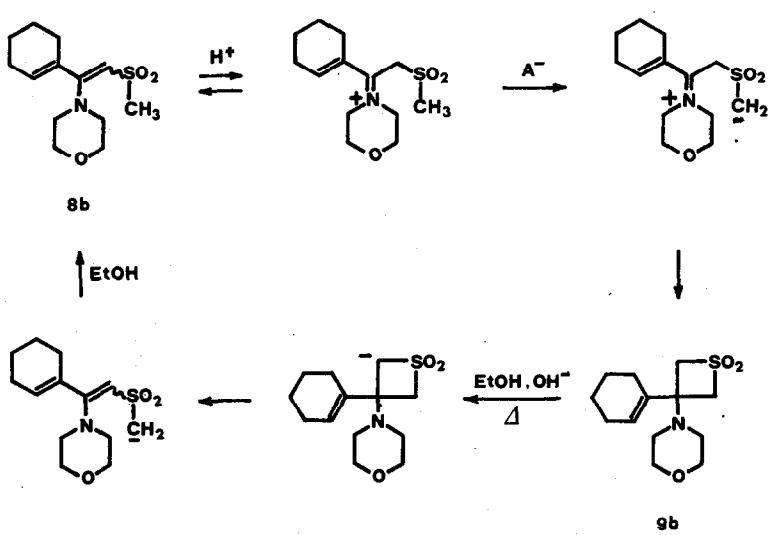
A very unusual behaviour was observed for compounds **8b** and **9b**. The attempted acidic hydrolysis of the enaminosulfone **8b** resulted in a rapid cyclization leading to **9b** in quantitative yield and not to the expected ketone **10b**, as has always occurred.[2] On the other hand, when **9b** was treated with alcoholic KOH under reflux, enamine **8b** was reobtained.[10] The situation could be rationalized as depicted in Scheme 2.

Surprisingly an analogous behaviour was not shown by the enaminosulfone **8c** which was dissolved in an acidic aqueous medium and led rapidly to the corresponding ketone **10c**. A further marked difference was observed in the case of the thietane 1,1-dioxides **9a** and **9c**, as they could not be converted into the corresponding open-chain enamines, even under vigorous conditions. Instead, all of them could be hydrolysed to the corresponding ketones **10a, b, c** but only under forcing conditions, i.e. reflux in a solution of water and concentrated hydrochloric acid in ratio 1:1 for 1 week. When **9a, b, c** were heated in an excess of morpholine, the adduct **11** was obtained in quantitative yield. This would indicate that the formation of the thietane 1,1-dioxides was reversible,



Scheme 1.

a: R = cyclohexyl-.
b: R = cyclohexen-1-yl-.
c: R = phenyl-.
R^1 = morpholino.
Compounds in brackets were not isolated.



Scheme 2.

