JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 8, 97–102 (1995)

KINETICS OF THE REACTION OF AMINES WITH 1,1,1-TRICHLORO-4-METHOXY-3-PENTEN-2-ONE

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The kinetics of the reaction of 1,1,1-trichloro-4-methoxy-3-penten-2-one with various aliphatic and aromatic amines was studied at 25 °C in water, dimethyl sulphoxide, methanol, ethanol, chloroform, toluene and hexane. The formation of the corresponding 1,1,1-trichloro-4-amino-3-penten-2-one is explained in terms of an addition–elimination mechanism.

INTRODUCTION

The behaviour of the trihalomethyl group as a nucleofuge has been known for a considerable time. The best known example of an organic transformation involving substitution of the $—CX_3$ group by a nucleophile is probably the classical haloform reaction.

We have been concerned for some time both with the synthetic use of trihalomethyl alcohols[1] and ketones[2–4] and with the mechanistic aspects involved in these transformations.[5–7] Thus, we have shown that trihalomethyl ketones are mild acylating agents, a property which justifies their commercial production (1,1,1-trichloroacetone, a mild and neutral acetylating agent, is newly available as a commercial product from Aldrich).

As an extension of this work, we became interested in trihalomethyl vinyl ketones and their reactions with nucleophiles. One of these ketones has been postulated in the preparation of isoxazole-5-carboxylic acid from trichloroacetyl chloride, ethyl vinyl ether and hydroxylamine.[8] More recently, the preparation of 1,1,1-trichloro-4-methoxy-3-penten-2-one (**1**) and its conversion into an isoxazole by hydroxylamine were described.[9]

We reasoned that **1**, beside being an obviously valuable synthetic intermediate, is also a very interesting substrate for mechanistic studies. Indeed, it exhibits two electrophilic centres, being liable in principle to both 1,2- and 1,4-additions by nucleophiles.

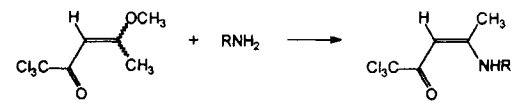
The reaction of **1** with a few amines has been described,[10] but no mechanistic studies have been carried out on this conversion. We therefore decided to investigate the details of the reaction of this trichloropentenone with various amines in different media. The results of these investigations are the subject of this paper.

RESULTS

The reaction of 1,1,1-trichloro-4-methoxy-3-penten-2-one with various amines was investigated at 25 °C in water, methanol, ethanol, dimethyl sulphoxide (DMSO), chloroform, toluene, and hexane. Characterization of the products of the reaction in hexane, employing benzylamine as nucleophile, showed that the reaction yielded the corresponding (*Z*)-alkylaminovinyl ketone (**2**) as the exclusive product (Scheme 1).

The reactions in water were carried out with benzylamine and various butylamines at different pH values. Table 1 gives the observed rate constants for the reaction of **1** with increasingly hindered amines (normal, secondary and tertiary) at pH 10·39. The observed rate constants for the reaction with benzylamine at pH 9·00, 9·33 and 10·00 are given in Table 2.

The amine concentrations in Tables 1 and 2 must be corrected to the concentration of the free base by taking into account the pH values of the medium and the pK_a value of each amine (9·35, 10·64, 10·56 and 10·68 for benzylamine, and *n*-, *sec*- and *tert*-butylamine, respectively[11]). Plots of k_{obs} against the concentration of free base yielded straight lines in all cases, showing that the reaction is first order in RNH_2. In addition, the second-order rate constants obtained from these plots decrease in the order benzylamine



(1) (2)

R= $C_6H_4CH_2$, n-C_4H_9, C_6H_5, p-OCH_3-C_6H_4, p-CH_3-C_6H_4, p-Cl-C_6H_4

Scheme 1

CCC 0894–3230/95/020097–06

Received 20 June 1994
Revised 23 September 1994

Table 1. Observed rate constants for the reaction of **1** with various butylamines (RNH_2) in water at 25 °C and pH 10·39

	10^2k_{obs} (s_{-1})		
[RNH_2] (M)	*n*-Butylamine	*sec*-Butylamine	*tert*-Butylamine
0·01	0·54	0·095	0·010
0·02	1·29	0·19	0·013
0·03	1·89	0·27	0·016
0·04	2·60	0·39	0·018
0·05	3·46	0·47	0·022
0·06	4·06	0·58	0·024

Table 2. Observed rate constants for the reaction of **1** with benzylamine in water at 25 °C and various pH values

