Amine catalysis in the vinylic substitution of α-methylthio-α-arylmethylene Meldrum's acids† and its absence in the substitution of methyl β-iodo-α-nitrocinnamate by amines‡§

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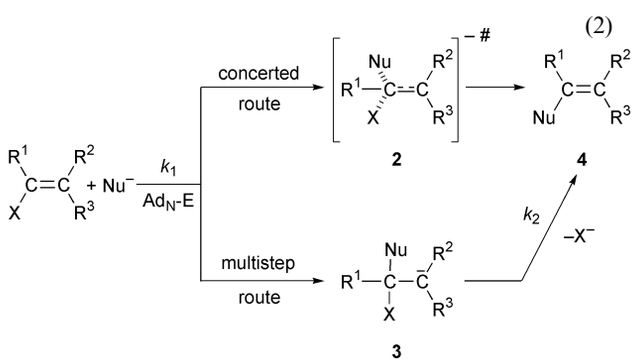
Substitution of the iodine of (*E*)- and (*Z*)-methyl β-iodo-α-nitrocinnamates (**5**) by amines gives identical (*Z*)-enamines with aniline (Ani) and piperidine (Pip). No amine catalysis was observed with Pip, Ani, morpholine (Mor), or *p*-$MeOC_6H_4NHMe$ (MMA) in MeCN nor with Pip or Mor in EtOH: k_{Pip}/k_{Mor} = 115–138 (MeCN), 3.3–6.9 (EtOH); k_{MeCN}/k_{EtOH} = 25.5 ± 2.2 (Pip), 0.79–1.16 (Mor); $k_{(Z)\text{-}5}/k_{(E)\text{-}5}$ = 1.3–2.9 (13.5 with MMA in MeCN). Replacement of the MeS group in six α-methylthio-α-arylmethylene Meldrum's acid (**6-X**) by Pip resulted in amine catalysis in MeCN and EtOH. In EtOH, the *p*-anisyl derivative (**6-MeO**) and in MeCN **6-MeO**, **6-Me** and **6-H** displayed second order catalysis in Pip. Other **6-X** compounds show orders between one and two in Pip with amine catalyzed (k_{3B})/non-catalyzed (k_2) rate coefficient ratios of 281–731 (EtOH) and 504–635 (MeCN) at 30 °C. k_{MeCN}/k_{EtOH} = 3.0–4.9. In MeCN $\Delta H^{\ddagger} = -0.8$ to -5.9 kcal mol^{-1} and $\Delta S^{\ddagger} = -50$ to -72 e.u. An intermediate zwitterion, **3a**, is formed in all cases. For system **5** the rate of I^- expulsion from **3a** exceeds its deprotonation rate, and the observed rate coefficient is composite: $k_{obs} = k_1k_2/k_{-1}$ in MeCN (k_1 = rate coefficient of nucleophilic attack) but $k_{obs} = k_1$ in EtOH. In MeCN the deprotonation is faster than the expulsion rate of MeS^-, and more so for **6-X** with X = *p*-Br, *p*-CF_3, *m*,*m*′-$(CF_3)_2$. Different electrophilicities of **6-X**, different extents of hydrogen bonding, steric and electronic effects account for the kinetic differences.

A major question concerning the mechanism of nucleophilic vinylic substitution of an electrophilic alkene [eqn. (1), X^- =

$$R^1C_\alpha(X)=C_\beta R^2R^3 + Nu^- \longrightarrow R^1C_\alpha(Nu)=C_\beta R^2R^3 + X^- \quad (1)$$

nucleofuge (leaving group), Nu^- = anionic nucleophile][1] is whether the reaction proceeds *via* a single step (concerted) route *via* transition state **2** [eqn. (2)] or whether it is a multi-step route



proceeding *via* formation of intermediate **3** which expels X^- to form the product **4**. Several major probes which were applied to answer this question[1g] are (a) the stereochemistry of the reaction, since an intermediate carbanion will give stereoconvergence of the product starting from the pure (*E*)- or (*Z*)-precursor;[1] (b) the element effect, *i.e.*, when X = halogen the concerted route would show k_F/k_{Cl}, $k_{Cl}/k_{Br} << 1$ and the multi-step route would give $k_F/k_{Cl} >> 1$, $k_{Br}/k_{Cl} \approx 1$);[1] (c) the kinetics, since a deviation from an overall second order reaction may indicate the formation of an intermediate;[1] (d) calculations which compare the energies, and hence the feasibility of both routes;[1g,2] and (e) attempts or success in direct observation of the intermediate **3**.[3] The main conclusion from the study of many systems is that the transition state is variable[1d,f] and that the reaction may be concerted when X is a very good nucleofuge and the alkene is only slightly electrophilic, whereas highly electrophilic alkenes, especially those carrying a poor or a moderate nucleofuge, react *via* the multi-step route.

A variation of eqn. (2) is when the nucleophile is neutral, mostly an amine. The first-formed intermediate is then the zwitterion **3a** rather than a carbanion[3b] [eqn. (2a)]. In moderately electrophilic alkenes, *i.e.*, when only one of the groups R^2 or R^3 is a strongly electron-withdrawing group (EWG) the kinetics are of an overall second order, *i.e.*, first order in the amine. However, with highly electrophilic alkenes when both R^2 and R^3 are strongly EWGs the reaction will proceed by two multi-step routes, a second order **1**⟶**3a**⟶**4** process and a third order **1**⟶**3a**⟶**3b**⟶**4** process. This is because the expulsion rate coefficient of X^- (k_2) in carbanions **3** is usually very high compared with the nucleophilic attack step k_1 which becomes rate determining, leading to an overall second order. In the zwitterion **3a** the expulsion rate of X^- is significantly reduced due to the strong electron withdrawal by the positively charged ammonio moiety. The longer life-time and the presence of the acidic proton in **3a** enables a rate limiting proton transfer from **3a** to another amine molecule (k_{3B}), forming carbanion **3b**, which expels X^- rapidly to form **4** [eqn. (2a)].

A steady state treatment of eqn. (2a) gives rate eqn. (3) and the observed *second order* rate coefficient k_{obs} is given by eqn. (4). The observed kinetics will depend on the relative

† The IUPAC name for Meldrum's acid is 2,2-dimethyl-1,3-dioxane-4,6-dione.

‡ Dedicated to the memory of Lennart Eberson, a friend and a great chemist.

§ Electronic supplementary information (ESI) available: stereoviews of compounds **7a** and **7b** and experimental details of X-ray crystallography. See http://www.rsc.org/suppdata/p2/b1/b103486n/

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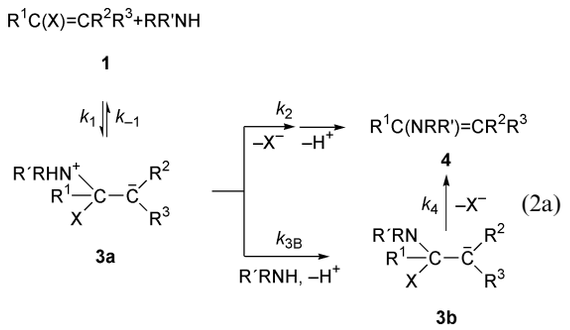


(2a)

$$\text{Rate} = k_1[\mathbf{1}][\text{Amine}]\{k_2 + k_{3B}[\text{Amine}]\}/\{k_{-1} + k_2 + k_{3B}[\text{Amine}]\} \quad (3)$$

$$k_{obs} = \text{Rate}/[\mathbf{1}][\text{Amine}] = k_1\{k_2 + k_{3B}[\text{Amine}]\}/\{k_{-1} + k_2 + k_{3B}[\text{Amine}]\} \quad (4)$$

importance of the competing non-catalyzed (k_2) and the base (B) catalyzed (k_{3B}) terms. If $k_{-1} < k_2 + k_{3B}[\text{Amine}]$ eqn. (5)

$$k_{obs} = k_1 \quad (5)$$

applies and k_1 becomes rate determining. This is expected to apply in most cases when X is a good nucleofuge. However, when X is a poor nucleofuge k_2 is smaller than in the previous case, and the inequality $k_{-1} > k_2 + k_{3B}[\text{Amine}]$ and hence eqn. (6) may apply, *i.e.*, both routes compete with one another.

$$k_{obs} = k_1k_2/k_{-1} + k_1k_3[\text{Amine}]/k_{-1} \quad (6)$$

Three kinetic situations could therefore be observed: (a) no dependence of k_{obs} on the amine [eqn. (5)]; (b) a linear k_{obs} *vs.* [Amine] plot [eqn. (6)] whose slope is k_1k_{3B}/k_{-1} and intercept k_1k_2/k_{-1} give the k_{3B}/k_2 ratios; (c) a non-linear k_{obs} *vs.* [Amine] plot [eqn. (4)] which leads to an inverted $1/k_{obs}$ *vs.* 1/[Amine] linear plot [eqn. (7)] whose intercept and slope are $1/k_1$ and k_{-1}/k_1k_{3B}, respectively.

$$1/k_{obs} = 1/k_1 + (k_{-1}/k_1k_3)(1/[\text{Amine}]) \quad (7)$$

The three situations were experimentally observed: (a) amine catalysis was not observed in the major part of vinylic substitutions which include moderately activated systems carrying good nucleofuges such as Cl, Br;[1] (b) linear k_{obs} *vs.* [Amine] plots were observed in the substitution of systems carrying poor nucleofuges such as F, OR, CN and the reactions were of a second order or of an order between 1 and 2 in the amine. In aprotic solvents the k_{3B}/k_2 ratios were usually higher than in protic solvents.[4]

Since amine catalysis serves as evidence for the multi-step route, a search of such catalysis for systems carrying a good nucleofuge, where unequivocal evidence for this route is meagre, was conducted. The prediction that in such systems the k_{3B}/k_2 ratios would be very low was fulfilled, but catalysis was observed only for the highly activated β,β-dicyano activated system **4** (X = Cl, Br)[4a,e] and for (*Z*)-α,β-dinitrostilbene.[4g] In all cases the k_{3B}/k_2 ratios were indeed low.

