Kinetic and Thermodynamic Parameters for the Alcoholysis of 2,2,2-Trichloro-1-arylethanones

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The reactions of 2,2,2-trichloro-1-phenylethanone (**1a**) and 2,2,2-trichloro-1-(*p*-chlorophenyl)-ethanone (**1b**) with MeOH, EtOH, Pr^{n}OH, and Bu^{n}OH in the presence of ethylamine resulted in the formation of the corresponding esters ArCOOR. When the process is carried out in the absence of ethylamine the reaction does not proceed beyond formation of the hemiacetal intermediate. The former reaction occurs through an addition–elimination process and the order of reactivity of the alcohols is MeOH > EtOH > Pr^{n}OH > Bu^{n}OH. If (**1a** or **b**) is treated with ethylamine in dioxane the corresponding amide ArCONHEt is the only reaction product.

Many reactions involving trihalogenomethyl as a leaving group are known, the iodoform reaction being a classic example of such processes.[1] However, systematic studies on the leaving group ability of CX_3, compared with other more common leaving groups, are scarce. In the past few years we have become interested in exploiting trihalogenomethyl as a leaving group in synthetic transformations, and have studied in some detail a few of these reactions from the mechanistic point of view.[2,3] The decomposition of the acaricide 2,2,2-trichloro-1,1-bis-(4-chlorophenyl)ethanol ('Kelthane') in the presence of base to give 4,4'-dichlorobenzophenone is an interesting reaction which represents a possible pathway for the *in vivo* degradation reaction of that pesticide.[4,5] The formation of benzaldehydes from 2,2,2-trihalogeno-1-arylethanols in aqueous base[3] is another useful transformation, occasionally exploited in some patents.[6–8]

In continuation of our work, we turned our attention to the reactivity of 2,2,2-trichloro-1-arylethanones (**1**) toward nucleophiles. These compounds have long been known to give the corresponding benzoic acid salts when treated with hydroxides, a reaction which can be conveniently used for the preparation of deuteriochloroform.[9–11] We have observed that treatment of ethanones (**1**) with alcohols in the presence of base affords the corresponding benzoic esters. The kinetic study of this alcoholysis, which illustrates some interesting features of compounds (**1**) as potentially useful benzoylating agents, is the subject of this report.

Experimental

The trichloroethanones (**1**) were prepared by chlorination of the corresponding acetophenones, following previously reported procedures:[12–14] 2,2,2-trichloro-1-phenylethanone (**1a**) had b.p. 142 °C at 25 mmHg (lit.,[15] 145 °C at 25 mmHg); 2,2,2-trichloro-1-(4-chlorophenyl)ethanone (**1b**) had b.p. 177 °C at 40 mmHg (lit.,[15] 181 °C at 45 mmHg). Both ethanones were further characterized by their i.r. and n.m.r. spectra and their purity confirmed by gas chromatography.

All alcohols were purchased from Merck and were purified following standard procedures.[16] Ethylamine was dried over sodium hydroxide pellets and redistilled before use. Alcoholic solutions of ethylamine were obtained by dilution of a stock solution, and the concentrations of amine determined by titration.

Reactions were followed spectroscopically with a Shimadzu UV 210-A spectrophotometer equipped with thermostatted water-jacketed cell compartments. Faster reactions ($t_{\frac{1}{2}} < 20$ s) were monitored with a Photophysics 1705 stopped-flow apparatus. Reaction rates were obtained by following the disappearance of the ethanones (**1a**) and (**1b**) at 259 and 269 nm, respectively. Reactions were followed for at least four half-lives and the linear plots of $\ln(A_t - A_\infty)$ against time yielded pseudo-first-order rate constants with deviations < 3%.

Chromatographic analyses of all products of the reactions were carried out with a C.G. 370 instrument, which employed an OV-17 column. The formation of intermediate hemiacetals, stable in the absence of base, was suggested by the rapid decrease of the absorbance maxima of ethanones (**1a** and **b**) when either of these compounds was added to an alcohol. That this decrease was due to a reversible equilibrium was shown by g.l.c. analyses of the resulting solutions, which yielded only two peaks for the alcohol and the original ethanone.