	10^2k_{obs} (s_{-1})		
[Benzylamine] (M)	pH 9·00	pH 9·33	pH 10·00
0·01	0·80	1·26	2·08
0·02	1·61	2·58	4·37
0·03	2·65	3·96	6·63
0·04	3·36	5·11	8·46
0·05	4·30	6·59	10·56
0·06	5·12	7·50	12·86
0·07	6·06	8·73	15·37
0·08	7·32	10·45	16·06
0·09	8·11	11·79	18·06
0·10	9·03	12·59	—

(2·67 l mol^{-1} s^{-1}) > *n*-butylamine (2·13 l mol^{-1} s^{-1}) > *sec*-butylamine (0·247 l mol^{-1} s^{-1}) > *tert*-butylamine ($9·20 \times 10^{-3}$ l mol^{-1} s^{-1}). This is an indication that the reaction rates depend on the bulk of the attacking amine.

The observed rate constants for the reaction of **1** with benzylamine at 25 °C in various solvents are given in Table 3. Plots of k_{obs} vs [RNH_2] (not shown) yielded straight lines for the reactions in ethanol, methanol, DMSO and chloroform, confirming a first-order dependence on the amine concentration in these solvents. In hexane and toluene these plots were curved, but reduced to straight lines (not shown) when the rate constants were plotted against $[RNH_2]^2$, indicating a second-order dependence on the amine concentration in these non-polar solvents. The second- and the third-order rate constants obtained from these straight-line plots are given in Table 4 for all the solvents employed.

The reaction of **1** in water with four substituted anilines was also investigated. Table 5 lists the observed rate constants for this reaction with *para*-substituted anilines at various amine concentrations and different pH values. Similar data are given for aniline at pH 6·63 in Table 6.

As mentioned above, the concentrations of the free amine must be deduced from the pH values of the medium and the pK_a values of each aniline, *p*-$XC_6H_4NH_2$ (5·29, 4·09, 4·60 and 3·99 for X = OMe, Me, H and Cl, respectively[12]). Plots of k_{obs} vs the concentration of free base (not shown) yielded second-order rate constants of $2·02 \times 10^{-1}$ l mol^{-1} s^{-1}

Table 3. Observed rate constants for the reaction of **1** with benzylamine at 25 °C in various solvents

	10^2k_{obs} (s_{-1})					
[RNH_2] (M)	Hexane	Toluene	Chloroform	Ethanol	Methanol	DMSO
0·01	—	—	—	—	0·10	3·25
0·02	—	—	—	—	0·26	4·30
0·03	—	—	—	—	0·45	5·98
0·04	—	—	—	—	0·61	10·26
0·05	—	—	—	—	0·79	12·87
0·06	—	—	—	—	0·99	15·49
0·07	—	—	—	—	1·08	18·01
0·08	—	—	—	—	1·27	21·11
0·09	—	—	—	—	1·44	22·18
0·10	0·10	0·075	0·068	2·25	1·59	25·77
0·20	0·22	0·15	0·15	4·21	—	—
0·30	0·52	0·38	0·24	6·43	—	—
0·40	0·60	0·46	0·38	8·14	—	—
0·50	0·84	1·07	0·50	10·10	—	—
0·60	1·11	1·73	0·58	12·22	—	—
0·70	1·46	2·36	0·72	14·19	—	—
0·80	1·89	3·22	0·84	15·78	—	—
0·90	2·41	4·23	0·99	18·11	—	—
1·00	2·97	5·34	1·12	20·04	—	—

Table 4. Second- and third-order rate constants for the reaction of **1** with benzylamine in various solvents

Solvent	$10^2 k$
Hexane	5·85[a]
Toluene	3·08[a]
Chloroform	1·18[b]
Ethanol	19·6[b]
Methanol	16·6[b]
DMSO	260[b]
Water	267[b]

[a] Third-order rate constants ($s^{-1} l^2 mol^{-2}$).
[b] Second-order rate constants ($s^{-1} l mol^{-1}$).

(X = OMe), $6{\cdot}59 \times 10^{-2}$ l mol^{-1} s^{-1} (X = Me), $3{\cdot}97 \times 10^{-2}$ l mol^{-1} s^{-1} (X = H) and $3{\cdot}30 \times 10^{-2}$ l mol^{-1} s^{-1} (X = Cl). The Hammett plots obtained with these values are shown in Figure 1.