$$\text{ArC(X)=C(CN)}_2$$

4, Ar = *p*-$Me_2NC_6H_4$, *p*-$O_2NC_6H_4$; X = Cl, Br

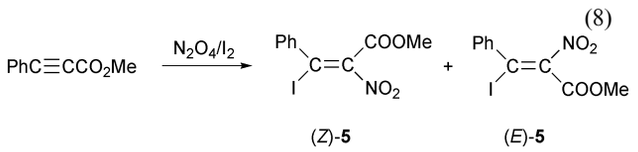
(c) Curved k_{obs} *vs.* [Amine] plots which give inverted $1/k_{obs}$ *vs.* 1/[Amine] plots were found for activated systems carrying poor nucleofuges such as OEt or OCH_2CF_3.[4c,f]

In the present work we extended these studies to two additional systems. We looked for amine catalysis in the reaction of β-iodo-α-nitrocinnamate **5**, a system highly activated by both NO_2 and CO_2Me groups, where the stereoconvergence in the substitution of (*E*)-**5** and (*Z*)-**5** by a thio-nucleophile[5] indicates a multi-step route although iodine is a good nucleofuge. Systems activated by a Meldrum's acid residue which are capable of an extensive negative charge dispersal are also expected to show amine catalysis. Since we were unable to prepare such systems which carry good nucleofuges we studied such systems (**6**) which carry the moderate nucleofuge MeS. Vinylic substitution in such systems was previously investigated with anionic nucleophiles.[3i,j,m] We expected to observe amine catalysis and to compare the observed ratios of rate coefficients with those of other activated systems.

Results

Precursors

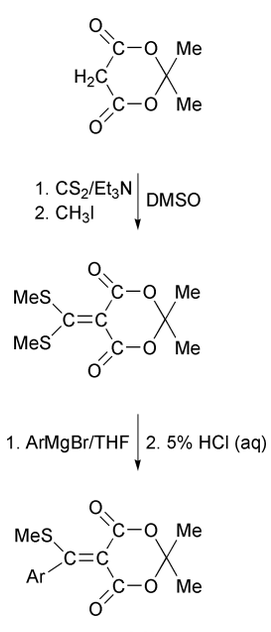
A mixture of (*E*)-**5** and (*Z*)-**5** was prepared by addition of nitrogen tetraoxide and iodine to methyl phenylpropiolate [eqn. (8)]. The preparation and separation to isomers[5] will be discussed elsewhere.



(8)

(*Z*)-**5** (*E*)-**5**

The six Meldrum's acid derivatives **6-X** (X = *p*-MeO, *p*-Me, H, *p*-Br, *m*-CF_3, *m*,*m*′-$(CF_3)_2$) were prepared in two consecutive steps. (1) Reaction of Meldrum's acid with CS_2 and Et_3N and alkylation of the formed dianion with methyl iodide in DMSO led to the 5-bis(methylthio)vinylidene derivative. (2) Vinylic substitution of a MeS group of the vinylidene derivative by an aryl group using arylmagnesium bromide [eqn. (9)].[6]



(9)

6-X

Substitution

A single geometrical isomer of each of the substitution products **7a**–**d** was obtained starting from either (*E*)-**5** or (*Z*)-**5** with aniline (Ani), piperidine (Pip), morpholine (Mor) or *p*-methoxy-*N*-methylaniline (MMA). Enamines **7a**–**d** were synthesised according to eqn. (10) on a preparative scale and identified. The substitution products **8-X** of **6-X** were prepared according to eqn. (11) and identified by microanalysis when sufficient material was available and by spectroscopic data (including HRMS) when available amounts were very small.

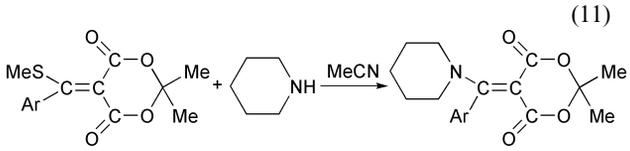
Table 1 Rate coefficients for the reaction of (*E*)-**5** and (*Z*)-**5** with amines at 30 °C[a]

Substrate	Amine	10^3[Amine]/M	Solvent	Order in amine	$10^3 k_{obs}$/M^{-1} s^{-1}
(*Z*)-**5**	Piperidine	1.1–1.9	MeCN	1	1770
(*E*)-**5**	Piperidine	72–95	MeCN	1	725
(*Z*)-**5**	Morpholine	0.75–10	MeCN	1	12.8
(*E*)-**5**	Morpholine	0.75–5.0	MeCN	1	6.3
(*Z*)-**5**	Aniline	9.1–35	MeCN	1	0.8
(*E*)-**5**	Aniline	5.0–24	MeCN	1	0.6
(*Z*)-**5**	*p*-$MeOC_6H_4NHMe$	49–80	MeCN	1	3.1
(*E*)-**5**	*p*-$MeOC_6H_4NHMe$	49–80	MeCN	1	0.2
(*Z*)-**5**	Piperidine	1.2–9.7	EtOH	1	76.0
(*E*)-**5**	Piperidine	5.0–25	EtOH	1	26.2
(*Z*)-**5**	Morpholine	5.0–29	EtOH	1	11.0
(*E*)-**5**	Morpholine	5.0–20	EtOH	1	8.0
(*Z*)-**5**	Aniline	6.0–290	THF[b]	1	0.16
(*E*)-**5**	1,3,5-(*t*-$Bu)_3C_6H_2NH_2$	10	MeCN	[c]	

[a] [Substrate] = 10^{-4} M. [b] Reaction in THF is very slow and no further experiments were conducted. [c] No reaction during 48 hours.

(*E*)-**5** or (*Z*)-**5** + RR´NH $\xrightarrow{\text{MeCN}}$ Ph(R´RN)C=C(COOMe)NO_2 (10)

7 a: RR´NH = Aniline (Ani)
b: RR´NH = Piperidine (Pip)
c: RR´NH = Morpholine (Mor)
d: RR´NH = *p*-$MeOC_6H_4NHMe$ (MMA)



(11)

6-X **8-X**

X = *p*-MeO (**6-OMe** and **8-OMe**), *p*-Me (**6-Me** and **8-Me**), H (**6-H** and **8-H**), *p*-Br (**6-Br** and **8-Br**), *p*-CF_3 (**6-CF_3** and **8-CF_3**), *m*,*m*´-$(CF_3)_2$((**6-CF_3**)$_2$ and **8-$(CF_3)_2$**)

Kinetics

The kinetics of the reaction of (*E*)-**5** and (*Z*)-**5** with piperidine, morpholine, aniline and *p*-methoxy-*N*-methylaniline in MeCN and of piperidine and morpholine in EtOH were followed. No reaction of (*E*)-**5** with the bulky amine 1,3,5-tri-*tert*-butylaniline in MeCN was observed after 48 hours at 30 °C. Also no (*E*)-**5** $\rightleftharpoons$ (*Z*)-**5** isomerization was observed during the substitution. All the reactions were of an overall second order, being first order each in the amine and the substrate. No amine catalysis was observed in spite of the use of amines within an appreciable pK_a range. The results are given in Table 1.

Three reactivity ratios of pairs of nucleophiles, *i.e.*, k_{Pip}/k_{Mor}, k_{Pip}/k_{Ani} and k_{Pip}/k_{MMA} are given in Table 2. Piperidine was always the most reactive nucleophile, *e.g.*, with (*Z*)-**5** in MeCN the relative reactivities were 1 ($PhNH_2$) < 4.1 (*p*-$MeOC_6H_4$-NHMe) < 16 (morpholine) < 2212 (piperidine). However, the relative reactivities were much smaller in the protic EtOH, *i.e.*, the k_{Pip}/k_{Mor} reactivity ratios were 20–35 fold higher in MeCN. Solvent effects k_{MeCN}/k_{EtOH} were strongly dependent on the amine. Aniline reacted five times faster with (*Z*)-**5** in MeCN than in THF (Table 3).

The relative reactivities of (*Z*)-**5** to (*E*)-**5** for piperidine, morpholine and aniline are similar, with (*Z*)-**5** being 1.3–2.9 fold more reactive in MeCN and EtOH. Only with *p*-methoxy-*N*-methylaniline does this ratio increase significantly in MeCN to 15.5 (Table 4).

Reaction of piperidine with 6-X

The substitution by amines was extended to system **6** carrying the SMe nucleofuge, and five single substituents and one pair of *m*-F in the aromatic ring (**6-X**). These are *a priori* better candidates to show amine catalysis than system **5** since MeS^- is a much poorer nucleofuge than I^- and the non-catalytic expulsion rate coefficient k_2 becomes less competitive with the catalyzed route (rate constant k_{3B}[Pip]). System **6** also enables a study of the substituent effect on the competition between the two routes.

Tables 5–7 give the rate coefficients for the reaction of **6-X** with piperidine in MeCN at 30 and 40 °C and in EtOH at 30 °C. D_∞ values were measured at ≥10 half-lives. The amine concentrations were much higher than those of **6-X**, and a pseudo first order equation was used. Several measurements were taken and the estimated errors in the rate coefficients and in the plots used to calculate them are $R^2 \geq 0.99$. Isosbestic points were detected for each of the reactions. The plots of the second order k_{obs} *vs.* [Amine] were usually linear [eqn. (12)]. Their slopes and intercepts are the rate coefficients k' and k''. Assuming that eqn. (2a) and hence eqn. (4) describe the mechanism, comparison of

Table 2 Relative rates of reactions of nucleophiles with (*E*)- and (*Z*)-**5** at 30 °C[a]

Substrate	Solvent	k_{Pip}/k_{Mor}	k_{Pip}/k_{Ani}	k_{Pip}/k_{MMA}
(*Z*)-**5**	MeCN	138	2212	571
(*E*)-**5**	MeCN	115	1208	3625
(*Z*)-**5**	EtOH	6.9		
(*E*)-**5**	EtOH	3.3		

[a] Pip = Piperidine. Mor = Morpholine. Ani = Aniline. MMA = *p*-Methoxy-*N*-methylaniline.

