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FUNCTIONALIZED ENAMINES—XXXII[1]

REACTION OF β-AMINO-α, β-UNSATURATED ESTERS AND AMIDES WITH BENZYL AND CINNAMYL BROMIDES

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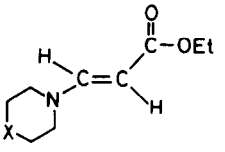
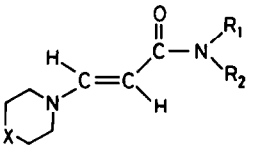
Abstract—Reactions of β-aminoacrylic esters (**1a–c**) and amides (**1d–o**) with benzyl bromide **2** and cinnamyl bromide **3** give products which are dependent both upon the nature of the amine component of the enamine and, in the case of the amides, upon the amine from which the amide is derived. The β-enamino esters react with benzyl bromide to yield predominantly dialkylated products in the case of the pyrrolidine ester **1a**. Reactions of the same esters with cinnamyl bromide yield mixtures of cinnamyl and 2-phenylpropenyl-substituted formylacetic esters. The enamino amides **1d–f** react to yield the expected alkylated derivatives. The anilides **1i–o** exhibit nucleophilic reactivity at the aniline nitrogen. A mechanism leading to the observed products is proposed.

β-Amino-α, β-unsaturated esters and amides represent interesting classes of functionalized enamines, both, in view of the additional potential nucleophilic centres and the influence which the ester and the amide group can exert upon the reactivity of the enamine system. The reaction of such β-enamino esters and amides with aryl diazonium salts has been recently applied, in this laboratory, to the synthesis of cinnoline[3] and imidazole[1] derivatives. As part of a general study of the reactivity patterns of β-enamino esters and amides with electrophiles, we report the results of the reaction of "functionalized enamines" **1a–o** with benzyl bromide (**2**) and cinnamyl bromide (**3**).

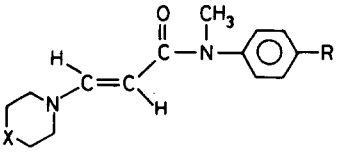
The β-enamino esters and amides **1a–o** were prepared by the addition of secondary amines to acetylenic esters and acetylenic amides (Scheme 1). Thus, addition of pyrrolidine, piperidine and morpholine to ethyl propiolate at room temperature gave the β-enamino esters **1a–c**, while an analogous reaction with the amides **4a–d** and the anilides **5a,b** resulted in the formation of β-enamino amides **1d–o**. The amide **1h** could, however, be more conveniently prepared by the reaction of morpholine with propiolic anhydride. The required propiolamides **4a–d** could be conveniently obtained by the aminolysis of methyl prepiolate with the corresponding secondary amines at −50° (Scheme 2).[4] The propiolanilides **5a,b** could not, however, be prepared by the last-mentioned procedure; the reaction of the anilines with propiolic ester took place only at room temperature and, under the conditions, led to the corresponding Michael



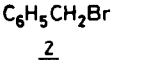
	X
1a	—
1b	CH_2
1c	O



	X	R R
1d	—	$(CH_2)_4$
1e	CH_2	$(CH_2)_4$
1f	O	$(CH_2)_4$
1g	O	$(CH_2)_5$
1h	O	$(CH_2)_2O(CH_2)_2$
1i	O	CH_3 ,CH_3



	X	R
1j	—	H
1k	CH_2	H
1l	O	H
1m	—	OCH_3
1n	CH_2	OCH_3
1o	O	OCH_3



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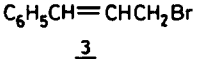

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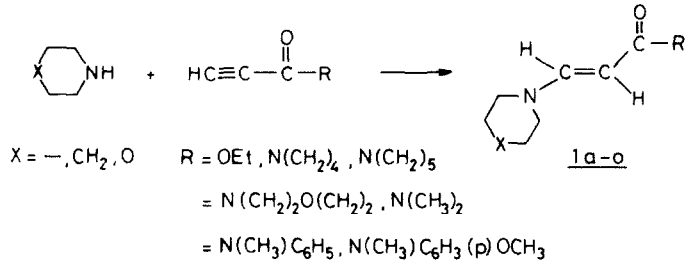
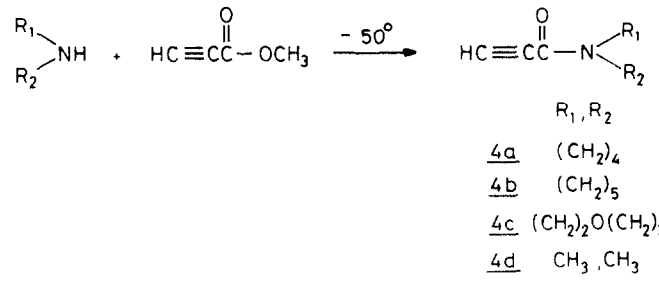


X = —, CH_2, O R = OEt, $N(CH_2)_4$, $N(CH_2)_5$
= $N(CH_2)_2O(CH_2)_2$, $N(CH_3)_2$
= $N(CH_3)C_6H_5$, $N(CH_3)C_6H_3$ (p) OCH_3

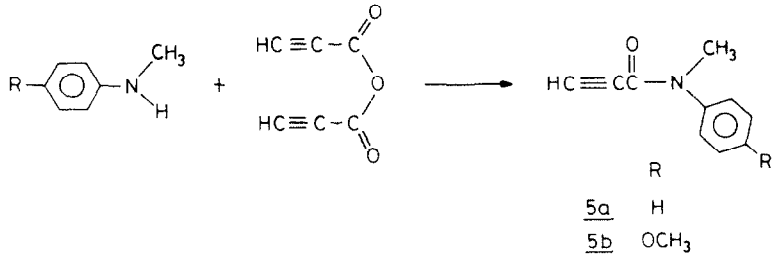
1a–o

Scheme 1.



	R_1, R_2
4a	$(CH_2)_4$
4b	$(CH_2)_5$
4c	$(CH_2)_2O(CH_2)_2$
4d	CH_3, CH_3

Scheme 2.



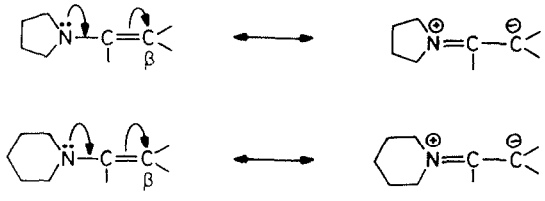
	R
5a	H
5b	OCH_3

Scheme 3.

adducts. The anilides **5a,d** were finally prepared by the reaction of N-methyl aniline and N-methyl 4-methoxy-aniline with propiolic anhydride[5] (Scheme 3).