Table 1. Kinetic data for the reaction of compounds (**1a** and **b**) with different alcohols in the presence of ethylamine at 25 °C

		$10^3k_{obs.}/s^{-1}$			
		Compound (**1a**)		Compound (**1b**)	
ROH	$10^3[EtNH_2]/M$	λ 230 nm[a]	λ 260 nm[b]	λ 238 nm[a]	λ 269 nm[b]
MeOH	1.25	53.5	52.5	160	161
EtOH	8.50	14.0	14.2	67.2	67.1
	85.0	154	155		
Pr^{n}OH	10.0			41.3	41.8
	85.0	53.1	53.4		
Bu^{n}OH	85.0	38.2	37.8	194	196

[a] Following the formation of the benzoic ester at 25 °C. [b] Following the disappearance of the ketone at 25 °C.

Results and Discussion

The reaction of 2,2,2-trichloro-1-arylethanones (**1**) with various alcohols in the presence of ethylamine leads to the formation of the corresponding benzoic esters ArCOOR. Figure 1 illustrates the course of the methanolysis of 2,2,2-trichloro-1-phenylethanone (**1a**) in the presence of ethylamine at 25 °C. When the ethanone (3.3×10^{-5}M) was added to a solution of ethylamine (3.3×10^{-4}M) in methanol, the initial absorption at 259 nm disappeared and a new band at 218 nm was observed, which was subsequently replaced by the final absorption of methyl benzoate at 228 nm. Similar behaviour was observed for the methanolysis of the ethanone (**1b**). The formation of an intermediate in the course of the reaction can be clearly detected in alcoholic solutions of the ethanones (**1**) in the absence of amine. Figure 2 shows the spectra of the ethanone (**1b**) in methanol at time zero (curve A) and after the equilibrium with the intermediate is attained (curve B). This mixture, when subjected to g.l.c. analysis, revealed only two peaks, corresponding to the starting trichloroethanone and methanol. Upon removal of the solvent the pure ketone was recovered unchanged, indicating a revers-

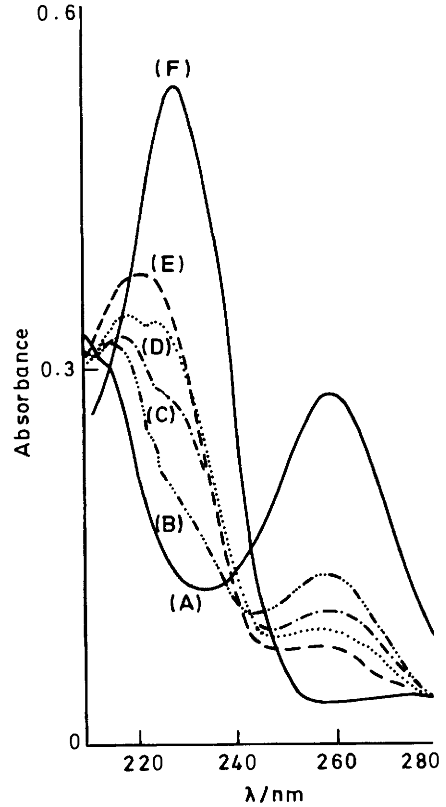


Figure 1. Methanolysis of compound (**1a**) (3.3×10^{-5}M) in the presence of ethylamine (3.3×10^{-4}M) at 25 °C. Spectra of the mixture at t 0 (A), 5 (B), 12 (C), 17 (D), 22 (E), and 37 s (F) of reaction