Table 3 Solvent effect on the relative reactivities of (*E*)-**5** and (*Z*)-**5** at 30 °C

System	k_{MeCN}/k_{EtOH}	k_{MeCN}/k_{THF}
Piperidine + (*Z*)-**5**	23.3	
Morpholine + (*Z*)-**5**	1.16	
Piperidine + (*E*)-**5**	27.7	
Morpholine + (*E*)-**5**	0.79	
Aniline + (*Z*)-**5**		5.0

Table 4 Reactivity differences of (*E*)-**5** and (*Z*)-**5** at 30 °C

Amine	Solvent	$k_{(Z)\text{-}5}/k_{(E)\text{-}5}$
Piperidine	MeCN	2.4
Piperidine	EtOH	2.9
Morpholine	MeCN	2.0
Morpholine	EtOH	1.4
Aniline	MeCN	1.3
p-$MeOC_6H_4NHMe$	MeCN	15.5

Table 5 Rate coefficients for the reactions of **6-X** with piperidine in EtOH at 30 °C

Substrate	10^3[Amine]/M	Order in amine	$k'/M^{-1}\ s^{-1}$	$k''/M^{-2}\ s^{-1}$	$k''/k' = k_{3B}/k_2/M^{-1}$	$k'''/M\ s$	$k''''/M^2\ s$	$k'''/k'''' = k_{3B}/k_1/M^{-1}$
6-MeO	6.2–11	2	0.0022	6.82	3100			
6-Me	7.4–12	1–2	0.018	7.12	395			
6-H	5.0–9.9	1–2	0.014	10.24	731			
6-Br	3.7–8.7	1–2	0.074	20.58	281			
6-CF_3	3.7–6.2	1–2	0.079	30.00	380			
6-$(CF_3)_2$	0.62–3.1	1–2				1.44	0.0021	686

Table 6 Rate coefficients for the reactions of **6-X** with piperidine in MeCN at 30 °C[a]

Substrate	10^3 [Amine]/M	Order in amine	$k'/M^{-1}\ s^{-1}$	$k''/M^{-2}\ s^{-1}$	$k''/k'/M^{-1}$
6-OMe	2.5–7.4	2	0.004	20.4	5100
6-Me	1.2–3.7	2	0.007	27.7	3960
6-H	3.7–6.2	2	0.036	34.8	9670
6-Br	1.2–3.7	1–2	0.12	76.2	635
6-CF_3	1.2–3.7	1–2	0.29	146.0	504
6-$(CF_3)_2$	0.6–1.8	1–2	0.58	341.0	589

[a] [Substrate] = 5.8–6.0 × 10^{-5} M.

Table 7 Rate coefficients for the reactions of **6-X** with piperidine in MeCN at 40 °C[a]

Substrate	10^3[Amine]/M	Order in amine	$k'/M^{-1}\ s^{-1}$	$k''/M^{-2}\ s^{-1}$	$k''/k'/M^{-1}$
6-OMe	2.2–3.7	2	0.0011	17.5	15910
6-Me	2.5–5.0	2	0.0017	20.9	12290
6-H	3.7–6.2	2	0.0013	27.3	21000
6-Br	1.2–3.7	1–2	0.093	61.0	656
6-CF_3	1.2–2.4	1–2	0.044	140.8	3200
6-$(CF_3)_2$	0.6–1.8	1–2	0.61	336.2	551

[a] [Substrate] = 5.8–6.0 × 10^{-5} M.

eqn. (4) and (12) give the k_{3B}/k_2 and k_{3B}/k_1 ratios in terms of k' and k'' [eqn. (13) and Tables 5–7].

$$k_{obs} = k' + k''[\text{Amine}] \quad (12)$$

$$k' = k_1k_2/k_{-1}; \quad k'' = k_1k_{3B}/k_{-1} \quad (13)$$

Compound **6-$(CF_3)_2$** reacted slowly both in EtOH or in EtOH containing Et_3N in the absence of piperidine. Substitution by EtO^- (and less likely by EtOH) may be responsible. The product was not isolated. The half-life of the reaction in EtOH was *ca.* 24 h at 30 °C ($k_{obs} = 1.16 \times 10^{-5}\ s^{-1}$), whereas with added piperidine the half-lives were 80–730 min, depending on the amine concentration.

The order of the reaction in the amine was substrate- and solvent-dependent. In EtOH only **6-OMe** having the least electron-withdrawing aryl group displayed a second order reaction in the amine. For all other substrates the order in the amine was between 1 and 2 and the catalysis was extensive, k''/k' ratios being 281–731. The reaction of **6-$(CF_3)_2$** with piperidine was the only one which did not give a linear k_{obs} *vs.* [Amine] plot [Fig. 1a, eqn. (14)]. However, a plot of $1/k_{obs}$ *vs.* 1/[Amine] was linear (Fig. 1b) and the derived k''' and k'''' terms and their mechanistic equivalents [eqn. (15)] are given in Table 5.

$$1/k_{obs} = k''' + k''''/[\text{Amine}] \quad (14)$$

$$k''' = 1/k_1; \quad k'''' = k_{-1}/k_2k_{3B} \quad (15)$$

The substitution rate increased on increasing the electron-withdrawing ability of the substituent except that **6-H** was slower than **6-Me**. In MeCN the dependence of the reaction rate on the substituents followed that in EtOH. However, the order in the amine was two for **6-OMe**, **6-Me** and **6-H** and only systems with more electron withdrawing substituents X displayed an order between 1 and 2 in the amine. Fig. 2 is a plot of the second order k_{obs} *vs.* [piperidine] for **6-OMe** in EtOH at 30 °C, and its linearity (and the small intercept) demonstrate the overall third order of the reaction.

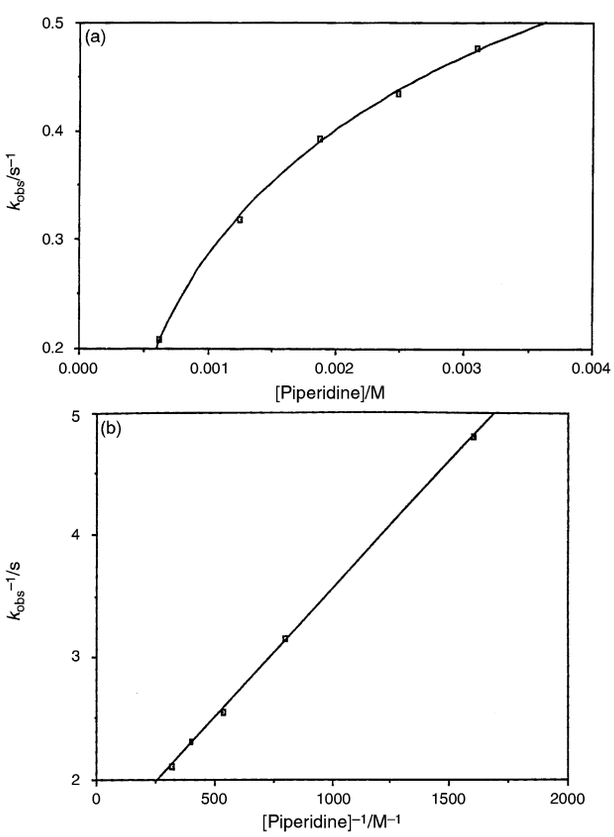


Fig. 1 (a) A k_{obs} *vs.* [Amine] plot for the reaction of piperidine with **6-$(CF_3)_2$** in EtOH at 30 °C. (b) A $1/k_{obs}$ *vs.* 1/[Amine] plot for the same reaction.

Table 8 Activation parameters for the reactions of **6-X** in MeCN[a]

Substrate	E_a/kcal mol^{-1}	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
6-OMe	−3.0	−3.6	−64.4
6-Me	−5.3	−5.9	−71.6
6-H	−1.1	−1.8	−57.5
6-Br	−1.1	−1.7	−55.7
6-CF$_3$	−0.2	−0.8	−69.5
6-(CF$_3$)$_2$	−0.3	−0.9	−49.9

[a] Based on k'' values.

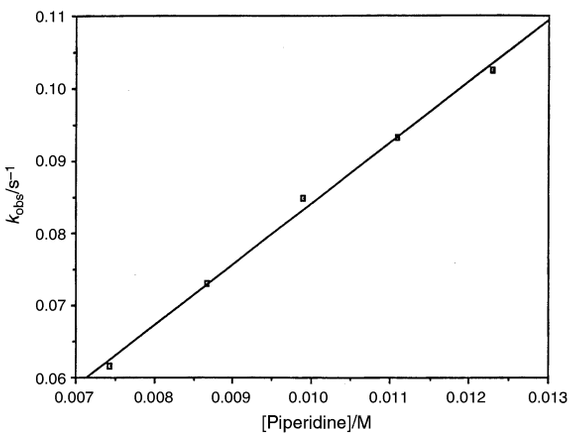


Fig. 2 A plot of k_{obs} of **6-OMe** *vs.* [piperidine] in EtOH at 30 °C.

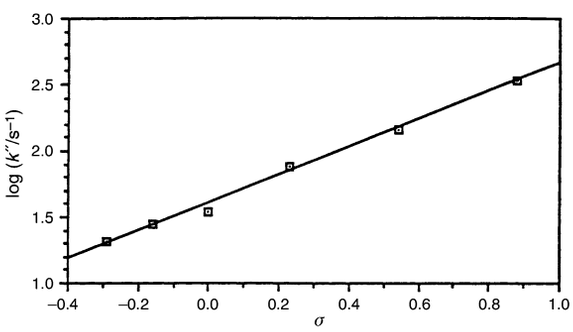


Fig. 3 A log k_{obs} *vs.* σ plot for **6-X** at 30 °C in MeCN.

Hammett plots of log k'' *vs.* σ values for **6-X** with piperidine in EtOH at 30 °C and in MeCN at 30 (Fig. 3) and 40 °C are linear except that in MeCN **6-H** shows slightly negative deviations at both temperatures, giving ρ values of 1.06 (30 °C) and 1.14 (40 °C) with correlation coefficients $R^2 > 0.98$. In EtOH the linearity is only approximate with $R^2 = 0.96$ and $\rho = 0.85$ (30 °C).