Table 1. Physical and analytical data for the products

Compound	Yield (%)	M.p./°C	Formula	Found(%) C	H	N	Required(%) C	H	N
3a	50	59-60[a]	$C_{14}H_{24}N_2O_5$	55.70	8.05	9.50	55.99	8.05	9.33
3b	40	96-7[a]	$C_{14}H_{22}N_2O_5$	55.55	7.39	9.21	56.36	7.43	9.39
3c	50	103-4[b]	$C_{14}H_{18}N_2O_5$	56.8	6.10	9.54	57.14	6.16	9.52
4a	75	104-5[c]	$C_{24}H_{41}N_5O_9$	52.9	7.53	12.7	53.03	7.60	12.88
4b	95	138-9[b]	$C_{24}H_{39}N_5O_9$	52.8	7.17	12.70	53.22	7.26	12.93
4c	95	112-4[b]	$C_{24}H_{35}N_5O_9$	53.6	6.71	13.3	53.62	6.56	13.0
5a	95	112-4[c]	$C_{20}H_{34}N_4O_9$	50.50	7.17	12.0	50.62	7.22	11.81
5b	100	113-5[d]	$C_{20}H_{32}N_4O_9$	50.60	6.93	11.60	50.84	6.83	11.86
5c	100	92-4[b]	$C_{20}H_{28}N_4O_9$	50.9	6.07	12.1	51.3	6.02	11.9
6a	52	138-40[b]	$C_{19}H_{26}N_2O_2$	72.2	8.45	8.57	72.6	8.45	8.90
6b	75	155[e]	$C_{19}H_{24}N_2O_2$	72.0	7.90	8.65	73.0	7.74	8.97
6c[13]	57	158-60[b]	$C_{19}H_{20}N_2O_2$	74.3	6.34	8.94	74.0	6.54	9.08
7a	95	73-4[b]	$C_{15}H_{19}NO_2$	73.56	7.83	5.78	73.44	7.81	5.71
7b	95	76-80[a]; 200[f]	$C_{21}H_{21}N_5O_5$[f]	59.6	5.18	16.5	59.57	5.0	16.54
7c[13]	100	104[b]	$C_{15}H_{13}NO_2$	75.1	5.53	5.86	75.30	5.48	5.85
8b	30	139-40[b]	$C_{13}H_{21}NO_3S$	57.3	7.63	5.22	57.5	7.80	5.16
8c	20	116-8[b]	$C_{13}H_{17}NO_3S$	58.2	6.45	5.27	58.4	6.41	5.24
9a	44	110-2[a]	$C_{13}H_{23}NO_3S$	56.9	8.59	5.16	57.1	8.48	5.12
9b	70	155[b]	$C_{13}H_{21}NO_3S$	57.8	7.83	5.17	57.5	7.80	5.16
9c	70	184-5[b]	$C_{13}H_{17}NO_3S$	58.4	6.43	5.34	58.4	6.41	5.24
10a	70	76[b]; 198-200[f]	$C_{15}H_{20}N_4O_6S$[f]	47.1	5.20	14.3	46.8	5.24	14.5
10b	70	73-4[a]	$C_9H_{14}O_3S$	53.4	6.78		53.5	6.98	
10c[14]	70	106[g]	$C_9H_{10}O_3S$	54.2	5.08		53.9	4.85	
12a	40	53-4							
13c	67	124[b]	$C_{20}H_{22}N_2O_3$	69.9	6.35	8.30	70.99	6.55	8.28
14a	100	60-1[a]	$C_{16}H_{21}NO_3$	70.1	7.60	4.94	69.79	7.69	5.09
14c[15]	100	98[g]	$C_{16}H_{15}NO_3$	71.3	5.85	5.45	71.36	5.61	5.20

[a]From light petroleum.
[b]From benzene-ligroin
[c]From cyclohexane-light petroleum
[d]From acetone
[e]From benzene
[f]2,4-Dinitrophenylhydrazone derivative
[g]From ethanol.

at least under the conditions used for trapping the sulfene, which is generally regarded as the actual electrophile.[11]

A study of the reactions of **1a, b, c** with βNS showed strong differences in their behaviour (Scheme 3). Reaction of **1a** gave the cyclic nitronic ester **12a**, **1b** gave a mixture of the octaline system **15** together with the open-chain enamine **13b**;[1] and **1c** gave only the one enamine **13c**. It has been reported[12] that the stability of cyclic nitronic esters is correlated with the presence of an alkyl or an aryl group at the sp^2 C atom. In fact **12a** was very unstable, as it underwent rapid hydrolysis to **14a** just on standing in the air at room temperature. Compound **12a** converted to the corresponding enamine **13a** immediately when dissolved in chloroform, benzene or acetone. The NMR spectrum of **12a** in fact showed complex signals for the nitromethylenic and vinyl protons in the range 4.60–5.30 δ, with area of approximately three protons. The complexity of the pattern did not allow any attribution to be made relative to the existence of E–Z isomers in the less substituted form, as already found in the reactions with DAD and PIC. No attribution has been made for **13c** either, which was the one isomer isolated from the reaction of **1c** with βNS. As to the reaction of **1b** with the same electrophile, it has been studied in detail and analytical and stereochemical aspects of **15** e **16** have been reported.[1] Finally acidic hydrolyses of the open-chain enamines **13a, b, c** gave the corresponding ketones **14a, b, c**. Routine spectral and analytical data for all the compounds are listed in Tables 1 and 2.