DISCUSSION

The kinetic observations presented above point to mechanisms of nucleophilic addition–elimination, as depicted in Scheme 2. This is a particular case of a

Table 5. Observed rate constants for the reaction of **1** with substituted anilines, p-$xC_6H_4NH_2$, in water at 25 °C and different pH values

	$10^2 k_{obs}$ (s_{-1})		
10^3[$ArNH_2$] (M)	p-Cl (pH 6·37)	p-CH_3 (pH 7·12)	p-OCH_3 (pH 7·37)
6·00	0·015	0·031	0·040
12·00	0·035	0·063	0·16
18·00	0·060	—	0·28
24·00	0·063	0·157	0·40
30·00	0·099	0·182	0·52

Table 6. Observed rate constants for reaction of **1** with aniline in water at 25 °C and pH 6·63

10^3[Aniline] (M)	$10^2 k_{obs}$ (s_{-1})	10^3[Aniline] (M)	$10^2 k_{obs}$ (s_{-1})
0·01	0·036	0·06	0·23
0·02	0·072	0·07	0·27
0·03	0·1	0·08	0·31
0·04	0·15	0·09	0·34
0·05	0·19	0·10	0·38

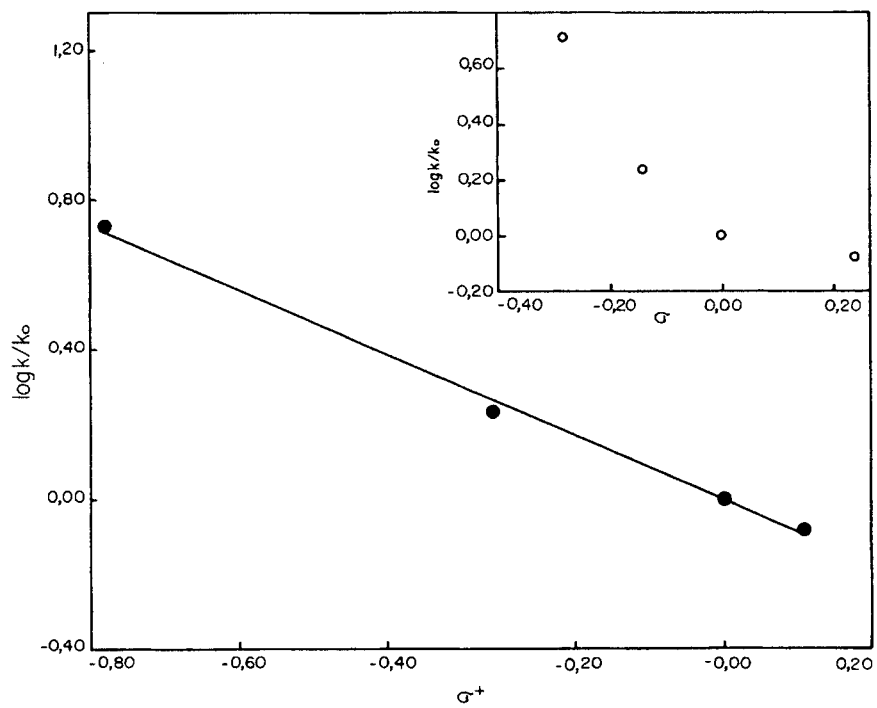
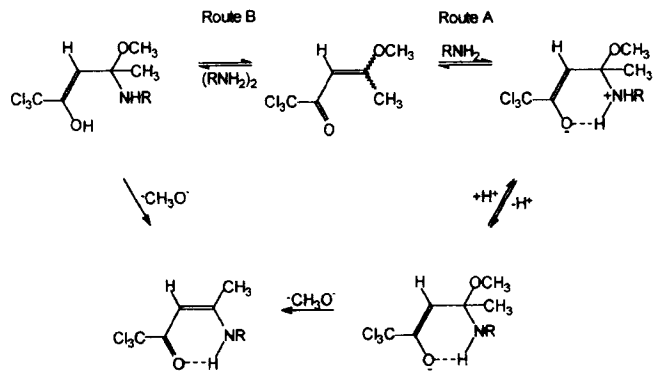


Figure 1. Plot of log (k/k_0) versus σ_+ for the reaction of **1** with p-$XC_6H_5NH_2$. Inset: corresponding plot of log(k/k_0) versus σ for the same reaction



Scheme 2

nucleophilic vinylic substitution, a general pattern of reaction which has been reviewed.[13-15]

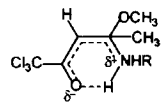
In our case, the trichloroacetyl group activates the vinyl ether towards an attack by the amine. Nucleophilic addition to the double bond leads to a cyclic intermediate which is stabilized by internal hydrogen bonding. Elimination of the methoxy group is facilitated by the adjacent nitrogen, which helps to stabilize the resulting positive charge in the form of an internal iminium ion.