With the caution required when using two close temperatures (30 and 40 °C) for calculating the activation parameters, all the E_a and $\Delta H^{\ddagger}$ values in MeCN are slightly negative ($E_a = -0.2$–-3.0 and $\Delta H^{\ddagger} = -0.8$–$-5.9$ kcal mol^{-1}) and the activation entropies are highly negative (−50–−72 e.u.) (Table 8).

The aprotic (MeCN) *vs.* protic (EtOH) reactivity ratios do not differ significantly with the substituent: $k_{MeCN}/k_{EtOH} = 3.0$–4.9, with the lowest value for **6-OMe** and the highest value for **6-(CF$_3$)$_2$** but with no observed trend for the whole set (Table 9).

Crystallographic data for the substituted enamines formed from 5 with piperidine and aniline

The solid state structures of the aniline and the piperidine enamines (**7a** and **7b**) formed by the substitution of either (*E*)-**5** or (*Z*)-**5** in MeCN with aniline and piperidine, respectively,

Table 9 k_{MeCN}/k_{EtOH} ratios in the reactions of **6-X** with piperidine at 30 °C

Substrate	k_{MeCN}/k_{EtOH}
6-OMe	3.0
6-Me	3.9
6-H	3.4
6-Br	3.7
6-CF$_3$	4.9

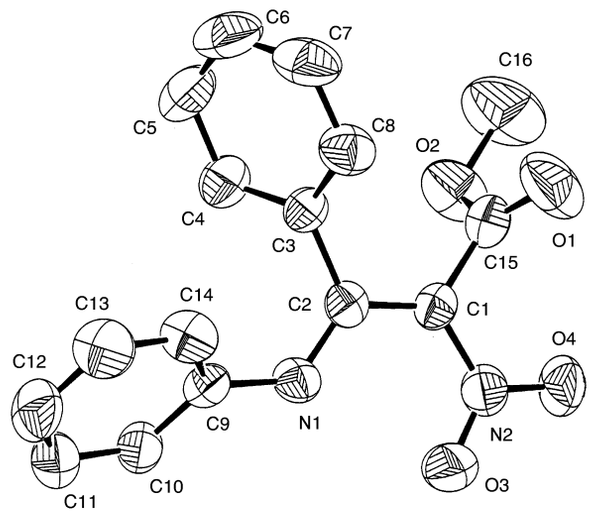


Fig. 4 An ORTEP drawing of **7a**.

were determined by X-ray diffractions of single crystals. The formation of the same product from both isomers is ascribed to post-isomerization, *i.e.*, a rapid isomerization of the least stable to the most stable enamine after substitution, a known phenomenon in the vinylic substitution by amines.[1a,7]

The structure around the double bond is of interest, since it was suggested for β-nitroenamines having an amino hydrogen that hydrogen bonding between the NH and the NO_2 groups determines the configuration[4g,8] However, in our system there are two EWGs, an NO_2 and a CO_2Me, and the question is which one will be the preferred acceptor of hydrogen bonding in **7a**. Moreover, since no N–H proton is present in **7b** a related question is what will be its structure in the absence of hydrogen bonding. It was previously suggested for similar β-nitroenamines that the NO_2 and amino groups will still be *cis* to one another,[4g] and the X-ray structure of PhC(NO_2)=C(Ph)NC_4H_8O (NC_4H_8O = morpholino) shows a (*Z*)-configuration.[9]

The ORTEP structure of **7a** is shown in Fig. 4 and bond lengths and angles are in Table 10. Analogous data for **7b** are given in Fig. 5 and Table 11. Additional data, including the stereoviews of **7a** and **7b** are available as supplementary data.§ In both **7a** and **7b** the amino and the nitro groups are *cis* to one another in a (*Z*)-configuration, suggesting a preferred hydrogen bonding to the nitro group. Although an $NO_2 \cdots HN$ hydrogen bonding may be important in the structure of **7a**, the similar structure of **7b** where such a bond is impossible may indicate that hydrogen bonding is not necessarily the major structure determining factor.

Interesting features are: (a) the long C(1)–C(2) bonds of 1.378 and 1.408 Å, resulting from the partial single bond character of the double bond due to the contribution of valence hybrid **9**; (b) the wider angles around the double bond are N(1)–C(2)–C(1) and C(2)–C(1)–C(15), *i.e.*, between pairs of *trans*-substituents and the double bond; (c) the double bond is twisted, by 4.2° for **7a** and by 32.6° for **7b**; (d) the dihedral angle of the Ph group and the C(3)–C(2)–N(1) plane is 24.9° for **7a** and 53° for **7b**.

Table 10 Selected bond lengths and angles for **7a**

Bond	Length/Å	Bonds	Angle/°
C(1)–C(2)	1.378(5)	C(2)–C(1)–C(15)	123.8(4)
C(1)–C(15)	1.487(6)	N(1)–C(2)–C(1)	124.3(4)
C(2)–C(3)	1.491(6)	N(1)–C(2)–C(3)	119.2(4)
C–C(Ar)	1.355(8)–1.389(6)	C(1)–C(2)–C(3)	116.5(4)
C–C(Ani)	1.368(7)–1.380(8)	C(2)–C(3)–C(4)	119.7(4)
O(1)–C(15)	1.187(5)	C(2)–C(3)–C(8)	120.8(4)
O(2)–C(15)	1.315(5)	C–C–C(Ar)	119.5(4)–120.8(5)
O(2)–O(14)	1.447(6)	N(1)–C(9)–C(10)	118.6(4)
N(2)–O	1.243(4)–1.244(4)	N(1)–C(9)–C(14)	121.6(4)
N(1)–C(2)	1.330(5)	C–C–C(Ani)	119.5(4)–120.8(5)
N(1)–C(9)	1.429(5)	O(1)–C(15)–O(2)	123.1(4)
		O(1)–C(15)–C(1)	125.8(5)
		O(2)–C(15)–C(1)	111.1(4)
		C(15)–O(2)–C(16)	115.9(4)
		C(2)–N(1)–C(9)	128.5(4)
		O(3)–N(2)–O(4)	121.1(4)
		2N–O–C	118.5(4)–120.5(4)
		N(2)–C(1)–C(2)	122.7(4)
		N(2)–C(1)–C(15)	113.4(4)
		N(2)–C(1)–C(15)–N(1)–C(2)–C(3)[a]	175.76
		C(15)–C(1)–N(2)–O(3)–O(4)[a]	178.27
		O(1)–O(2)–C(15)–C(1)–N(2)[a]	80.21
		Ph–C(2)–N(1)[a]	114.87
		Ani–C(2)–C(3)[a]	48.57

[a] Dihedral angle.

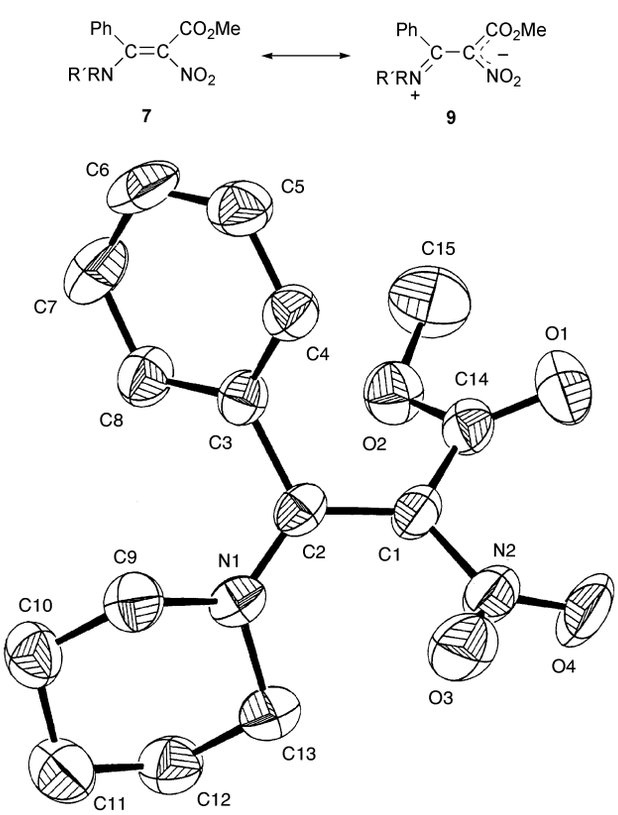


Fig. 5 An ORTEP drawing of **7b**.

Discussion

The study of amine catalysis in the substitution of aromatic and vinylic systems carrying a poor nucleofuge has been used to investigate whether the substitution is a single-step or multi-step process. For a first order reaction in the amine the kinetics are of little help in answering the question since both the single step and the multi-step routes are first order in the amine. However, if the reaction displays amine catalysis, *i.e.*, a kinetic order in the amine greater than one, it is clear that an intermediate which is formed in the reaction with one amine molecule reacts further with a second amine molecule. The difference between an anionic and a neutral amine nucleophile is that the intermediate in the multi-step route is the zwitterion **3a** [eqn. (2a)], rather than the carbanion **3b** [eqn. (2a)]. Electron-withdrawal by the ammonio moiety of **3a** reduces the expulsion rate k_2 of the nucleofuge, compared with the related value from the corresponding anion **3b** when the neutral amino group assists the nucleofuge expulsion by the resonative electron-donation of its non-bonded electron pairs.

Reactions of the α-nitro activated system

In the study of system **5** we intended to find out if increased activation in a system which carries simultaneously the two strong electron-withdrawing groups CO_2Me and NO_2 but also a good iodo nucleofuge would show amine catalysis. β-Chloro- or β-iodo-α-nitrostilbene[4g] or β-chloro-α-nitrostyrene[10] do not show amine catalysis on substitution by amines. We assume that the activation is sufficient to give a multi-step route *via* zwitterion **3a** judged by (a) previous studies of system **5** with a thio nucleophile,[3i,j,m] (b) the pK_a(CH_2YY')'s in 1 : 1 DMSO–H_2O of $CH_2(NO_2)CO_2Me$ (5.95)[3m] and $CH_2(CN)_2$ (10.21)[3m] and the correlations between pK_a(CH_2YY') and the equilibrium constant for intermediate formation or the life-time of the intermediate and (c) the mild catalysis observed for **4**, X = Cl, Br.[4a,f] However, higher electron withdrawal also means a higher acidity of the ammonio hydrogen, and if the rate of this proton expulsion is roughly correlated with its acidity, the k_{3B} term should also increase for system **5**, unless k_{3B} is diffusion controlled and insensitive to substitution. Consequently, it is difficult to predict how the k_{3B}/k_2 ratio will be affected for **5**.