REACTION OF β-ENAMINO ESTERS WITH BENZYL AND CINNAMYL BROMIDE

In a systematic study of the reaction of enamines and dienamines derived from different bases, with electrophiles,[6,7] it has been shown that the course of the reaction is influenced by the amine-component of the enamine system. The observed difference between the reactivity of pyrrolidine and piperidine enamines has been rationalized on the basis of a stronger nucleophilic character of the β-carbon of the pyrrolidine-enamine as compared to the corresponding piperidine-enamine. This difference has been attributed to the greater contribution of the dipolar ionic structure of the pyrrolidine-enamine as a result of the localization of the double bond exocyclic to the 5-membered pyrrolidine ring.[8] A higher electron density at the β-carbon of pyrrolidine enamines and dienamines is suggested by relevant NMR spectral data.[9]

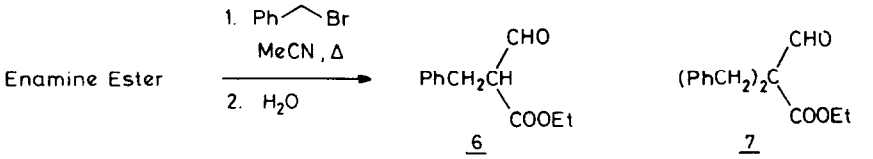


The enamine esters **1a–c** underwent reaction with benzyl bromide (**2**), in refluxing acetonitrile, to give, after hydrolysis, varying amounts of mono- and di-substituted α-formylacetates **6** and **7** respectively. In addition, in the reaction of **1b** and **1c** piperidinium bromide (17%) and morpholium bromide (28%) and N-benzylmorpholine (11%), respectively, were isolated. An analogous reaction of **1a–c** with cinnamyl bromide yielded mixtures of aldehydic esters **8** and **9**. The results are presented in Table 1.

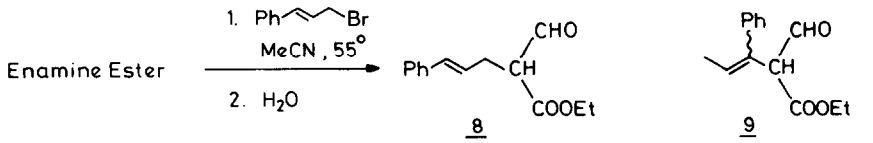
Inspection of the data presented in Table 1 show that the "isolated" yields of the C-alkylated products in both reactions range from 45 to 60% (lower limit). However, taking the aforementioned N-alkylated products into consideration, the variation in the composition of the mixtures is sufficiently significant to allow conclusions regarding the reactivity pattern of the enamine esters.

The reaction of **1a–c** with benzyl bromide reveals the important influence of the base-component. Even if the formation of some disubstituted product **7** in the reaction of **1b** may have escaped isolation, it is abundantly evident that the predominant product from **1a** is **7**, while from **1b**, **6** is the sole product. Since pyrrolidine and piperidine have very similar basicities (pKa values: pyrrolidine = 11.3; piperidine = 11.2), the explanation for the difference in the reactivity pattern may once again be sought in the ring size of the two cyclic amines. Iminium salt intermediates **a** from C-alkylation of **1a** and **1b** (Scheme 4) would be expected to deprotonate to enamine esters of type **b** by transfer of the proton to the starting

Table 1. Reaction of β-enamino esters with benzyl and cinnamyl bromides

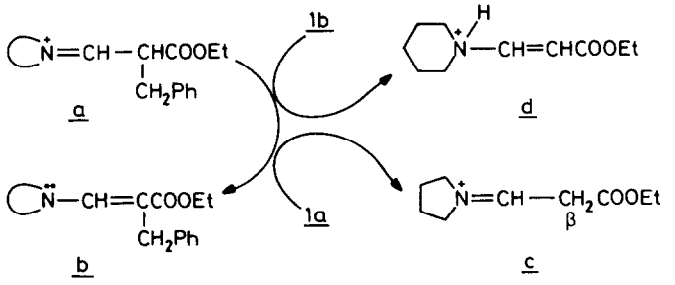


	C-Alkylation	6	7
1a	52%	12% (23%)	40% (77%)
1b	58%	58% (100%)	—
1c	44%	22% (50%)	22% (50%)

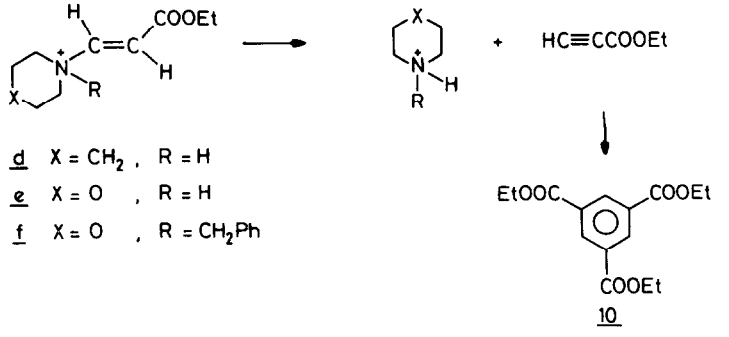


	C-Alkylation	8	9
1a	55%	21% (38%)	34% (62%)
1b	59%	49% (83%)	10% (17%)
1c	49%	37% (76%)	12% (24%)

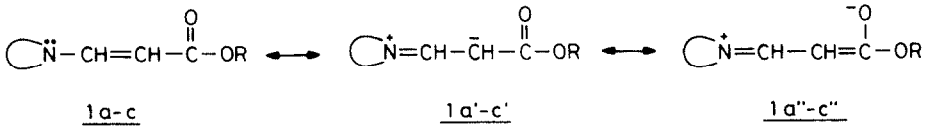
enamine esters. However, in view of the difference in charge distribution in the β-enamino esters **1a** and **1b**, due to the favoured exocyclic double bond in the pyrrolidine derivative, protonation of **1a** occurs at the β-carbon leading to **c**, while **1b** would be expected to protonate at the nitrogen (intermediate **d**). The latter presumably accounts for the formation of piperidine hydrobromide via the elimination sequence described in Scheme 5. That ethyl propiolate can be readily produced is supported by the formation of **10** in the reaction of **1a** with cinnamyl bromide under the reaction conditions. The nucleophilicity of the β-carbon of the pyrrolidine intermedate **b**, derived from **a** is again displayed in the second alkylation step leading finally to product **7**. As



Scheme 4.



Scheme 5.