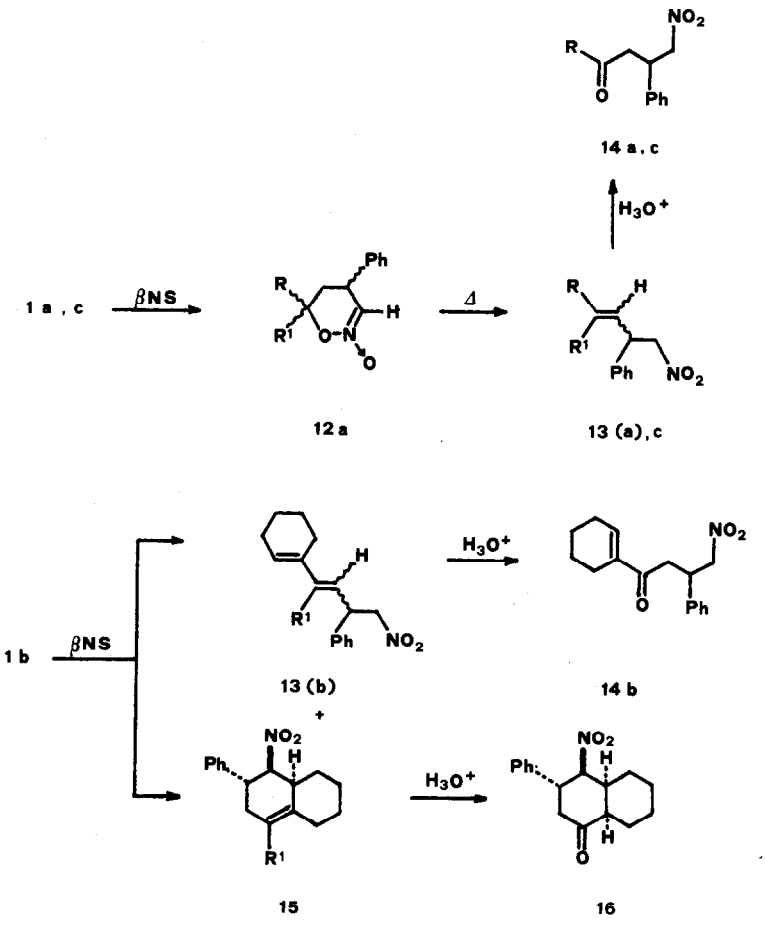
It is evident from these results that the most interes-