The basicity and nucleophilicity of the amine should also affect rate constants k_{3B} and k_1 and, since the catalysis for systems **4** was observed with weak anilino nucleophiles, we used both weakly basic primary and secondary aniline bases, *i.e.*, aniline [pK_a(H_2O) = 4.6][11a] and *p*-$MeOC_6H_4NHMe$ [pK_a-(H_2O) = 5.36],[11b] and more basic amines such as morpholine and piperidine [pK_a(H_2O) = 8.33 and 11.12, respectively].[11a] Whereas the latter amines gave convenient rates the former were rather slow.

The lack of observed amine catalysis, regardless of the amine used, could be due to two different reasons: either to the

Table 11 Selected bond lengths and angles for **7b**

Bond	Length/Å	Bonds	Angle/°
O(1)–C(14)	1.208(4)	C(14)–O(2)–C(15)	117.1(3)
O(2)–C(14)	1.350(4)	C(2)–N(1)–C(9)	123.8(3)
O(2)–C(15)	1.440(5)	C(2)–N(1)–C(13)	122.8(3)
O(3)–N(2)	1.232(4)	C(9)–N(1)–C(13)	113.2(3)
O(4)–N(2)	1.243(4)	O(3)–N(2)–O(4)	121.9(3)
N(1)–C(1)	1.331(4)	O(3)–N(2)–C(1)	119.7(3)
N(1)–C(9)	1.480(4)	O(4)–N(2)–C(1)	118.3(3)
N(1)–C(13)	1.466(4)	N(2)–C(1)–C(2)	120.9(3)
4C–C(Pip)	1.511(5)–1.518(5)	N(2)–C(1)–C(14)	116.8(3)
N(2)–C(1)	1.415(4)	C(2)–C(1)–C(14)	122.2(3)
C(1)–C(2)	1.408(4)	N(1)–C(2)–C(1)	124.2(3)
C(1)–C(14)	1.456(5)	N(1)–C(2)–C(3)	117.8(3)
C(2)–C(3)	1.495(4)	C(1)–C(2)–C(3)	118.0(3)
C–C(Ar)	1.370(5)–1.384(5)	C(2)–C(3)–C(4)	119.8(3)
		C(2)–C(3)–C(8)	120.2(3)
		C–C–C(Ar)	119.6(3)–120.2(3)
		N–C–C(Pip)	109.6(3)–111.5(3)
		C–C–C(Pip)	110.5(3)–112.3(3)
		O(1)–C(14)–O(2)	121.7(3)
		O(1)–C(14)–C(1)	127.4(3)
		O(2)–C(14)–C(1)	110.9(3)
		N(2)–C(1)–C(14)–N(1)–C(2)–C(3)[a]	147.36
		Ph–C(14)–C(1)–N(2)[a]	110.86
		Ph–C(2)–N(1)[a]	53.00

[a] Dihedral angle.

inequality $k_2 + k_{3B}$[Amine] >> k_{-1} [$k_{obs} = k_1$, eqn. (5)] or to $k_{-1} > k_2 >> k_{3B}$[Amine] [$k_{obs} = k_1k_2/k_{-1}$, eqn. (6)].

Three factors that should contribute to the different behavior of systems **4** (X = Cl, Br) and **5** are a difference in the extent of transition state imbalance, as observed for addition of amines to benzylidenemalononitriles and to nitro-activated alkenes,[12] and steric and hydrogen bonding effects. System **5** is more crowded than system **4** and the same applies for the derived zwitterions **10** and **11**. This will make k_1 smaller and k_{-1}, k_2 and k_{3B} higher for the reaction of **5** *via* **10** than for the reaction of **4** *via* **11**. The lack of reactivity of 2,4,6-tri-*tert*-butylaniline with (*E*)-**5** is probably due to a very low k_1/k_{-1} equilibrium combined with the relatively low amine basicity.

$RR'HN^+C(Ph)(I)–C^-(NO_2)CO_2Me$

10

$RR'NH^+C(Ar)(Br)–C^-(CN)_2$

11

Hydrogen bonding of the ammonio hydrogen in **10** with either the NO_2 or the CO_2Me group will give a six membered ring whereas the hydrogen bond acceptor cyano nitrogens in zwitterion **11** are too remote from the ammonio proton to form an intramolecular hydrogen bond. This should increase k_1 and reduce k_{3B} for **10** compared with **11** whereas k_{3B} will be less affected, thus decreasing the k_{3B}/k_2 ratio for **10**. We note that the (*Z*)-configuration of **7a** resembles the X-ray determined (*Z*)-configuration of solid $MeNHCH=C(NO_2)CO_2Me$,[13] and that the (*Z*)-configuration is mostly preferred over the (*E*)-configuration in the solid,[14] whereas both isomers prevail in solution.[14b] The (*Z*)-configuration for **7b** is reminiscent of that in α-morpholino-β-nitrostilbene.[9]

Although the zwitterion **10** derived from weakly basic amines such as aniline should be more acidic (and hence display larger k_{3B}) compared with those derived from piperidine and morpholine, catalysis was not observed even in reactions of the former amines.

The much larger k_{Pip}/k_{Mor} ratios in MeCN (115–138) than in EtOH (3.3–6.9) have a mechanistic significance. Many k_{Pip}/k_{Mor} ratios which were determined for the addition of amines to electrophilic alkenes are summarized in Bernasconi's review.[15] The ratios for the nucleophilic attack step (analogous to k_1) in protic media (H_2O, DMSO–H_2O) are relatively small (1.5–9.7), with the value of 23.6 for α-cyano-4-nitrostilbene[16] being an exception. The values of the ratios in the aprotic MeCN (5.8) and $CHCl_3$ (12) for the addition to benzylidene Meldrum's acid are larger than those (1.54–2.4) in the protic media. The ratios in EtOH resemble the values of the ratios (3.3–9.5) observed in the substitution of related nitro-activated systems in both EtOH and MeCN.[4g] Dissection of the overall k_{Pip}/k_{Mor} ratios to their k_1, k_{-1} and k_2 components was achieved only in the single case of the nitro-activated compound **12** in DMSO–H_2O (1 : 1), and were determined as 3.7, 0.028 and 55.3, respectively.[3c] Based on the relatively low k_1^{Pip}/k_1^{Mor} ratios and the k_2^{Pip}/k_2^{Mor} ratios which are only *ca.* 2.5 times lower than those found by us for **10** we conclude that the relatively high observed rate coefficients are composite, *i.e.*, $k_{obs} = k_1k_2/k_{-1}$ and their ratio is given by eqn. (16). Indeed, the k_{Pip}/k_{Mor} ratio for **12** calculated from the right hand side of eqn. (16) is 7500. Although the nucleofuge, solvent and the intermediate (**3b** for **12**, **3a** for **10**) are different, it is clear that a relatively high ratio is expected for a composite k_{obs}. Consequently, the rate of iodide expulsion from **10** becomes sufficiently slow to make it part of the rate determining step and the ratio reflects the combination of an increase in both the k_1^{Pip}/k_{-1}^{Pip} *vs.* k_1^{Mor}/k_{-1}^{Mor} (= K_1^{Pip}/K_1^{Mor} when $K = k_1/k_{-1}$) and the k_2^{Pip}/k_2^{Mor} terms.

$PhC(OMe)=C(NO_2)Ph$

12

$$k_{Pip}/k_{Mor} = k_1^{Pip}k_2^{Pip}k_{-1}^{Mor}/k_1^{Mor}k_2^{Mor}k_{-1}^{Pip} \qquad (16)$$

In conclusion, the k_{Pip}/k_{Mor} ratio can be much higher when k_{obs} is a product of the rate coefficients for the single steps, rather than when it is the rate coefficient for the first, nucleophilic attack step. A similar conclusion was reached for the reactions of α-halo-β-nitrostilbenes (halogen = Cl, I) with amines based on the k_I/k_{Cl} relative reactivity ratios.[4g]

Based on this analysis, the lower ratios in EtOH reflect a rate determining nucleophilic attack (k_1). We ascribe this both to the presence of hydrogen bonds between the solvent and the amines which apparently reduce k_1 more than they affect k_{-1} and k_2,

and to an electrophilic solvent assistance to the expulsion of the nucleofuge which increases k_2. The overall result is that the k_{Pip}/k_{Mor} ratio is similar to the k_1^{Pip}/k_1^{Mor} ratio.

Hydrogen bonding and a change in the rate determining step are also responsible for the solvent reactivity ratios k_{MeCN}/k_{EtOH} which are more than an order of magnitude higher for piperidine (23.3–27.7) than for morpholine (0.79–1.16). The trends of the values are reminiscent of those (Pip: 8.2–16.7; Mor: 2.4–6.2) for the reaction of amines with (*E*)-PhC(Cl)=C(Ph)NO_2.[4g] An *a posteriori* explanation is that EtOH···HNR hydrogen bonds (stronger for Pip) reduce the nucleophilicity whereas intramolecular hydrogen formed in the transition state leading to **10** (stronger for the morpholinium ion) which increase the nucleophilicity account qualitatively for the results.

The single k_{MeCN}/k_{THF} ratio with aniline is 5.0 which resembles the ratio for the reaction of ArC(X)=C(CO_2Et)$_2$, X = the very good nucleofuges OTf, OMs; Ar = Ph, *p*-$O_2NC_6H_4$ with piperidine and morpholine.[18] This ratio for an amine which forms stronger intramolecular hydrogen bonds in **10** than piperidine or morpholine is ascribed to higher stabilization of the transition state leading to **10** in the more polar solvent.