1a-c 1a'-c' 1a''-c''

Table 2. Chemical shifts of C_α-H in **1a–c** and C_β-H in **1f–e**

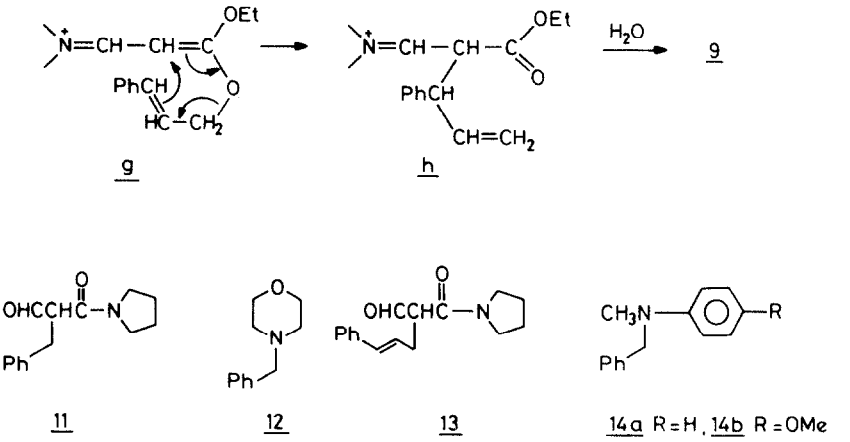
	δC_α-H		δC_β-H
1a	7.73	**1f**	4.96
1b	7.38	**1g**	5.11
1c	7.34	**1h**	5.04
		1i	5.05

anticipated, due to both electronic and steric considerations, the corresponding piperidine containing intermediate **b** would have a weak tendency to exhibit a double alkylation. It is felt, however, that the total absence of **7** from **1b** (Table 1) is due to our inability to isolate it from the reaction mixture rather than its formation. In case of **1c**, (lower) amounts of the C-alkylation products have been found and, in addition, low enamine type activity is evidenced by the isolation of morpholine hydrobromide and N-benzylmorpholine, presumably from intermediate **f** (Scheme 5).

The reaction of **1a–c** with cinnamyl bromide (**3**) gives in each case a mixture of two C_β-alkylation products; one containing the cinnamyl moiety (**8**) and the other in which the cinnamyl group has rearranged (**9**). Inspection of the data presented in Table 1 suggests that **1a** gives **9** as the major product while **1b** and **1c** lead predominantly to the cinnamyl derivative **8**. These results are in contrast to the pattern of reaction observed for the reaction of enamines and dienamines with allylic halides, where the pyrrolidine derivatives give the normal allylic substitution while the corresponding piperidine and morpholine systems lead to products containing the rearranged (allylic) electrophile. In considering the properties of **1a–c**, it should be recognized that the β-enamino esters contain an additional nucleophilic centre at the carbonyl oxygen, which will express itself most strongly in the case of the pyrrolidine ester **1a** (**1a–c** ⟷ **1a'–c'** ⟷ **1a''–c''**). The relatively large contribution of dipolar structure **1a''**, in **1a**, compared to **1b** and **1c**, is reflected in the chemical shifts of the C_α-H (Table 2).

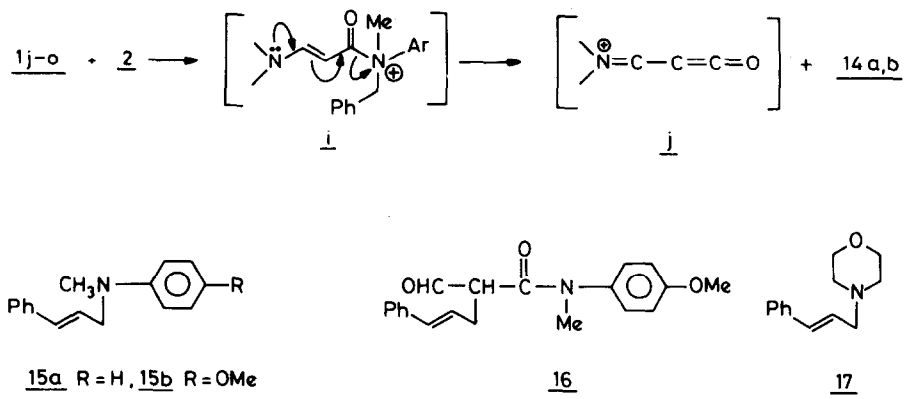
As a consequence, O-alkylation of the enamine esters would be anticipated to be most significant in the reaction of **1a**. The O-alkylation of enamino ketones has been well documented.[10–12] The formation of **9** in the reaction with cinnamyl bromide can be rationalized in terms of the sequence described in Scheme 6. O-alkylation of **1a–c** would lead to intermediates of type **g** (Scheme 6) which can undergo a Claisen ([3, 3]-sigmatropic) rearrangement[13] to intermediates **h**. An overall tautomeric shift in **h** (to the conjugated aryl system) and subsequent hydrolysis, would give product **9**.

It is possible that the modest yields of the C-alkylation products of the reaction of **1a–c** with **2** and **3** (Table 1)



11 **12** **13** **14a** R=H, **14b** R=OMe

Scheme 6.



Scheme 7.

might, amongst other factors (e.g. N-alkylation), reflect O-alkylation intermediates which, after hydrolysis, are lost as the water soluble enol of $CH_2(CHO)COOEt$.

REACTION OF β-ENAMINO AMIDES WITH BENZYL AND CINNAMYL BROMIDES

The reactions of **1d–f** with **2** (CH_3CN, 60°), followed by hydrolysis gave the same C_β-alkylated amide **11**, in 40–52% yield. Under the same reaction conditions **1g–i** yielded N-benzylmorpholine (**12**).

In β-enamino-amides the electron-release by the amide nitrogen (amide resonance) is cross-conjugated with the resonance of the conjugated enamine (N–C=C–C=O). The greater the contribution of the amide resonance, the higher will be the electron density on the β-carbon. This is clearly seen in the chemical shifts of the C_β-protons in the enamine amides **1f–i**,[4] the most significant change in the chemical shift being in going from **1f** to **1g** (Table 2). The high field shift of the C_β-proton of **1f** can again be attributed to the dominant amide resonance involving a double bond exocyclic to the five-membered pyrrolidine ring. The difference in electron densities at the β-carbons of **1f** and **1g** provide an explanation of the different reactivity patterns of the two structurally critical β-enamino amides, which differ only in the structure of the amide base. In this context is should be noted that **1d–f** exhibit normal enamine type reactivity, while **1g–i**, in analogy to the reactions of enamines, dienamines and enamino esters, react via the morpholine nitrogen.

The reactions of **1d–f** with **3** led in all cases to the normal alkylation product **13**. This result is consistent with the reaction of these enamine amides with **2**, but in sharp contrast to analogous reactions of the enamino esters **1a–c** with **3** (Table 1). Once again the amide resonance suppresses the resonance contribution of structures analogous to **1a″–c″** and thereby the O-alkylation of **1d–f**. A rearrangement of the type described in Scheme 6 is consequently not observed for the enamine amides.