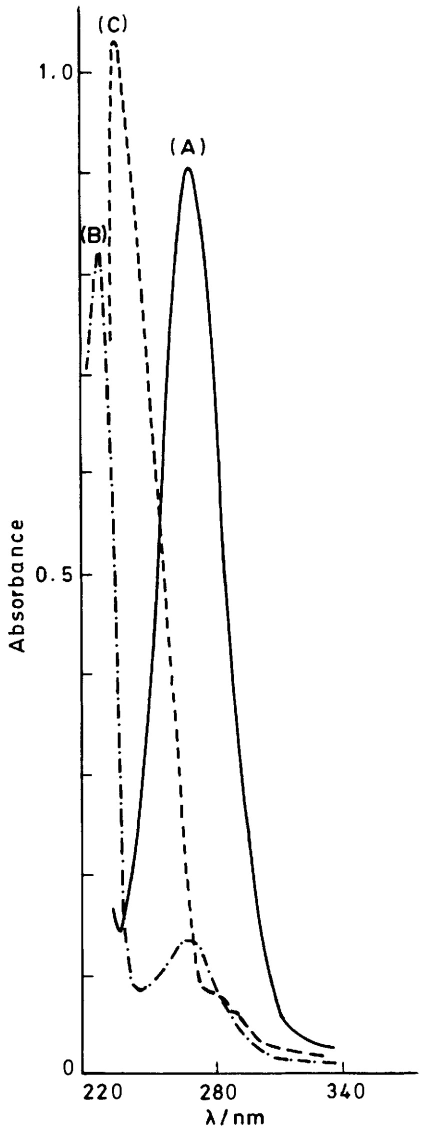


Figure 2. U.v. spectra of compound (**1b**) in methanol at time zero (A), after the equilibrium with the hemiacetal is attained (B), and of the ester product (C) after addition of ethylamine to the hemiacetal solution

Table 2. Values for the equilibrium constants for hemiacetal formation[a,b]

	a_m(equilibrium mixture)/ l mol^{-1} cm^{-1}		(**1a**)		(**1b**)	
ROH	(**1a**)	(**1b**)	K_h	$K_{eq.}$/l mol^{-1}	K_h	$K_{eq.}$/l mol^{-1}
MeOH	3 489	1 734	2.08	0.083	8.86	0.36
EtOH	6 980	4 118	0.43	0.025	2.49	0.15
Pr^{n}OH	7 035	4 467	0.42	0.031	2.19	0.16
Bu^{n}OH	7 004	4 145	0.43	0.039	2.47	0.23

[a] The values of $a_{m(ketone)}$ were 9 844 and 13 312 l mol^{-1} cm^{-1} for compounds (**1a** and **b**) respectively and were measured in 1,4-dioxane in the absence of alcohol. [b] The values of $a_{m(hemiacetal)}$ were assumed to be the same as the molar absorptivities of 2,2,2-trichloro-1-phenylethanol (a_m 396 l mol^{-1} cm^{-1}) and 2,2,2-trichloro-1-(*p*-chlorophenyl)ethanol (a_m 428 l mol^{-1} cm^{-1}) for the hemiacetals (**2a** and **b**), respectively

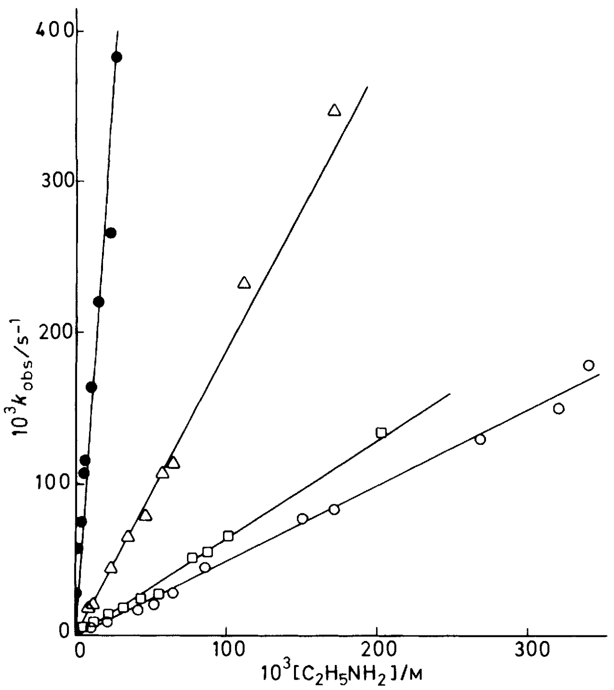


Figure 3. Plot of $k_{obs.}$ *versus* concentration of $EtNH_2$ for the reaction of compound (**1a**) with MeOH (●), EtOH (△), Pr^{n}OH (□), and Bu^{n}OH (○) at 25 °C