The higher reactivity of the (*Z*)-isomer compared with the (*E*)-isomer reflects a lower crowding in (*Z*)-**5** than in (*E*)-**5** which enables a less hindered approach of the nucleophile to the double bond. This is corroborated by the 5–10 times higher ratio for the most hindered nucleophile studied, *i.e.*, *p*-$MeOC_6H_4NHMe$ where the combined higher steric congestion in the transition state make (*Z*)-**5** much more reactive than (*E*)-**5** compared with less bulky amines. Steric effects in the nucleophile were reflected in the substitution of **12** by the nucleophiles $MeONH_2$ and MeONHMe which have similar pK_a's but differ in the steric bulk around the nitrogen. The reactivity of the latter is reduced significantly, mainly due to a decrease in k_{-1} by two orders of magnitude.[3g]

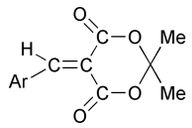
Reactions of 6-X

Since the highly reactive **6-X** system had not hitherto been studied with amines, variables in this reaction were investigated. It is not surprising that in contrast with **5**, a strong amine catalysis was observed for all systems **6-X** under a variety of experimental conditions since, in contrast with I^-, MeS^- is regarded at most as a moderate nucleofuge judged by the "rank" (nucleofugality) of PhS^-.[19] Consequently, high k_{3B}/k_2 ratios with piperidine indicate a strong contribution of the catalytic route, which reach a maximum when k_2 is negligible and the reaction order in the amine is two.

It should be mentioned that an alternative to the last step of the substitution ought also to be considered. This is the specific base general acid catalyzed route where following a fast deprotonation of **3a** by the amine, the ammonium ion formed electrophilically catalyzed the nucleofuge expulsion in a slow step. This route was suggested for the expulsion of the very poor nucleofuge CN^-[4d] but was excluded for a better nucleofuge like F^- by the observation of an added base (amine) rather than ammonium ion catalysis for **4**, X = F.[4a] Hence, only eqn. (3) will be discussed here.

The change in the substituents of **6-X** covers the whole range from the resonative electron-donating MeO to the strong electron withdrawing two *m*-CF_3 groups. This change is accompanied by a change in the reaction order in both MeCN and EtOH from a second order in the amine for the most electron donating substituent to an order between first and second in the amine as the aryl group becomes more electron withdrawing.

Electron withdrawal increases the rate of nucleophilic attack (*i.e.*, of k_1) in nucleophilic reactions on electrophilic alkenes. A relevant reaction is the nucleophilic addition reaction to **13**,[17b,c,20] the analog of **6** carrying an α-H rather than α-SMe: k_1 increases and k_{-1} decreases with the increased σ_X, and hence $K = k_1/k_{-1}$ also increases with σ_X.



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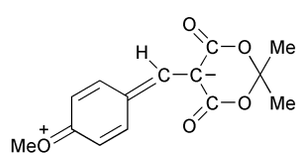
Electron-withdrawing substituents are expected to increase the electrophilicity of C_α with a consequent increase in k_1 and to increase the acidity of the zwitterion, thus decreasing k_{3B} and increase the difficulty in expelling the nucleofuge, thus decreasing k_2. The result is an increase in the k_{3B}/k_2 ratio, until k_2 becomes rate determining. The observed increase in k'' values is therefore ascribed to a combination of an increase in k_{3B} and k_1 and a decrease in the k_{-1} values.

This analysis also suggests a regular increase of k' values on increasing the electron-withdrawal by X. This was observed in most cases and the few deviations are ascribed to a high error in k' which is obtained as a small value from the intercept of the k_{obs} *vs.* [Amine] plot.

The Hammett correlations of log k'' *vs.* σ_X in MeCN at 30 and 40 °C are linear. The slopes ρ are positive (1.06–1.14) and relatively low. They are comparable to the values summarized for many nucleophilic reactions with electrophilic alkenes.[21] Since k'' is a composite value, the linearity of the plots indicates also a linearity in the Hammett plots of the logarithms of the individual rate constants k_1, k_2 and k_{3B} *vs.* σ_X. We noted above that $K = k_1/k_{-1}$ increases for **13** with electron withdrawing substituents.[17b,c,20] Similar behavior in our system together with a parallel increase in k_{3B} due to increased acidity of the ammonio group of **3a** will lead to a positive ρ.

In EtOH the ρ value for log k'' *vs.* σ_X is lower (0.85) and the linearity is poorer than in MeCN. This is mainly due to very similar reaction rates of **6-OMe** and **6-Me** which lead to a slightly positive deviation of **6-OMe** from the plot. A similar deviation was also observed in the log k_1 *vs.* σ_X for the substitution of **6-X** by $HOCH_2CH_2S^-$ in 1 : 1 DMSO–H_2O,[22] whereas in the reaction of **13** the *p*-MeO derivative behaved normally. The difference was ascribed by Bernasconi[22] to a difference in the ground state resonative stabilization by *p*-MeO in both cases. In **13** the only stabilization is by the *p*-MeO group (*cf.* the dipolar hybrid **14**) whereas in **6-MeO** the SMe plays this role more effectively (*cf.* **15**) so that the demand for resonance



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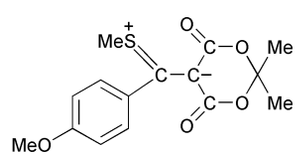

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contribution by *p*-MeO decreases. These effects also operate in our case, but since the effect is small and the rate constant is composite a detailed analysis is unwarranted.

An important mechanistic point is that in EtOH all the reactions, except that of **6-MeO** are between first and second order in the amine, whereas in MeCN only the reactions of **6-X**, where X = EWG (*p*-Br, *p*-CF_3, *m*,*m*′-$(CF_3)_2$), have a mixed order, and those reactions for X = H and electron-donating substituents are second order in the amine. This is ascribed to the higher basicity of EtOH which introduces an additional deprotonation step of the zwitterion with EtOH, acting as a base. This effect is diminished for **6-MeO** since electron-donation by MeO reduces the acidity of the zwitterion, and the deprotonation is then carried out exclusively by the more basic amine. We note that EtOH, in contrast with MeCN, can increase k_2 by electrophilic catalysis *via* hydrogen bonding to the MeS^- expulsion and that lower k_{3B}/k_2 ratios in MeCN compared with alcohols were previously observed.[4a]

Another interesting phenomenon in EtOH is that the only reaction which does not give a linear k_{obs} *vs.* [Amine] plot is that of the most reactive substrate **6-(CF$_3$)$_2$**. Since the inverted $1/k_{obs}$ *vs.* 1/[Amine] plot according to eqn. (7) is linear, $k_{-1} \sim k_2 + k_{3B}$[Amine] in contrast with the other cases where $k_{-1} >> k_2 + k_{3B}$[Amine]. In **6-(CF$_3$)$_2$** the acidity of the ammonio group is the highest of all our systems. This increases k_{3B}[Amine] (unless k_{3b} is diffusion controlled) and in parallel decreases both k_{-1} and k_2 until, in spite of the lower basicity of the deprotonating base the condition above is apparently fulfilled. The value of k_1 was calculated from eqn. (15) but we have no value in a related system for comparison.

As for **5**, the reactions in MeCN are faster than those in EtOH, but only by a moderate factor (k_{MeCN}/k_{EtOH} (30 °C) = 3.0–4.9). Again the explanation is reduced reactivity of the piperidine by hydrogen bonding to the EtOH.

The activation parameters for the catalyzed process (Table 8) are characterized by negative activation enthalpies (and energies) and high negative activation entropies. Negative or very small activation enthalpies and very highly negative activation entropies were previously observed in similar vinylic substitutions of poor leaving groups by amines.[4a,b,d–f,23a] Whereas the negative activation energies seem unusual, the accumulating evidence and examples indicate that such behavior is common rather than exceptional for this type of reaction in aprotic media. Examples are the displacement of $CF_3CH_2O^-$ from compound **4**, X = CF_3CH_2O, by amines in MeCN ($\Delta H^{\ddagger}$ = 11–−16 kcal mol^{-1} for the catalyzed reaction), the displacement of EtO^- from **4**, X = EtO^-, with piperidine in MeCN ($\Delta H^{\ddagger}$ = 0.6 kcal mol^{-1} for the catalyzed reaction), of F^- by morpholine from **4**, X = F ($\Delta H^{\ddagger}$ = −3.2 kcal mol^{-1}),[4g] or the displacement of CN^- from tricyanovinyl chloride by aliphatic amines in $CHCl_3$ ($\Delta H^{\ddagger}$ = 1.4–2.6 kcal mol^{-1}).[23a] Other examples, which include addition of amines to electrophilic alkenes, show similar low $\Delta H^{\ddagger}$ (2–2.4 kcal mol^{-1}) and high negative $\Delta S^{\ddagger}$ values[23b,c] and are collected in ref. 4*g*.

The low and especially the negative $\Delta H^{\ddagger}$ values serve as strong evidence against a single-step substitution but they fit a multi-step reaction where $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are composite, and are the sums of the corresponding values for the individual steps [eqn. (17) and (18)]. In eqn. (17) and (18) ΔH° and ΔS° are the

$$\Delta H^{\ddagger} = \Delta H_1^{\ddagger} - \Delta H_{-1}^{\ddagger} + \Delta H_{3B}^{\ddagger} \text{ (or } \Delta H_2^{\ddagger}) = \Delta H^{\circ} + \Delta H_{3B}^{\ddagger} \text{ (or } \Delta H_2^{\ddagger}) \quad (17)$$

$$\Delta S^{\ddagger} = \Delta S_1^{\ddagger} - \Delta S_{-1}^{\ddagger} + \Delta S_{3B}^{\ddagger} \text{ (or } \Delta S_2^{\ddagger}) = \Delta S^{\circ} + \Delta S_{3B}^{\ddagger} \text{ (or } \Delta S_2^{\ddagger}) \quad (18)$$

corresponding enthalpies for the equilibrium of the first nucleophilic attack step, $\Delta H_{3B}^{\ddagger}$, $\Delta S_{3B}^{\ddagger}$ are the terms for the catalyzed process and $\Delta H_2^{\ddagger}$, $\Delta S_2^{\ddagger}$ are those for the uncatalyzed process.The low $\Delta H^{\ddagger}$ terms arise mainly from the ΔH° terms. This conclusion is based on reactions where no leaving group is expelled, especially on the ΔH° values of −13–−21 kcal mol^{-1} (ΔS° = −27–−51 e.u.) for the nucleophilic addition of tri-*n*-butylphosphine to ArCH=C(CN)$_2$ which gives the zwitterion **16**.[24]

$$ArCH(P^+Bu_3)–C^-(CN)_2$$
16

If similar ΔH° values apply in our system, the addition of a not too high $\Delta H_{3B}^{\ddagger}$ or $\Delta H_2^{\ddagger}$ term will give an overall negative $\Delta H^{\ddagger}$.