The reactivity pattern of the enamino anilides **1j–o** deserves a separate discussion. With benzyl bromide, these compounds reaction to yield the benzyl substituted anilines **14a** and **14b**, as the only isolable products. The yields of the latter ranged from 24–49%. Even in the event that other products might have escaped identification, the result clearly points to the high nucleophilic character of the aromatic amine moieties in these systems. Scheme 7 accounts for the formation of the observed anilines. Attack on the benzyl carbon results in an acyl ammonium cation (**i**) which could fragment into **j** and **14a,b** or hydrolize to **14a,b**. The fate of **j** should lead to products that would not be recognized under conditions of the workup of the reaction mixtures (Experimental). Two points require further comment when **1d–f** are compared with **1j–o**. The nucleophilicity of the anilino nitrogen is at first surprising. However, when the contribution of the amide resonance is taken into consideration, the amide nitrogens in **1d–f** would be expected to be more electropositive in comparison with the corresponding nitrogens in the anilides. This rationalization is supported by the red shift of the λ_{max}, in the UV spectra, in going from **1d–i** (282–292 nm) to **1j–o** (292–300 nm). Linear enamine ketones exhibit a λ_{max} at 300–307 nm,[15] which value, when compared with the λ_{max} of the enamine amides, shows the influence of the amide nitrogen upon the $\rangle N\text{–}C\text{=}C\text{–}C\text{=}O$ chromophore.

The second point relates to the fragmentation of intermediate **i** in Scheme 7. Here, the low basicity of the aromatic amines (compared with the aliphatic amines) should facilitate the loss of the substituted anilines from **i**. This explains why **14a,b** are formed in case of the anilides without hydrolysis. It cannot be excluded, however, that during the chromatographic workup, some **i** is directly hydrolyzed to **14a,b**.

Reaction of **1j – o** with cinnamyl bromide (**3**) results, in all cases, in the formation of cinnamyl anilines **15a,b**. The formation of the latter products occurs in a manner analogous to that described for **14a,b**. In the case of enamine amides **1m–o**, C_β-alkylation product **16** is also obtained, following hydrolysis. This is in accord with the expected influence of the β-methoxy group in the anilide moiety. An increase in the amide resonance due to electron donation will, as a consequence, increase the nucleophilic character of the enamine β-carbon. The yields of **16** from **1m**, **1n** and **1o** (37%, 32% and 3%, respectively) are in line with the anticipated effects of the base-components of the enamine amides **1m–o**. In this connection it is significant that in case of **1o** a substantial amount (33%) of N-cinnamylmorpholine (**17**) is isolated from the reaction mixture.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Unicam SP 200 or a Perkin–Elmer 257 spectrometer. The absorptions are given in cm^{-1}. UV spectra were recorded on a Cary 14 spectrometer. The absorptions are given in nm. The molar

extinction coefficients are given in brackets. NMR spectra were run on Varian Associates Model A-60, A-60D, HA-100 and XL-100 instruments. The chemical shifts (δ) are given in ppm, using TMS as an internal standard. For the resonance signals the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Spin–spin coupling constants (J) are given in Hertz. Mass spectra were obtained with a Varian Mat-711 spectrometer. Analyses were carried out by Mr. H. Pieters of the Microanalytical Department of this laboratory.

Propiolamides **4a,d**

General procedure. To a 10% solution of the amine (10 mmol) in a 1:1 mixture of methanol and water, cooled to −50°, methyl propiolate (10 mmol) was added in small portions. The mixture was stirred for 3 h at −50° and subsequently 50 ml 2 N HCl was added. After standing 16 h at room temperature the red coloured solution was extracted with $CHCl_3$ and washed with a saturated $NaHCO_3$ solution and water. Drying the mixture and evaporation of the solvents yielded the propyiolamide, which was recrystallized from EtOAc/cyclohexane. N, N-tetramethyleneproiolamide (**4a**). M.p. 90–91°; yield 45%. IR ($CHCl_3$): 1620 (C=O), 2100 (C≡C), 3330 (≡C–H); PMR ($CDCl_3$): 1.93 (m, 4H, $\underline{CH_2}$–CH_2–N), 3.07 (s, 1H, ≡C–H), 3.58 (m, 4H, CH_2–N). N, N-dimethyl propiolamide (**4d**). M.p. 73–74°; yield 60%. IR ($CHCl_3$): 1630 (C=O), 2100 (C≡C), 3330 (≡C–H); PMR ($CDCl_3$): 2.97 (s, 3H, CH_3),3.11 (s, 1H, ≡C–H), 3.22 (s, 3H, CH_3).

Propiolamides **5a,b**

General procedure. To a soln of propiolic anhydride (10 mmol) dissolved in diëthyl ether at 0° the aniline (20 mmol) was added in small portions. The mixture was stirred 2 h and subsequently washed with 1 N HCl, saturated $NaHCO_3$ solution and water. After drying the mixture and evaporation of the solvent the propiolamide was isolated, which was recrystallized from diïsopropyl ether. N-phenyl-N-methyl propiolamide (**5a**). M.p. 78–79°; yield 21%. IR ($CHCl_3$): 1600 (C=C), 1630 (C=O), 2120 (C≡C), 3330 (≡C–H); PMR ($CDCl_3$): 2.80 (s, 1H, ≡C–H), 3.34 (s, 3H, CH_3), 7.40 (s, 5H, aromatic protons). N-p-methoxyphenyl-N-methyl propiolamide (**5b**) M.p. 82–83°; yield 30%. IR ($CHCl_3$): 1640 (C=O), 2110 (C≡C), 3350 (≡C–H); PMR ($CDCl_3$): 2.80 (s, 1H, ≡C–H), 3.26 (s, 3H, CH_3–N), 3.80 (s, 3H, CH_3), 6.85–7.20 (AB, 4H, aromatic protons).