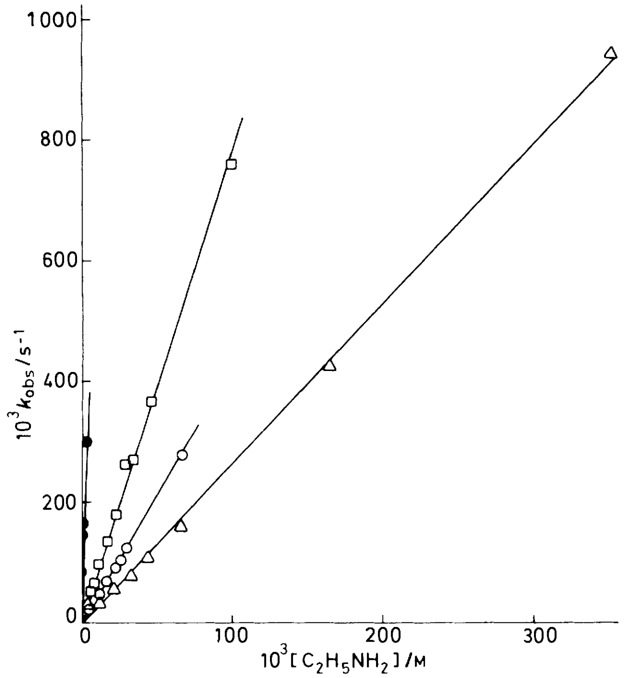
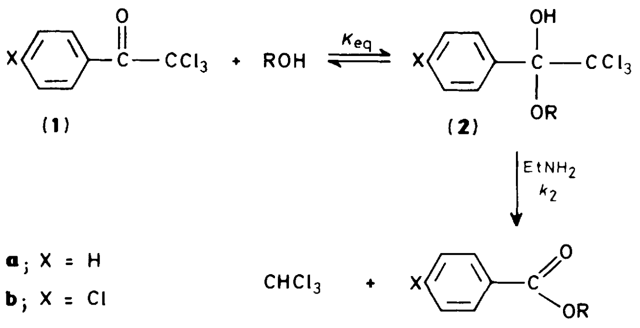


Figure 4. Plot of $k_{obs.}$ *versus* concentration of $EtNH_2$ for the reaction of compound (**1b**) with MeOH (●), EtOH (□), Pr^{n}OH (○), and Bu^{n}OH (△) at 25 °C

ible hemiacetal formation. When ethylamine was then added to this equilibrium mixture, the band at 224 nm (curve B) was replaced by the absorption of methyl *p*-chlorobenzoate at 238 nm (curve C).

The ketone–hemiacetal equilibrium is slowly attained in solutions of (**1a** and **b**) in the pure alcohols. However, trace amounts of added acid or base are sufficient to accelerate this process to a considerable extent. From the absorptions of the ketones in the pure alcohols at time zero and from absorption data similar to those shown in Figure 1, one can estimate that the second-order rate constants for the base-catalysed hemiacetalization in methanol for compounds (**1a** and **b**) should be greater than 500 and 1 000 l mol^{-1} s^{-1} respectively.



Scheme 1.

Figures 3 and 4 are plots of the variation of the alcoholysis rate constants with increasing concentrations of ethylamine. For all the alcohols studied the rate constants increase linearly with the amine concentration, an indication of a first-order dependence of the reaction on the basic catalyst.

The mechanism depicted in Scheme 1, which consists of an initial reversible, fast addition step followed by the amine-catalysed decomposition of the intermediate hemiacetal, accommodates all the above observations.

In order to obtain values for the rate-determining constant k_2, we needed to evaluate the equilibrium constant $K_{eq.}$ for acetal formation.

This was accomplished by spectrophotometric measurements, using equation (1), where a_m represents the molar absorptivity

$$K_{eq.}[\mathrm{ROH}] = K_h = \frac{a_m(\text{ketone}) - a_m(\text{equil. mixture})}{a_m(\text{equil. mixture}) - a_m(\text{hemiacetal})} \quad (1)$$

of the different species in equilibrium, at 259 and 269 nm for compounds (**1a** and **b**), respectively.

Table 2 lists $K_{eq.}$ and K_h values for the different systems under study. Since we could not isolate the hemiacetal intermediates and determine their molar absorptivities, we attempted to prepare the corresponding acetals. Unfortunately, despite all efforts in a variety of experimental conditions, we could not isolate them. Our failure was probably due to the high degree of steric strain around the central carbon atom of these compounds.[17] We were thus forced to use the molar absorptivity of 2,2,2-trichloro-1-arylethanols,[3] as structurally related analogues of the hemiacetals (**2**). Our choice, though not ideal, seems justified by the lack of other alternatives.

Equation (2) relates the observed first-order rate constant

$$k_{obs.} = \frac{k_2K_{eq.}[\mathrm{ROH}][\mathrm{EtNH_2}]}{1 + K_{eq.}[\mathrm{ROH}]} \quad (2)$$

$k_{obs.}$ to the second-order rate constant k_2, according to the mechanism shown in Scheme 1. From the plots of $k_{obs.}$ *versus* $[\mathrm{EtNH_2}]$ (Figures 3 and 4), and by using the $K_{eq.}$ values of Table 2, the rate constants k_2 were calculated (Table 3).