The high negative entropies of activation are ascribed to the assembly of two or three molecules in the rate determining step of the substitution reaction, coupled with the formation of a zwitterion intermediate. The transition state, being much more organized than the reactants, leads to a high negative $\Delta S^{\ddagger}$ regardless of whether the rate coefficient for the reaction is k_1, k_1k_{3B}/k_{-1} or k_1k_2/k_{-1}.

Experimental

General

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with Bruker DRX-400 and AMX-300 spectrometers. IR spectra were recorded with a Nicolet Impact 400 spectrometer. X-Ray diffraction was conducted with a Philips PW 100 diffractometer. The UV spectra were obtained and the kinetic study conducted using a Contron UNIKON 930 spectrophotometer.

(*E*)-Methyl α-nitro-β-anilinocinnamate (7a)

A mixture of (*Z*)-**5** (0.2 g, 0.6 mmol) and aniline (0.27 ml, 3.0 mmol) in MeCN (11 ml) was stirred for 3 days at room temperature under argon. The solvent was evaporated and the residue was recrystallized from EtOH giving **7a** as yellow needles (0.1 g, 0.33 mmol, 56%), mp 168 °C. The spectral data are given in Table 12.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.21; H, 4.88; N, 9.19%.

Crystallographic data: space group $P2_1/c$; a = 11.452(2), b = 8.899(1), c = 15.330(3) Å, V = 1502.2(6) Å^3, Z = 4, ρ_{calc} = 1.32 g cm^{-3}; μ(Mo-K$_\alpha$) = 0.90 cm^{-1}; no. of unique reflections 2255, no. of reflections with $I \geq 2\sigma_I$ 1380, R = 0.062, R_W = 0.070. CCDC reference number 168692.

(*E*)-Methyl α-nitro-β-piperidinocinnamate (7b)

A $CaCl_2$-protected solution containing (*E*)-**5** (0.12 g, 0.36 mmol) and piperidine (0.1 ml, 1.1 mmol) in MeCN (7 ml) was stirred at room temperature for 24 h. The solvent was evaporated and the remainder was recrystallized from EtOH, giving yellow crystals of **7b** (47 mg, 0.16 mmol, 45%), mp 130 °C. The spectral data are given in Table 12.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.77; H, 5.98; N, 9.66%.

Crystallographic data: space group $P2_1/c$; a = 8.344(2), b = 10.309(2), c = 17.769(2) Å, V = 1496.2 Å^3, Z = 4, ρ_{calc} = 1.29 g cm^{-3}; μ(Mo-K$_\alpha$) = 0.88 cm^{-1}; no. of unique reflections 2821, no. of reflections with $I \geq 3\sigma_I$ 1789, R = 0.050, R_W = 0.077. CCDC reference number 168693.

(*E*)-Methyl α-nitro-β-morpholinocinnamate (7c)

A solution containing (*E*)-**5** (0.15 g, 0.45 mmol) and morpholine (0.12 ml, 1.35 mmol) in MeCN (10 ml) was stirred under $CaCl_2$ at room temperature for 165 min. The solvent was evaporated and the remainder was washed with water and recrystallized from ethanol giving **7c** (0.1 g, 0.34 mmol, 76%), mp 188 °C. The spectral data are given in Table 12.

Anal. Calcd. for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.53. Found: C, 57.37; H, 5.59; N, 9.47%.

(*E*)-Methyl α-nitro-β-*N*-methyl-*p*-anilinocinnamate (7d)

A $CaCl_2$-protected solution containing (*Z*)-**5** (0.1 g, 0.3 mmol) and *p*-methoxy-*N*-methylaniline (0.08 g, 0.6 mmol) in MeCN (10 ml) was stirred at room temperature for 22 h and then poured into water and extracted with ether (3 × 20 ml). The combined organic fractions were dried ($CaCl_2$) and the solvent was evaporated. The mixture was separated on a preparative TLC plate using 3 : 7 ether–petroleum ether (40–60 °C) as the eluent. The second fraction was recrystallized from EtOH giving **7d** (22 mg, 0.064 mmol, 21%), mp 100 °C. The spectral data are given in Table 12.

Table 12 Spectral data for **7a**–**d** and **8-X**

Cmpd.	UV (MeCN) λ_{max}/nm (ε)[a]	^{1}H NMR δ($CDCl_3$)/ppm	^{13}C NMR δ($CDCl_3$)/ppm	MS *m*/*z* (relative %, assignment)
7a	361 (5800)	3.48 (3H, s, MeO), 6.74–7.38 (10H, m, Ani, Ph), 10.81 (NH)	52.69 (OMe), 120.82, 124.59, 125.87, 126.72, 128.30, 128.65, 128.77, 129.12, 129.43, 130.16, 130.74 (C=C, Ani, Ph)[b]	298 (18, M), 252 (33, M − NO_2), 251 (19, M − HNO_2), 220 (100, M − NO_2 − MeOH), 193 (43, M − NO_2 − CO_2Me), 180 (43, M − NO_2 − CO_2Me − CH), 165 (18, M − NO_2 − CO_2Me − C_2H_4), 105 (32, $[PhNHCH]^+$)
7b	274 (20900), 388 (15900)	1.79 (6H, s, $(CH_2)_3$), 3.28 (4H, s, $N(CH_2)_2$), 3.51 (s, 3H, OMe), 7.39–7.55 (5H, m, Ph)	23.34 ($CH_2CH_2CH_2$), 26.70 ($N(CH_2)_2$), 51.70 (CH_2N), 53.38 (OMe), 120.72, 128.99, 129.45, 131.87, 134.23, 163.97 (Ph, 2C=C), 166.90 (C=O)	290 (4, M), 244 (100, M − NO_2), 212 (25, M − NO_2 − MeOH), 184 (6, M − CO_2Me − HNO_2), 117 (15, $C(NO_2)CO_2Me$), 105 (14, $PhCNH_2^+$)
7c	275 (11560), 386 (8300)	3.34 (4H, t, $N(CH_2)_2$), 3.54 (3H, s, Me), 3.87 (4H, t, $O(CH_2)_2$), 7.48–7.58 (5H, m, Ph)	51.99, 52.02 (CH_2N, OCH_3), 66.80 (OCH_2), 121.89, 129.24, 129.66, 132.12, 133.28, 163.62 (Ph, 2C=C), 165.04 (C=O)	292 (100, M), 262 (2, M − OCH_2), 206 (5, M − C_4H_8NO), 191 (15, M − C_4H_8NO − Me), 171 (55, M − C_4H_8O − OMe)
7d	401 (10900)	3.39 (3H, s, NMe), 3.49 (s, 3H, COOMe), 3.72 (s, 3H, C_6H_4OMe), 6.90 (4H, q, Ar, J = 8.0 Hz), 7.26–7.40 (m, 5H, Ph)	45.11 (NMe), 51.98 (COOMe), 55.41 (C_6H_4*OMe*), 114.47, 126.83, 128.64, 130.42, 131.18, 134.23, 138.12, 158.20 (C=C, An, Ph), 163.66 (C=O)	342 (11, M), 296 (74, M − NO_2), 264 (100, M − NO_2 − MeOH), 249 (7, M − Me − OMe − NO_2 − H), 237 (56, M − CO_2Me − NO_2), 222 (7, M − CO_2Me − NO_2 − Me), 210 (15), 118 (80, $[PhCNMe]^+$), 117 (19, $[C_6H_4N(Me)C]^+$), 105 (42, $[C_6H_4NMe]^+$)
8-MeO	311 (9500)	1.71 (6H, s, 2Me), 1.83–1.84 (6H, m, $(CH_2)_3$), 3.52 (2H, t, J = 5.8 Hz, CH_2N), 3.78 (2H, t, J = 5.6 Hz, CH_2N), 3.86 (3H, s, OMe), 7.18 (4H, q, Ar, J = 6.9 Hz)		345 (100, M), 277 (4, M − C_5H_8)
8-Me	335 (9800)	1.71 (6H, s, 2Me), 1.82–1.86 (6H, m, $(CH_2)_3$), 2.42 (3H, s, Me), 3.48 (2H, t, J = 4.8 Hz, CH_2N), 3.71 (2H, t, J = 4.6 Hz, CH_2N), 7.27 (4H, q, Ar, J = 8.0 Hz)		329 (34, M), 271 (25, M − $OCMe_2$), 243 (7, M − $OCMe_2CO$), 227 (100, M − $COOCMe_2O$), 198 (34), 170 (22)
8-H	338 (9300)	1.71 (6H, s, 2Me), 1.81–1.85 (6H, m, $(CH_2)_3$), 3.46 (2H, t, J = 5.6 Hz, CH_2N), 3.73 (2H, t, J = 5.7 Hz, CH_2N), 7.52 (5H, m, Ph)		315 (100, M), 257 (38, M − $OCMe_2$), 228 (26, M − $OCMe_2$ − CO − H), 213 (75, M − $OCMe_2$ − CO_2), 184 (73, M − CMe_2 − $2CO_2$ − H), 156 (29, M − CMe_2 − $2CO_2$ − H − $MeCH_2$), 129 (31, M − CMe_2 − $2CO_2$ − $4CH_2$), 102 (35, $[PhC_2H]^+$)
8-Br	341 (9200)	1.70 (6H, s, 2Me), 1.89–1.91 (6H, m, $(CH_2)_3$), 3.48 (2H, t, J = 5.6 Hz, CH_2N), 3.68 (2H, t, J = 5.7 Hz, CH_2N), 7.40 (4H, q, Ar, J = 9.0 Hz)		395, 393 (84, 77, M), 337, 335 (59, 51, M − $OCMe_2$), 293, 291 (100, 99, M − $OCMe_2$ − CO_2), 264, 262 (47, 40, M − $OCMe_2$ − CO − H), 209, 207 (24, 23, M − CMe_2 − $2CO_2$ − $4CH_2$), 182, 180 (42, 36, M − CMe_2 − $2CO_2$ − $5CH_2$ − CH), 162 (12, M − Br − NC_5H_{10} − CMe_2 − 2CH), 128 (16, $[C_6H_4C_2NCH_2]^+$)
8-CF_3	338 (3700)	1.72 (6H, s, 2Me), 1.83–1.89 (6H, m, $(CH_2)_3$), 3.36 (2H, t, J = 5.4 Hz, CH_2N), 3.67 (2H, t, J = 5.6 Hz), 7.45 (4H, q, Ar, J = 8.5 Hz)		383 (13, M), 366 (8, M − OH), 325 (20, M − $OCMe_2$), 299 (21, M − Me − CF_3), 282 (47, M − CF_3 − $2CH_2$), 254 (100, M − NC_5H_{10} − CO_2H), 253 (16, M − CMe_2 − $2CO_2$), 197 (27, M − CMe_2 − $2CO_2$ − $4CH_2$)
8-(CF_3)$_2$	343 (8700)	1.71 (6H, s, 2Me), 1.82–1.89 (6H, m, $(CH_2)_3$), 3.35 (2H, t, J = 5.4 Hz, CH_2N), 3.70 (2H, t, J = 5.8 Hz, CH_2N), 7.85 (1H, s, Ar), 8.03 (2H, s, Ar)		451 (10, M), 422 (19, M − Me − CH_2), 394 (100, MH − $OCMe_2$), 374 (27, M − C(O)Me_2 − F), 349 (9, M − C(O)Me_2 − CO_2), 326 (16, M − CMe_2 − C_5H_{10} − CH), 243 (12)