Enamine esters and amides **1a–o**

General procedure. To a soln of the acetylenic ester or the amide (1 mmol), dissolved in MeCN (25 ml), secondary amine (1 mmol) was added and the mixture stirred 1 h at room temperature. The solvent was evaporated. The enamine ester (**1a–c**) was distilled under reduced pressure and the enamine amide (**1d–f, 1i, j, 1, m, n, o**) recrystallized from EtOAc; **1g, h, k** were oils. Yield: 70–95%. Ethyl 3-pyrrolidinylpropenoate (**1a**). IR ($CHCl_3$): 1600 (C=C), 1665 (C=O); PMR ($CDCl_3$): 1.27 (t, 3H, CH_3), 1.95 (m, 4H, $\underline{CH_2}$–CH_2–N), 3.30 (m, 4H, CH_2–N), 4.16 (q, 2H, CH_3–O), 4.50 (d, 1H, C_2–H, J = 12.5), 7.72 (d, 1H, C_3–H, J = 12.5); ^{13}C NMR ($CDCl_3$): 14.7 (CH_3), 25.3 ($\underline{CH_2}$–CH_2–N), 48.8 (CH_2–N), 58.5 (CH_2–O), 84.6 (C_2), 169.2 (C=O); UV (C_2H_5OH): 287 (26,000). Ethyl 3-piperidinylpropenoate (**1b**). IR ($CHCl_3$): 1600 (C=C), 1670 (C=O); PMR ($CDCl_3$): 1.32 (t, 3H, CH_3), 1.58 (broad s, 6H, $\underline{(CH_2)_3}$–CH_2–N), 3.19 (broad s, 4H, CH_2–N), 4.13 (q, 2H, CH_2–O), 4.61 (d, 1H, C_2–H, J = 12.5), 7.38 (d, 1H, C_3–H, J = 12.5); ^{13}C NMR ($CDCl_3$): 14.7 (CH_3), 24.1 ($\underline{CH_2}$–$(CH_2)_2$–N), 25.5 ($\underline{CH_2}$–CH_2–N), 49.9 (CH_2–N), 58.6 (CH_2–O), 83.9 (C_2), 151.7 (C_3), 169.7 (C=O). Ethyl 3-morpholinylpropenoate (**1c**). IR ($CHCl_3$): 1610 (C=O); 1670 (C=O) PMR ($CDCl_3$): 1.23 (t, 3H, CH_3), 3.20–3.71 (A_2B_2, 8H, morph.–H), 4.12 (q, 2H, CH_3–$\underline{CH_2}$–O), 4.68 (d, 1H, C_2–H, C_2H, J = 12.5), 7.34 (d, 1H, C_3–H, J = 12.5); ^{13}C NMR ($CDCl_3$): 14.6 (CH_3), 48.5 (CH_2–N), 58.8 (CH_3–H_2–O), 66.0 (CH_2–O), 85.9 (C_2), 151.5 (C_3), 168.9 (C=O). N, N-tetramethylene 3-pyrrolidinylpropenamide (**1d**). M.p. 71–73°. IR ($CHCl_3$): 1550 (C=C), 1635 (C=O); PMR ($CDCl_3$): 1.90 (m, 8H, $\underline{CH_2}$–CH_2–N), 3.24 (m, 4H, CH_2–N-en.), 3.45 (m, 4H, CH_2–N-am.), 4.59 (d, 1H, C_2–H, J = 12.5), 7.64 (d, 1H, C_3–H, J = 12.5); ^{13}C NMR ($CDCl_3$): 25.3 ($\underline{CH_2}$–CH_2–N), 45.8 (CH_2–N-en.), 49.2 (CH_2–N–am.), 86.6 (C_2), 146.5 (C_3), 167.7 (C=O); UV (C_2H_5OH): 292 (30,000). (Found: C, 67.76; H, 9.17; N, 14.29. Calc. for $C_{11}H_{18}N_2O$: C, 68.04; H, 9.28; N, 14.43%.) N, N-tetramethylene 3-piperidinylpropenoamide (**1e**). M.p. 87–88°. IR ($CHCl_3$): 1550 (C=C), 1630 (C=O); PMR ($CDCl_3$): 1.58 (broad s, 6H, $\underline{(CH_2)_3}$–CH_2–N–pip.), 1.84 (m, 4H, $\underline{CH_2}$–N–pyr.), 3.16 (broad s, 4H, CH_2–N–pip.), 3.46 (m, 4H, $\underline{CH_2}$–N pyr.), 4.77 (d, 1H, C_2–H, J = 12.0), 7.42 (d, 1H, C_3–H, J = 12.0); ^{13}C NMR ($CDCl_3$): 24.3 ($\underline{CH_2}$–$(CH_2)_2$–N–pip.), 25.4 ($\underline{CH_2}$–CH_2–N–pip.), 45.8 (CH_2–N–pip.), 45.8 (CH_2–N–pip.), 49.8 (CH_2–N–pyr.), 86.1 (C_2), 150.2 (C_3), 167.9 (C=O); UV (C_2H_5OH): 290 (31,500). (Found: C, 69.25; H, 9.67; N, 13.47. Calc. for $C_{12}H_{20}N_2O$: C, 69.28; H: 9.62; N, 13.46%.) N, N-tetramethylene 3-morpholinylpropenoamide (**1f**). M.p. 97–98°. IR ($CHCl_3$): 1560 (C=C), 1640 (C=O); PMR ($CDCl_3$): 1.90 (m, 4H, $\underline{CH_2}$–CH_2–N–pyr.), 3.23–3.78 (A_2B_2, 8H, morph.–H), 3.52 (m, 4H, $\underline{CH_2}$–N–pyr.), 4.96 (d, 1H, C_2–H, J = 13.0), 7.50 (d, 1H, C_3–H, J = 13.0); ^{13}C NMR ($CDCl_3$): 25.5 ($\underline{CH_2}$–CH_2–N–pyr.), 45.8 (CH_2–N–morph.), 48.8 (CH_2–N–pyr), 66.2 (CH_2–O), 88.2 (C_2), 150.0 (C_3), 167.1 (C=O); UV (C_2H_5OH): 287 (27,000). (Found: C, 62.85; H, 8.63; N, 13.26. Calc. for $C_{12}H_{20}N_2O_2$: C, 62.86; H, 8.57; N, 13.33%.) N, N-pentamethylene 3-morpholinylpropenoamide (**1g**). IR ($CHCl_3$): 1560, 1635 (C=O); PMR ($CDCl_3$): 1.60 (broad s, 6H, $\underline{(CH_2)_3}$–CH_2–N), 3.50 (broad s, 4H, CH_2–N–pip.), 3.17–3.74 (A_2B_2, 8H, morph.–H), 5.10 (d, 1H, C_2–H, J = 12.5), 7.47 (d, 1H, C_3–H, J = 12.5). N, N-ethyleneoxyethylene 3-morpholinylpropenoamide (**1h**). **1h** could more conveniently be synthezised by reaction of propynoic anhydride with morpholine. To a soln of propiolic anhydride (10 mmol) dissolved in diëthyl ether at 0° morpholine (30 mmol) was added in small portions. The mixture was stirred 2 h at room temperature and subsequently washed with water. After drying the ether soln and evaporation the residue was chromatographed on silicagel. Elution with EtOAc/iPrOH (4:1) yielded **1h** (65%). IR ($CHCl_3$): 1560 (C=C), 1640 (C=O); PMR ($CDCl_3$): 3.23 (m, 4H, CH_2–N–en.), 3.70 (m, 12H, CH_2–am., CH_2–O), 5.04 (d, 1H, C_2–H, J = 12.5), 7.50 (d, 1H, C_3–H, J = 12.5); ^{13}C NMR ($CDCl_3$): 44.0 (CH_2–N–en.), 48.6 (CH_2–N–am.), 66.1–66.8 (CH_2–O), 84.7 (C_2), 151.4 (C_3), 167.8 (C=O). (Found: C, 58.29; H, 8.04; N, 12.30. Calc. for $C_{11}H_{18}N_2O_3$: C, 58.41; H, 7.96; N, 12.39%.) N, N-dimethyl 3-morpholinylpropenoamide (**1i**). M.p. 72–74°. IR ($CHCl_3$): 1565 (C=C), 1640 (C=O); PMR ($CDCl_3$): 2.99 (s, 6H, CH_3), 3.19–3.73 (A_2B_2, 8H, morph.–H), 5.05 (d, 1H, C_2–H, J = 12.5), 7.43 (d, 1H, C_3–H, J = 12.5); ^{13}C NMR ($CDCl_3$): 36.0 (CH_3), 48.6 (CH_2–N), 66.1 (CH_2–O), 86.1 (C_2), 150.5 (C_3), 168.3 (C=O); UV (C_2H_5OH): 285 (30,000). (Found: C, 58.55; H, 8.84; N, 15.13. Calc. for $C_9H_{16}N_2O_2$: C, 58.70; H, 8.70; N, 15.22%.) N-phenyl N-methyl 3-pyrrolidinylpropenoamide (**1j**). M.p. 123–125°. IR ($CHCl_3$): 1550 (C=C), 1630 (C=O); PMR ($CDCl_3$): 1.82 (m, 4H, $\underline{CH_2}$–CH_2–N), 3.09 (m, 4H, CH_2–N), 3.30 (s, 3H, CH_3), 4.37 (d, 1H, C_2–H, J = 12.5), 7.31 (s, 5H, aromatic protons), 7.69 (d, 1H, C_3–H, J = 12.5); UV (C_2H_5OH): 298 (27,000). (Found: C, 73.13; H, 7.89; N, 12.12. Calc. for $C_{14}H_{18}N_2O$: C, 73.04; H, 7.83; N, 12.17%.) N-phenyl-N-methyl 3-piperidinylpropenoamide (**1k**). IR ($CHCl_3$): 1565 (C=C), 1635 (C=O); PMR ($CDCl_3$): 1.49 (broad s, 6H, $\underline{(CH_2)_3}$–CH_2–N), 2.97 (broad s, 4H, CH_2–N), 3.30 (s, 3H, CH_3), 4.51 (d, 1H, C_2–H, J = 12.5), 7.24 (s, 5H, aromatic protons, d, 1H, C_3–H); UV (C_2H_5OH): 296 (28,000). N-phenyl N-methyl 3-morpholinylpropenoamide (**1l**). M.p. 91–92°. IR ($CHCl_3$): 1570 (C=C), 1640 (C=O); PMR ($CDCl_3$): 2.99–3.62 (A_2B_2, 8H, morph.–H), 3.30 (s, 3H, CH_3), 4.59 (d, 1H, C_2–H, J = 12.5), 7.30 (s, 5H, aromatic protons), 7.37 (d, 1H, C_3–H), J = 12.5); UV (C_2H_5OH): 292 (30,000). (Found: C, 68.10; H, 7.20; N, 11.22. Calc. for $C_{14}H_{18}N_2O_2$: C, 68.29; H, 7.32; N, 11.38%.) N-p-methoxyphenyl-N-methyl 3-pyrrolidinylpropenoamide (**1m**). M.p. 108–109°. IR ($CHCl_3$): 1560 (C=C), 1635 (C=O); PMR ($CDCl_3$): 1.83 (m, 4H, $\underline{CH_2}$–CH_2–N), 3.10 (m, 4H, CH_2–N), 3.25 (s, 3H, CH_3–N), 3.82 (s, 3H, CH_3–O), 4.31 (d, 1H, C_2–H, J = 13.0), 6.85–7.14 (AB, 4H, aromatic protons), 7.66 (d, 1H, C_3–H, J = 13.0); ^{13}C NMR ($CDCl_3$): 25.2 ($\underline{CH_2}$–CH_2–N), 37.1 (CH_2–N), 49.0 (CH_3–N), 55.4 (CH_3–O), 87.0 (C_2), 114.4–128.8 (C-arom.), 146.7 (C_3); UV (C_2H_5OH): 300 (26,000). (Found: C, 69.40; H, 7.61; N, 10.77. Calc. for $C_{15}H_{20}N_2O_2$: C, 69.23; H, 7.69; N, 10.77%.) N-p-methoxyphenyl-N-methyl 3-piperidinylpropenoamide (**1n**). M.p. 116–117°. IR ($CHCl_3$): 1560 (C=C), 1635 (C=O); PMR ($CDCl_3$): 1.50 (broad s, 6H, $\underline{(CH_2)_3}$–CH_2–N), 2.99 (broad s, 4H, CH_2–N),