Table 2. Some significant IR and ^1H NMR data for compounds reported in Table 1

Compound	ν_{max}/cm^{-1} (Nujol)	Chemical shift(δ) for $CDCl_3$ solns relative to TMS
1a	1605(C=C-N)[a]	3.85,3.75(1.5H,2s,C=C$\underline{H}_2$)
1b	1630,1590(C=C-C=C)[a] N	5.9(1H,C=C$\underline{H}$);4.05,3.85(2H,2s,C=C$\underline{H}_2$)
3a	3300(NH);1748,1720(CO_2Et);1705(CO)	2.35(1H,C$\underline{H}$CO);4.45(2H,bs,C$\underline{H}_2$N);7.02(1H,bsN$\underline{H}$)
3b	3290(NH);1742,1710(CO_2Et);1665(CO)	5.28(2H,s,C$\underline{H}_2$N);7.85(2H,N$\underline{H}$,C=C$\underline{H}$)
3c	3275(NH);1730,1710(CO_2Et);1680(CO)	5.53(2H,s,C$\underline{H}_2$N);8.24(1H,bs,N$\underline{H}$);8.48,8.93(5H,m,Ph)
4a	3280(NH);1745,1725,1700(CO_2Et);1620(C=C-N)	2.1(1H,C$\underline{H}$-C=C);6.9,7.25(2H,bs,N$\underline{H}$)
4b	3340,3290(NH);1756,1745,1728,1700(CO_2Et); 1625(C=C-N)	5.8(1H,C=C$\underline{H}$);6.4,8.4(2H,2s,N$\underline{H}$)
4c	3280(NH);1750,1732,1700(CO_2Et);1638(C=C-N); 750,698(Ph)	6.65,8.65(2H,2bs,N$\underline{H}$);7.4(5H,m,Ph)
5a	3320(NH);1740,1710(CO_2Et);1685(CO)	2.92(1H,C$\underline{H}$CO);6.09(1H,bs,C$\underline{H}$N);7.37(2H,bs,N$\underline{H}$)
5b	3350,3330(NH);1742,1730,1715(CO_2Et);1678(CO); 1638(C=C)	6.38(1H,bs,C$\underline{H}$N);7.5(2H,bs,N$\underline{H}$)
5c	3300(NH);1730(CO_2Et);1680(CO);768,692(Ph)	6.65(1H,bs,C$\underline{H}$N);7.60(5H,m,Ph);8.50(2H,bs,N$\underline{H}$)
6a	3270,3120(NH);1640,1590,1540(N-C=C-CO)	4.90(0.5H,s,C=C$\underline{H}$);5.20(0.5H,s,C=C$\underline{H}$);7.30(5H,m,Ph); 8.05(1H,bs,N$\underline{H}$)
6b	3280,3250,3180,3120(NH);1650,1575,1525 (N-C=C-CO)	4.9(1H,s,N-C=C$\underline{H}$);6.05(1H,C=C$\underline{H}$);7.50(5H,m,Ph);7.90 (1H,bs,N$\underline{H}$)
6c	3250(NH);1650,1595,1545(N-C=C-CO);1613, 1572,1490,760,690(Ph)	5.18(1H,C=C$\underline{H}$);6.98(1H,bs,N$\underline{H}$);7.23,7.55(5H,m,Ph)
7a	3140(NH);1695(CO);1665,1560(CONH);1605,750, 690(Ph)	3.65(2H,s,C$\underline{H}_2$CO);7.39(5H,m,Ph);9.23(1H,bs,N$\underline{H}$)