[a] Measured in $dm^3\ mol^{-1}\ cm^{-1}$. [b] Too weak to be observed.

Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.08; H, 5.33; N, 8.01%.

Synthesis of 6-X

Compound **6-H** was prepared following literature methods.[6] The other derivatives were prepared by a similar procedure and purified by chromatography or recrystallization from EtOAc–petroleum ether. The detailed procedure is given for **6-$(CF_3)_2$** followed by specific data for the other derivatives.

2,2-Dimethyl-5-[3,5-bis(trifluoromethyl)-α-thiomethoxybenzylidene]-1,3-dioxane-4,6-dione [6-$(CF_3)_2$]

A solution of the Grignard reagent prepared from 3,5-bis(trifluoromethyl)bromobenzene (0.41 g, 1.4 mmol) and Mg turnings (35 mg, 1.4 mmol) in dry THF (2.0 ml) was added dropwise to a solution of isopropylidene bis(methylthio)methylenemalonate (100 mg, 0.4 mmol)[25] in dry THF (3.0 ml), and stirred at room temperature for 2 h. A solution of 5% aq. HCl (2 ml) was added dropwise to the mixture, which was then extracted with dichloromethane (2 × 5 ml), washed with water (3 × 10 ml) and dried (Na_2SO_4). After removal of the solvent, the crude product was purified by silica gel chromatography using 1 : 4 EtOAc–petroleum ether as an eluent to give 144 mg (86.3%) of a white solid mp 151–152 °C; ^{1}H NMR ($CDCl_3$) δ: 1.78 (s, 6H), 1.87 (s, 3H), 7.53 (s, 2H), 7.96 (s, 1H); IR (Nujol) 985, 1291, 1376, 1719, 1746 cm^{-1}. Anal. Calcd for $C_{16}H_{12}O_4F_6S$: C, 46.38; H, 2.92. Found: C, 46.33; H, 3.10%.

5-(*p*-Methoxy-α-thiomethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (6-MeO)

Starting with 0.45 g of isopropylidene bis(methylthio)methylenemalonate (1.8 mmol), 0.25 g (44.7%) of a yellow solid, mp 171–173 °C was obtained. ^{1}H NMR ($CDCl_3$) δ: 1.78 (s, 6H), 1.95 (s, 3H), 3.86 (s, 3H), 7.00 (m, 4H); IR (Nujol) 834, 1025, 1295, 1493, 1611, 1723, 1749 cm^{-1}; MS (CI) *m*/*z* (%) 308 (M^-, 100), 293 (9.4). Anal. Calcd for $C_{15}H_{16}O_5S$: C, 58.43; H, 5.23; S, 10.40. Found: C, 58.56; H, 5.24; S, 9.96%.

5-(*p*-Methyl-α-thiomethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (6-Me)

Starting with 0.45 g of isopropylidene bis(methylthio)methylenemalonate (1.8 mmol), 0.41 g (77.4%) of a very slightly yellow–white solid, mp 169–171 °C was obtained. ^{1}H NMR ($CDCl_3$) δ: 1.77 (s, 6H), 1.91 (s, 3H), 2.41 (s, 3H), 6.95–6.97 (m, 2H), 7.28–7.30 (m, 2H); IR (Nujol) 670, 815, 1012, 1209, 1295, 1460, 1723, 1749 cm^{-1}; MS (CI) *m*/*z* (%) 292 (M^-, 100.0), 277 (10.4). Anal. Calcd for $C_{15}H_{16}O_4S$: C, 61.62; H, 5.52; S, 10.97. Found: C, 61.55; H, 5.44; S, 10.86%.

5-(*p*-Bromo-α-thiomethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (6-Br)

Starting with 0.45 g of isopropylidene bis(methylthio)methylenemalonate (1.8 mmol), 0.32 g (39.0%) of a very slightly yellow–white solid, mp 168–170 °C was obtained. ^{1}H NMR ($CDCl_3$) δ: 1.76 (s, 6H), 1.92 (s, 3H), 6.95–6.97 (m, 2H), 7.62–7.64 (m, 2H); IR (Nujol) 802, 894, 1209, 1282, 1497, 1519, 1703, 1743 cm^{-1}; MS (CI) *m*/*z* (%) 358 (M^- + 2, 100), 356 (M^-, 90.6), 343 (34.4), 341 (25.5), 278 (2.8). Anal. Calcd for $C_{14}H_{13}O_4BrS$: C, 47.07; H, 3.67; Br, 22.37; S, 8.98. Found: C, 47.00; H, 3.77; Br, 22.70; S, 8.81%.

5-(*p*-Trifluoromethyl-α-thiomethoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (6-CF_3)

Starting with 100 mg of isopropylidene bis(methylthio)methylenemalonate (0.4 mmol), 46.0 mg (33.0%) of a white solid, mp 162–164 °C was obtained. ^{1}H NMR ($CDCl_3$) δ: 1.77 (s, 6H), 1.88 (s, 3H), 7.21 (d, J = 8.10 Hz, 2H), 7.76 (d, J = 8.10 Hz, 2H); IR (Nujol) 834, 1089, 1294, 1493, 1712, 1742 cm^{-1}. Anal. Calcd for $C_{15}H_{13}O_4F_3S$: C, 52.02; H, 3.78. Found: C, 52.28; H, 4.02%.

2,2-Dimethyl-5-[piperidino(3,5-trifluoromethylphenyl)-methylene]-1,3-dioxane-4,6-dione (8-$(CF_3)_2$)

A $CaCl_2$-protected solution containing **6-$(CF_3)_2$** (0.14 g, 0.34 mmol) and piperidine (0.08 ml, 0.84 mmol) in MeCN (5 ml) was stirred for 28 h. The solvent was evaporated and the remainder was recrystallized twice from ethanol, giving **8-$(CF_3)_2$** (70 mg, 0.15 mmol, 46%), mp 184–185 °C. The spectral data are in Table 12. Anal. Calcd. for $C_{20}H_{19}NF_6O_4$: C, 53.22; H, 4.24; N, 3.10. Found: C, 53.26; H, 4.28; N, 3.14%.

2,2-Dimethyl-5-[piperidino(*p*-methoxyphenyl)methylene-1,3-dioxane-4,6-dione (8-OMe)

A $CaCl_2$-protected solution containing **6-OMe** (30 mg, 0.097 mmol) and piperidine (0.024 ml, 0.25 mmol) was stirred at room temperature for 48 h. The solvent was evaporated and recrystallization from EtOH gave **8-OMe** (27 mg, 0.078 mmol, 81%), mp 204 °C. The spectral data are given in Table 12. Anal. Calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.89; H, 6.67; N, 3.90%.

2,2-Dimethyl-5-[piperidino(*p*-bromophenyl)[or phenyl, *p*-tolyl, *p*-trifluoromethylphenyl]methylene]-1,3-dioxane-4,6-dione (8-Br or 8-H, 8-Me, 8-CF_3)

A $CaCl_2$-protected solution containing piperidine (0.01 ml, 0.1 mmol) and **6-Br** (4.5 mg, 0.013 mmol) or **6-H** (2.5 mg, 0.009 mmol) or **6-Me** (5 mg, 0.015 mmol) or **6-CF_3** (5 mg, 0.013 mmol) in MeCN (5 ml) was stirred at room temperature for 24 h and the solvent was then evaporated giving **8-Br**, **8-H**, **8-Me** and **8-CF_3**, respectively as determined by HRMS. **8-Br**, Calcd. for $C_{18}H_{20}{}^{79}BrNO_4$: 393.0576. Found: 393.0583. **8-H**, Calcd. for $C_{18}H_{21}NO_4$: 315.1470. Found: 315.1451. **8-Me**, Calcd. for $C_{18}H_{23}NO_4$: 329.1627. Found: 329.1649. **8-CF_3**, Calcd. for $C_{19}H_{20}NF_3O_4$: 383.1344. Found: 383.1383. The spectral data of the four compounds are given in Table 12.

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