3.26 (s, 3H, CH_3–N), 3.80 (s, 3H, CH_3–O), 4.46 (d, 1H, C_2–H, $J = 13.0$), 6.87–7.12 (AB, 4H, aromatic protons), 7.38 (d, 1H, C_3–H, $J = 13.0$); ^{13}C NMR ($CDCl_3$): 24.2 ($\underline{CH_2}$–$(CH_2)_2$–N), 25.3 (CH_2–CH_2–N), 37.1 (CH_2–N), 49.7 (CH_3–N), 55.4 (CH_3–O), 86.2 (C_2), 114.4–128.7 (C-arom.), 150.4 (C_3); UV (C_2H_5OH): 297 (27,500). (Found: C, 69.91; H, 8.09; N, 10.29. Calc. for $C_{16}H_{22}N_2O_2$: C, 70.07; H, 8.03; N, 10.21%.) N-p-methoxyphenyl-N-methyl 3-morpholinylpropenoamide (**1o**). M.p. 109–110°. IR ($CHCl_3$): 1560, 1635 (C=O); PMR ($CDCl_3$): 2.99–3.61 (A_2B_2, 8H, morph.-H), 3.26 (s, 3H, CH_3–N), 3.80 (s, 3H, CH_3–O), 4.56 (d, 1H, C_2–H, $J = 13.5$), 6.87–7.12 (AB, 4H, aromatic protons), 7.32 (d, 1H, C_3–H, $J = 13.5$); ^{13}C NMR ($CDCl_3$): 37.2 (CH_2–N), 48.6 (CH_3–N), 55.4 (CH_3–O), 66.1 (CH_2–O), 88.3 (C_2), 114.6–128.8 (C-arom.), 150.2 (C_3); UV (C_2H_5OH): 293 (20,000). (Found: C, 65.14; H, 7.26; N, 10.14. Calc. for $C_{15}H_{20}N_2O_3$: C, 65.22; H, 7.24; N, 10.15%.)

Reactions of enamine esters with benzyl bromide and cinnamyl bromide.