7b	3270,3190,3140(NH);1670(CO);1650,1635,1600 (C=C,Ph);1655,1550(CONH)	3.9(2H,s,$C\underline{H}_2CO$);7.4(6H,m,C=C$\underline{H}$,Ph);9.4(1H,bs,N$\underline{H}$)
7c	3260(NH);1700(CO);1660,1565(CONH);1613,1600 1500,740,685(Ph)	4.13(2H,s,$C\underline{H}_2CO$);7.35,8.00(10H,m,Ph);9.30(1H,bs,N$\underline{H}$)
8b	1650,1555(C=C-C=C);1275,1115(SO_2)	3.0(3H,s,$SO_2C\underline{H}_3$);5.12(1H,s,N-C=C$\underline{H}$);5.90(1H,C=C$\underline{H}$)
8c	1550(C=C-N);1300,1280,1115(SO_2);1605,750(Ph)	2.68(3H,s,$SO_2C\underline{H}_3$);5.47(1H,s,N-C=C$\underline{H}$);7.5(5H,m,Ph)
9a	1315,1125,1115(SO_2);1105(CH_2-O-CH_2)	2.65(4H,m,$C\underline{H}_2NC\underline{H}_2$);3.73(4H,m,$C\underline{H}_2OC\underline{H}_2$);4.09(4H,s, $C\underline{H}_2SO_2C\underline{H}_2$)
9b	1650(C=C);1320,1310,1115(SO_2),1108(CH_2-O-CH_2)	2.55(4H,m,$C\underline{H}_2NC\underline{H}_2$);3.75(4H,m,$C\underline{H}_2OC\underline{H}_2$);4.25(4H,s, $C\underline{H}_2SO_2C\underline{H}_2$);5.85(1H,bt,C=C$\underline{H}$)
9c	1498,760,698(Ph);1320,1160,1125(SO_2); 1110(CH_2-O-CH_2)	2.3(4H,m,$C\underline{H}_2NC\underline{H}_2$);3.73(4H,m,$C\underline{H}_2OC\underline{H}_2$);4.25(4H,s, $C\underline{H}_2SO_2C\underline{H}_2$);7.32(5H,m,Ph)
10a	1700(CO)1320,1300,1150,1135(SO_2)	2.58(1H,C$\underline{H}$CO);3.12(3H,s,$SO_2C\underline{H}_3$);4.17(2H,s,$C\underline{H}_2SO_2$)
10b	1660,1635(C=C-C=O);1320,1305,1120(SO_2)	3.15(3H,s,$SO_2C\underline{H}_3$);4.40(2H,s,$C\underline{H}_2SO_2$);7.20(1H,bt,C=C$\underline{H}$)
10c	1675(CO);1300,1280,1115(SO_2);1598,1580,760 705(Ph)	3.12(3H,s,$SO_2C\underline{H}_3$);4.66(2H,s,$C\underline{H}_2SO_2$);7.71(5H,m,Ph)
12a	1620(C=N);1600,1490,760,692(Ph)	
13a	1634(C=C-N);1550(NO_2);1600,1580,690(Ph)[b]	3.65(5H,m,$C\underline{H}_2OC\underline{H}_2$,C$\underline{H}$Ph);4.60-5.30(3H,m,$C\underline{H}_2NO_2$,C=CH); 7.3(5H,Ph)
13c	1615(C=C-N);1550(NO_2);1595,1490,750,695(Ph)	4.05(1H,m,C$\underline{H}$Ph);4.53(2H,dd,$C\underline{H}_2NO_2$);4.73(1H,d (J=9.5 Hz), C=C$\underline{H}$)
14a	1690(CO);1545(NO_2);1600,1500,760,698(Ph)	2.3(1H,C$\underline{H}$CO);2.95(2H,d (J=6.5Hz),$C\underline{H}_2CO$);4.08(1H,m,C$\underline{H}$Ph); 4.72(2H,dd (J=9.0 Hz,J_2=6.5 Hz),$C\underline{H}_2NO_2$);7.3(5H,Ph)
14c	1690(CO);1548(NO_2);1600,740,680(Ph)	3.47(2H,d (J=7.5 Hz),$C\underline{H}_2CO$);4.28(1H,m,C$\underline{H}$Ph);4.84(2H,dd (J_1=2.5 Hz,J_2=7.5 Hz),$C\underline{H}_2NO_2$);7.2-8.1(5H,Ph)

[a]Film
[b]Spectrum of **12a** for $CDCl_3$ soln.



Scheme 3.

a: R = cyclohexyl-.
b: R = cyclohexen-1-yl-.
c: R = phenyl-.
R^1 = morpholino.
Compounds in brackets wer note isolated.

ting enamine is surely that derived from (cyclohexen-1-yl)-methyl ketone. Its unusual behaviour opens up new areas especially in the annulation reactions.

EXPERIMENTAL

M.ps were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 257 spectrometer and NMR spectra on a JNM-60-HL Jeol spectrometer.

1a: b.p.$_{1.5mmHg}$ 97–8°
1b: b.p.$_{5mmHg}$ 110°

General procedure

Reaction of **1** *with DAD in ratio* **1:1**. DAD in dry ether was added dropwise to a soln of the enamine in the same solvent, at 5°. The mixture was kept at 5° for 48 hr. A TLC showed that the crude mixture consisted of adducts **2** and **4**. It was hydrolysed and chromatographed on SiO_2. Elution with acetone–benzene 5% gave **3** and **5** respectively.