If a comparison is made between $K_{eq.}$ values for (**1a** and **b**) hemiacetals with the same OR group (Table 2), it is clear that the equilibrium constant increases significantly on going from (**1a**) to (**1b**), showing that the electron-attracting chlorine substituent favours the hemiacetal formation. On the other hand the hemiacetal intermediates from the same substrate with different alkoxide groups break down with rates which decrease in the order MeO > EtO > PrO > BuO. This observation seems to imply that, as steric strain increases, the rate of decomposition of the hemiacetal intermediates decreases. This is the opposite of what should be observed on the basis of steric acceleration effects. Clearly, the causes of this order of reactivity are to be sought elsewhere. Solvent effects are probably much more important in determining the relative ease of decomposition of these intermediates. Figure 5 shows a plot of log k_2 *versus* E_T values[18] for the two series of hemiacetals (**2**). The rate constant increases significantly with an increase in polarity of the solvent. According to Hughes–Ingold electrostatic theory,[19] the rate of a reaction in which charge development occurs on going from the ground state to the transition state should increase with increasing polarity of the medium. Our results suggest some sort of charge development in the course of the amine-catalysed decomposition of (2).

Table 3. Second-order rate constants for the reaction of compounds (**1a** and **b**) with different alcohols in the presence of ethylamine at 25 °C

	k_2/l mol^{-1} s^{-1}	
Alcohol	(**1a**)	(**1b**)
MeOH	22.90	95.10
EtOH	4.60	10.30
Pr^{n}OH	2.13	5.49
Bu^{n}OH	1.70	3.47

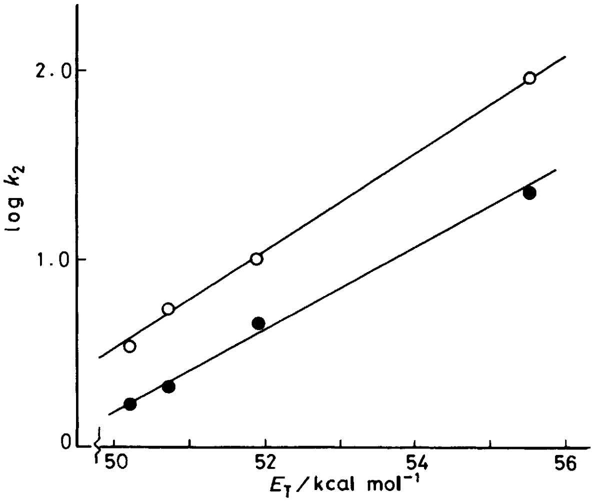


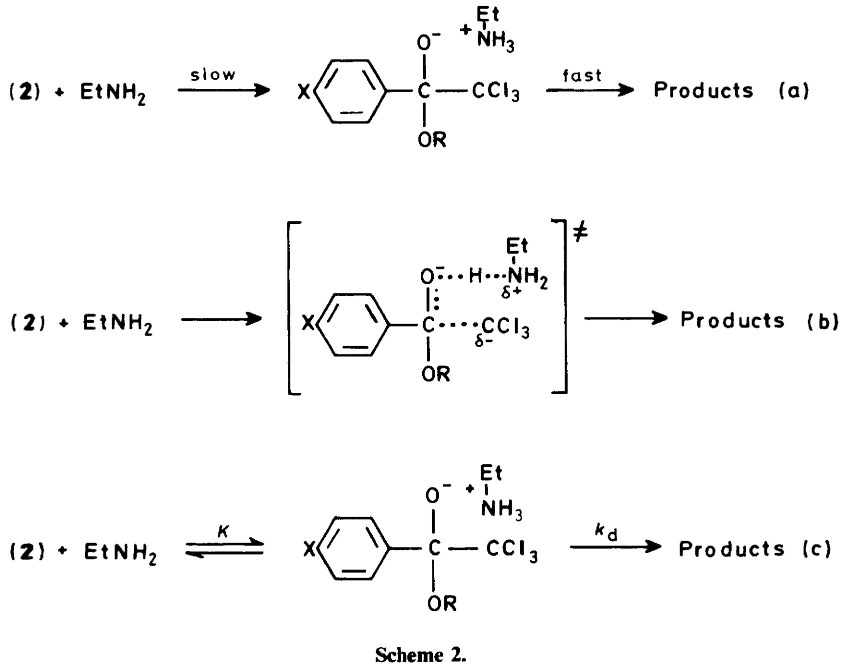
Figure 5. Plot of log k_2 *versus* E_T values for the reaction of compounds (**1a**) (●) and (**1b**) (○) with MeOH, EtOH, Pr^{n}OH, and Bu^{n}OH in the presence of ethylamine