General procedure. A soln of the enamine ester (**1a–c**, 1 mmol) and the bromide (**2**, **3**, 1 mmol) in MeCN was stirred at elevated temperature as described in the sequel, 0.01 N HCl and THF was added and the mixture was stirred 24 h at room temperature. After evaporation of the solvents water was added and the mixture was extracted with EtOAc. $NaHCO_3$ was added and the aqueous soln was again extracted with EtOAc. The EtOAc extracts were dried and the solvent was evaporated. The residue was chromatographed on a silicagel thick layer plate (2 mm). Starting with ethyl 3-pyrrolidinylpropenoate (**1a**) and benzyl bromide the reaction was carried out 16 h in refluxing MeCN. Elution with $CHCl_3$/cyclohexane (5:1) yielded ethyl 2-benzyl-3-oxopropanoate (**6**, 12%) IR ($CHCl_3$): 1600 (C=C–arom), 1660 (C=C–OH), 1720 (C=O); PMR ($CDCl_3$): 1.42 (2xt, 3H, CH_3), 3.50 (m, 2H, CH_2-arom.), 4.48 (2xq, 2H, CH_2–O), 7.20 (m, 5H, aromatic protons), 8.84 (s, 1H, =C–OH) and ethyl 2, 2-dibenzyl-3-oxopropanoate (**7**, 40%) 2, 4-dinitrophenylhydrazone of **7** mp 118–119° (ethanol); IR ($CHCl_3$): 1600 (C=C), 1715 (C=O); PMR ($CDCl_3$): 1.04 (t, 3H, CH_3), 3.20 (s, 4H, CH_2-arom.), 4.04 (q, 2H, CH_2–O), 7.18 (s, 10H, aromatic protons), 9.79 (s, 1H, H–C=O); MS: 268 (M^+–CHO). (Found: C, 62.23; H, 5.03; N, 11.91. Calc. for $C_{24}H_{24}N_4O_6$, 2, 4-dinitrophenyl-hydrazone of **7**: C, 62.14; H, 5.17; N, 12.05%.)

Starting with ethyl 3-piperidinylpropenoate (**1b**) and benzyl bromide the reaction was carried out 16 h in refluxing MeCN. The precipitate formed at this stage was filtered off from the solution. This precipitate was identified as piperidinium bromide (17%). Elution with $CHCl_3$/cyclohexane (5:1) yielded **6** (58%).

Starting with ethyl 3-morpholinylpropenoate (**1c**) and benzyl bromide the reaction was carried out 40 h in refluxing MeCN. The precipitate formed at this stage was filtered from the solution and after separation identified as a mixture of morpholinium bromide (28%) and N-benzyl-morpholine (11%) IR ($CHCl_3$): 1600 (C=C); PMR ($CDCl_3$): 2.45 (m, 4H, CH_2–N), 3.52 (s, 2H, CH_2-arom), 3.70 (m, 4H, CH_2–O), 7.37 (s, 5H, aromatic protons). Elution with $CHCl_3$/cyclohexane (5:1) yielded **6** (22%) and **7** (22%).

Starting with **1a** and cinnamyl bromide the reaction was carried out 16 h at 55°. Elution with $CHCl_3$/cyclohexane (3:1) yielded ethyl 2-formyl-5-phenyl-4-pentenoate (**8**, 21%) IR ($CHCl_3$): 1600 (C=C–arom.), 1660 (C=C–OH), 1715 (C=O); PMR ($CDCl_3$): 1.24 (2xt, 3H, CH_3), 2.76–2.96 (m, 2H, CH_2–CH=), 3.38 (m, 1H, CH), 4.21 (q, 2H, CH_2–O), 6.30 (m, 2H, CH=CH), 7.26 (s, 5H, aromatic protons), 8.92 (s, 1H, =CH–OH), 9.81 (d, 1H, H–C=O); MS: $m/e = 232$, ethyl 2-formyl-3-phenyl-3-pentenoate (**9**, 34%) IR ($CHCl_3$): 1600 (C=C), 1720 (C=O); PMR ($CDCl_3$): 1.23 (t, 3H, $\underline{CH_3}$–CH_2), 2.75 (d, 3H, $\underline{CH_2}$–CH), 4.25 (q, 2H, CH_2), ±6.30 (m, 2H, CH), **7** 33 (s, 5H, aromatic protons), 9.91 (s, 1H, H–C=O); MS: $m/e = 232$ and 1, 3, 5-tricarbo-ethoxybenzene (**10**, 1%) IR ($CHCl_3$): 1600 (C=C), 1710 (C=O); PMR ($CDCl_3$): 1.43 (t, 9H, CH_3), 4.44 (q, 6H, CH_2), 8.82 (s, 3H, aromatic protons); MS: $m/e = 294$.

Starting with **1b** and cinnamyl bromide the reaction was carried out 16 h at 55°. Elution with $CHCl_3$/cyclohexane (3:1) yielded **8** (49%) and **9** (10%). Starting with **1c** and cinnamyl bromide the reaction was carried out 16 h at 55°. Elution with $CHCl_3$/cyclohexane (3:1) yielded **8** (37%) and **9** (12%).

Reactions of enamine amides with benzyl bromide and cinnamyl bromide

General procedure. A soln of the enamine amide (**1d–o**, 1 mmol) and the bromide (**2**, **3**; 1 mmol) in MeCN was stirred 16 h att 60°. Triethylamine was added and the mixture was stirred 1 h at room temperature. After evaporation of the solvent the residue was chromatographed on a silica gel column (12 mm × 30 cm).

Starting with N, N-tetramethylene 3-pyrrolidinylpropenoamide (**1d**) and benzyl bromide elution was carried out with EtOAc/$CHCl_3$ (4:1) and yielded N, N-tetramethylene 2-benzyl-3-oxopropanoamide (**11**, 51%) 2, 4-dinitrophenylhydrazone of **11** mp 156–159° (EtOAc); IR ($CHCl_3$): 1620 (N–C=O), 1710 (H–C=O); PMR ($CDCl_3$): 1.70 (m, 4H, $\underline{CH_2}$–CH_2–N), ±3.30 (m, 7H, CH_2–N, CH, CH_2-arom.), 7.20 (s, 5H, aromatic protons), 9.71 (d, 1H, H–C=O); MS: $m/e = 231$. (Found: C, 58.39; H, 5.17; N, 16.96. Calc. for $C_{20}H_{21}N_5O_5$ 2, 4-dinitrophenylhydrazone of **11**: C, 58.39, H, 5.11; N, 17.03%.)

Starting with N, N-tetramethylene 3-piperidinylpropenoamide (**1e**) and benzyl bromide and following the usual workup elution was carried out with EtOAc/$CHCl_3$ (4:1), yield of **11** 52%.

Starting with N, N-tetramethylene 3-morpholinylpropenoamide (**1f**) and benzyl bromide and following the usual workup, elution was carried out with EtOAc/$CHCl_3$ (4:1); yield of **11** 40%.

Starting with N, N-pentamethylene 3-morpholinyl-propenoamide (**1g**) and benzyl bromide the reaction was carried out 72 h at 60° (instead of 16 h as described in the general procedure). Following the usual workup elution was carried out with EtOAc/$CHCl_3$ (1:1); yield of **12** 73%. Starting with N, N-ethyleneoxy-ethylene 3-morpholinylpropenoamide (**1h**) and benzyl bromide the reaction was carried out 16 h in refluxing MeCN (instead of 60° as described in the general procedure). Elution with EtOAc/CHCl (1:1) yielded **12** (62%).