Reaction of **1** *with DAD in ratio* **1:2**. The above reaction was performed in order to isolate **4**. After standing at 5° for 72 hr, removal of the solvent left an oily residue which crystallized from a suitable solvent (Table 1) to afford **4**. Acidic hydrolysis of **4** with 1N HCl in acetone–water afforded the corresponding ketone **5**, in quantitative yield.

Reaction of **1** *with PIC*. PIC was added to a soln of **1** in dry ether, at 5°. After standing at 5° for 24 hr a crystalline product **6** was filtered off and crystallized from suitable solvents. A considerable amount of N-phenyl-carbamoyl-morpholine also separated. The product **6** was then hydrolysed with HCl 1:4 in acetone-water for 24 hr, to afford **7** in quantitative yield.

Reaction of **1a** *with MsCl*. MsCl was added dropwise to a 1:1 mixture of enamine **1a** and NEt_3 in dry ether, at 5°. The hydrochloride salt was filtered off. The mother liquors were kept at 5° for 12 hr and **9a** formed.

Reaction of **1b** (**1c**) *with MsCl*. MsCl was added to a mixture of **1b** (**1c**) and NEt_3 in ratio 1:1, in dry ether, at 0°. The hydrochloride salt was filtered off, the solvent was removed from the mother liquors. The oily residue which contained a mixture of **8b** (**8c**) and **9b** (**9c**), was fractionally crystallized and the products isolated.

Acidic hydrolyses of the thietane 1,1-*dioxides* **9**. A soln of **9** in acetone, acidified to pH 2, was refluxed for 1 week, cooled and extracted with benzene. Removal of the solvent left an oil which crystallized from the suitable solvent, to afford **10**.

Reaction of **1a** *with βNS*. βNS was added dropwise to a soln of **1a** in dry ether, at 0°. After 2 hr at 5°, a crystalline product, **12a**, was filtered off and analysed. Hydrolysis of **12a**, carried out in water led to the corresponding ketone **14a**.

Reaction of **1c** *with βNS*. βNS was added dropwise to a soln of **1c** in dry ether, at 5°. After standing at 5° for 48 hr, a solid formed and was isolated, **13c**. Enamine **13c** was dissolved in acetone and hydrolysed with HCl 1:4, affording **14c** in quantitative yield.

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REFERENCES

[1]G. Pitacco, A. Risaliti, M. L. Trevisan and E. Valentin, *Tetrahedron* **33**, 3145 (1977).
[2]S. Bradamante, S. Maiorana and G. Pagani, *J. Chem. Soc.* Perkin I, 282 (1970).
[3]W. A. White and H. Weingarten, *J. Org. Chem.* **32**, 213 (1967).
[4]R. Carlson and L. Nilsson, *Acta Chem. Scand. B* **31**, 732 (1977).
[5]M. E. Munk and Y. K. Kim, *J. Org. Chem.* **30**, 3705 (1965).
[6]R. Stradi, D. Pocar and C. Cassio, *J. Chem. Soc.* Perkin I, 2671 (1974).
[7]W. E. Truce and D. W. Onken, *J. Org. Chem.* **40**, 3200 (1975).
[8]H. Mazarguil and A. Lattes, *Bull. Soc. Chim. Fr.* 319 (1969).
[9]F. P. Colonna, M. Forchiassin, G. Pitacco, A. Risaliti and E. Valentin, *Tetrahedron* **26**, 5289 (1970).
[10]J. N. Wells and F. S. Abbott, *J. Medic. Chem.* **9**, 489 (1966).
[11]G. Opitz, *Angew. Chem.* Intern. Edit. **6**, 107 (1967).
[12]A. T. Nielsen and T. G. Archibald, *Tetrahedron* **26**, 3475 (1970).
[13]S. Hünig, K. Hübner and E. Benzing, *Chem. Ber.* **95**, 926 (1962).
[14]L. Field and J. W. McFarland, *J. Am. Chem. Soc.* **75**, 5583 (1953).
[15]Milton C. Kloetzel, *Ibid.* **69**, 2271 (1947).