Three kinetically indistinguishable[20] mechanisms may be proposed to rationalize the preceding observations (Scheme 2).

The mechanism represented in (a) corresponds to an $(E_1cB)_I$-type elimination. Though consistent with the polarity acceleration observed for the reaction, it postulates a rate-limiting proton transfer from an oxygen to a nitrogen atom, slower than the subsequent C–CCl$_3$ bond-breaking. This seems to us rather unlikely, as proton transfers between heteroatoms are in general considerably fast processes. In fact, $(E_1cB)_I$-type processes are only likely to occur where proton abstraction by base is a relatively slow process as is the case for proton transfer from carbon.

Mechanisms (b) and (c) correspond to *E*2- and E_1cB-type eliminations respectively. The bimolecular process (b) postulates a transition state more polar than the reagents, consistent with the polarity acceleration observed. The E_1cB mechanism (c) assumes that the reversible proton transfer to ethylamine is a fast pre-equilibrium process, as compared with the C–CCl$_3$ bond-breaking. In this case, the second-order rate constant k_2 for the amine-catalysed decomposition of (2) is a composite of two terms, a pre-equilibrium constant *K* and the k_d step, $k_2 = Kk_d$. An increase in the polarity of the solvent would shift this pre-equilibrium to the right (increase *K*), thereby increasing the overall k_2 value.

In spite of the fact that mechanism (b) and (c) are compatible with the experimental observations presented in this work, and that we cannot reject either of them, it seems to us that a proton



Scheme 2.

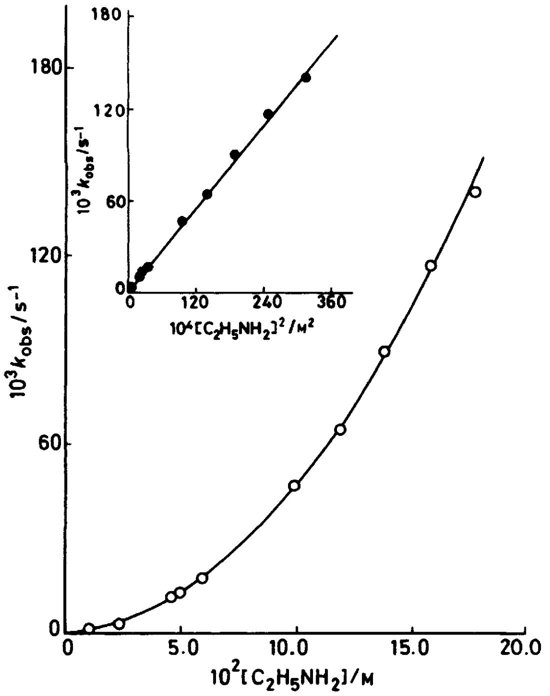


Figure 6. Plot of k_{obs} *versus* $[EtNH_2]$ for the reaction of the ethanone (**1a**) with ethylamine in dioxane at 25 °C. The insert plots the same kinetic constants *versus* $[EtNH_2]^2$

transfer between an oxygen and a nitrogen atom should be a faster process than C–CCl_3 bond-breaking. Accordingly, route (c) should be the most plausible choice.

If the reaction of (**1a**) and $EtNH_2$ is carried out in *p*-dioxane in the absence of alcohols, *N*-ethylbenzamide is obtained as the product. The kinetics of the process are complex, being second order with respect to the amine and first order with respect to (**1a**) (Figure 6). This result suggests that either the addition of ethylamine or the decomposition of the zwitterionic tetrahedral intermediate is catalysed by base.

We are currently studying the reaction of compounds (**1a** and **b**) with several amines in aprotic solvents in order to shed some light on the mechanism of this reaction and to exploit the synthetic applications of this particular reactions.

Acknowledgements

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