Starting with N, N-dimethyl 3-morpholinylpropenoamide (**1i**) and benzyl bromide and following the usual workup elution was carried out with EtOAc/$CHCl_3$ (1:1); yield of **12** 49%.

Starting with **1d** and cinnamyl bromide and following the usual workup elution was carried out with EtOAc/$CHCl_3$ (4:1); yield of 2-formyl-5-phenyl-4-pentenoamide (**13**) 56%. 2, 4-Dinitrophenylhydrazone of **13** mp 206–207° (EtOAc); IR ($CHCl_3$): 1630 (N–C=O), 1715 (H–C=O); PMR ($CDCl_3$): 1.90 (m, 4H, CH_2–CH_2–N), 2.90 (dd, 2H, $\underline{CH_2}$–CH), 3.58 (m, 4H, CH_2–N), ±6.45 (m, 2H, CH=CH), 4.20 (m, 1H, CH), 7.39 (s, 5H, aromatic protons), 9.95 (d, 1H, H–C=O); MS: $m/e = 257$. (Found: C, 60.53; H, 5.33; N, 15.91. Calc. for $C_{22}H_{20}N_4O_5$ 2, 4-dinitrophenylhydrazone of **13**: C, 60.41; H, 5.26; N, 16.02%.) Starting with **1e** and cinnamyl bromide and following the usual workup elution was carried out with EtOAc/$CHCl_3$ (4:1); yield of **13** 55%.

Starting with **1f** and cinnamyl bromide and following the usual workup elution was carried out with EtOAc/$CHCl_3$ (4:1); yield of **13** 43%.

Starting with N-phenyl N-methyl 3-pyrrolidinylpropenoamide (**1j**) and benzyl bromide and following the usual workup, elution was carried out with $CHCl_3$/cyclohexane (5:3); yield of N-benzyl, N-methylaniline (**14a**) 31%. IR ($CHCl_3$): 1595 (C=C); PMR ($CDCl_3$): 2.99 (s, 3H, CH_3), (s, 2H, CH_2), 6.80–7.25, 7.30 (m, s, 10H, aromatic protons).

Starting with N-phenyl, N-methyl 3-piperidinlypropenoamide (**1k**) and benzyl bromide and following the usual workup elution was carried out with $CHCl_3$/cyclohexane (5:3); yield of **14a** 34%.

Starting with N-phenyl N-methyl 3-morpholinylpropenoamide (**11**) and benzyl bromide the reaction was carried out 16 h in refluxing MeCN (instead of 60° as described in the general procedure). Elution was carried out with $CHCl_3$/cyclohexane (5:3); yield of **14a** 49%.

Starting with N-p-methoxyphenyl-N-methyl 3-piperidinyl-propenoamide (**1m**) and benzyl bromide and following the usual workup elution was carried out with $CHCl_3$/cyclohexane (5:3); yield of N-benzyl, N-methyl-p-methoxy-aniline (**14b**) 44%. IR ($CHCl_3$): 1600 (C=C); PMR ($CDCl_3$): 2.88 (s, 3H, CH_3–N), 3.72 (s, 3H, CH_3–O), 4.40 (s, 2H, CH_2), 6.78 (s, 4H, CH_3O-aromatic protons), 7.26 (s, 5H, aromatic protons).

Starting with N-p-methoxypyenyl-N-methyl 3-piperidinyl-propenoamide (**1n**) and benzyl bromide and following the usual

workup elution was carried out with $CHCl_3$/cyclohexane (5:3); yield of **14b** 48%.

Starting with N-p-methoxyphenyl N-methyl 3-morpholinyl-propenoamide (**1o**) and benzyl bromide the reaction was carried out 100 h at 60° (instead of 16 h as described in the general procedure). Elution was carried out with $CHCl_3$/cyclohexane (5:3); yield of **14b** 15%.

Starting with **1j** and cinnamyl bromide and following the usual workup elution was carried out with $CHCl_3$/cyclohexane (5:3); yield of N-cinnamyl, N-methylaniline (**15a**) 19%. IR ($CHCl_3$): 1590 (C=C); PMR ($CDCl_3$): 2.92 (s, 3H, CH_3), 4.02 (d, 2H, CH_2), ±6.43 (m, 2H, CH=CH), 7.24 (s, 5H, aromatic protons).

Starting with **1k** and cinnamyl bromide and following the usual workup elution was carried out with $CHCl_3$/cyclohexane (5:3); yield of **15a** 9%.

Starting with **1l** and cinnamyl bromide and following the usual workup elution was carried out with $CHCl_3$/cyclohexane (5:3); yield of **15a** 5%.

Starting with **1m** and cinnamyl bromide and following the usual workup elution was carried out with $CHCl_3$/cyclohexane (5:1); yield of N-cinnamyl-N-methyl-p-methoxy-aniline (**15b**) 6%, IR ($CHCl_3$): 1590, 1610 (C=C); PMR ($CDCl_3$): 2.89 (s, 3H, CH_3-N), 3.76 (s, 3H, CH_3-O), 3.97 (d, 2H, CH_2), 6.40 (m, 2H, CH=CH), 6.82–7.30 (m, 9H, aromatic protons), and N-p-methoxy-phenyl-N-methyl 2-formyl-5-phenyl-4-pentenoamide (**16**) 37%, mp 154–156°; IR ($CHCl_3$): 1635 (N-C=O); PMR ($CDCl_3$): 2.73 (m, 2H, CH_2), 3.28 (s, 3H, CH_3-N), 3.47 (dt, 1H, CH), 3.82 (s, 3H, CH_3-O), 6.00 (m, 2H, CH=CH), 7.00–7.32, 7.32 (AB, s, 9H, aromatic protons), 9.62 (d, 1H, H-C=O). (*Found*: C, 61.89; H, 4.92; N, 13.74. Calc. for $C_{26}H_{25}N_5O_6$ 2, 4-dinitrophenylhydrazone of **16**: C, 62.03; H, 4.97; N, 13.92%.)

Starting with **1n** and cinnamyl bromide and following the usual workup elution was carried out with $CHCl_3$/cyclohexane (2:1); yield of **15b** 13% and **16** 32%.

Starting with **1o** and cinnamyl bromide and following the usual workup elution was carried out with $CHCl_3$/cyclohexane (2:1); yield of **15b** 10%, **16** 3% and N-cinnamylmorpholine (**17**) 33%, IR ($CHCl_3$): 1600 (C=C); PMR ($CDCl_3$): 2.50 (m, 4H, CH_2-CH_2-N), 3.15 (d, 2H, CH_2-CH=), 3.75 (m, 4H, CH_2-O), 6.25 (m, 2H, CH=CH), 7.32 (s, 5H, aromatic protons).

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