The kinetic data provide enough evidence to support this mechanism. First, the order of the reaction is dependent on the nature of the solvent and the effect cannot be ascribed solely to polarity.[16] The rates were second order in amine concentration in the less polar solvents hexane and toluene, being first order in the other media. The second-order dependence in non-polar solvents probably arises from association effects, being a common feature in the aminolysis of similar substrates in non-polar media.[7] Indeed, the higher order in amine concentration in hexane and toluene may indicate a change in mechanism, since poor donor solvents can hardly disrupt hydrogen bonding association between amine molecules. Thus, whereas a tetrahedral zwitterionic intermediate is favoured in more polar media (route A in Scheme 2), in non-polar solvents, such as hexane and toluene, a neutral intermediate is certainly low in energy than the zwitterionic intermediate (route B in Scheme 2). The pre-association of the amines, through hydrogen bonding complexation, followed by a concerted attack of the dimeric nucleophile at the reaction centre (through the geometrically more favourable six-membered transition state) is to be preferred to a high-entropy, three-body transition state.[7,17]

The acceleration brought about by an increase in the polarity of the solvent (Table 3) is a good indication that the rate-determining step involves a more polar transition state than the ground state. This applies equally well to both the addition and elimination steps, since both lead to charged intermediates. The unexpectedly high reaction rate in DMSO, where the reaction proceeds as fast as in water (see Table 4), deserves further comment. Water is in fact a more polar solvent than DMSO, a solvent which is even less polar than either ethanol or methanol. The large rate acceleration observed in DMSO cannot be explained solely in terms of its polarity, but also of its high donicity. This points to a protophilic role played by the solvent, which probably increases the nucleophilicity of the attacking amine.

The basicity (or the nucleophilicity) of the amine seems to be less important than its steric bulk. This is shown by a comparison of the reactivities of various alkylamines in water. Benzylamine, with a pK_a value of 9·35, is slightly more reactive than *n*-butylamine ($pK_a = 10·64$) in water. On the other hand, the reactivity of three butylamines with similar pK_a values decreases steadily with the increasing steric bulk of the amine. This observation suggests that the rate-determining step is the nucleophile addition to the activated double bond. One would in fact expect the opposite effect if the elimination were the slowest step of the process. The elimination of the methoxy group decreases the steric compression of the intermediate, as the crowded sp^3 β-carbon is relieved to assume its original sp^2 hybridization. Bulkier groups R would obviously accelerate this step, in disagreement with what is observed.

The Hammett plot in Figure 1, with a good correlation with σ^+ values, is surprising. The reaction of 1,1,-dicyano-2-(4-dimethylaminophenyl)-2-chloroethylene with aromatic amines at 30 °C yielded a ρ value of −3·92. Correlation with σ^+ was poor.[14] These observations from addition-elimination processes where the attacking nucleophile is an aromatic amine are apparently at variance with our findings of a good correlation with σ^+ values ($r = 0·996$) and a smaller value of ρ^+ (−0·88). Attempts to explain these discrepancies should recognize that the substrates of the two reactions are different. It is also noteworthy that in all reported



Scheme 3

Hammett plots, the rate constants corresponding to the *p*-OMe-substituted aniline gave rise to deviating points, an observation that the authors did not try to explain.[14] Indeed, we believe that the observed correlation with σ^+ lacks any theoretical significance, since these particular correlations should be applied only when an electron-deficient, positively charged centre is developing on the pathway to the transition state. In our case, the positive charge is developed in a fully saturated nitrogen atom; therefore there is no possibility of conjugation with 4-substituents in the aniline. Thus, despite the poorer linear correlation obtained with σ (inset in Figure 1, $r = 0{\cdot}895$), we favour the correlation with the Hammett σ values, and then the curve can be considered as indicating perhaps a change in transition state structure.

The limiting ρ value of $-3{\cdot}33$ observed for the electron-releasing substituents points to a positive charge build-up on the nitrogen atom of the amine in the transition state, a result which agrees reasonably well with the value of $-3{\cdot}92$ reported for the reaction of aromatic amines with 1,1-dicyano-2-(4-dimethylaminophenyl)-2-chloroethylene. The change in the slope observed with the electron-withdrawing substituents is in agreement with a rate-determining attack of the amine, in which the transition state is reached rather early along the reaction coordinate. This early transition state should be possible because of the role played by the carbonyl group, which, by developing some negative charge on the oxygen atom, helps stabilize and reduce the developing positive charge on the amine nitrogen in the transition state (Scheme 3).

In conclusion, we propose two stepwise mechanisms to explain our data on the reaction of 1,1,1,1-trichloro-4-methoxy-3-penten-2-one with amines. In all cases, the reaction leads to exclusive nucleophilic substitution of the methoxy group to give the corresponding 4-aminopentenone. In non-polar solvents such as hexane and toluene, the reaction proceeds through the concentrated attack of an amine dimer to form a neutral intermediate. In the second stepwise mechanism, in polar solvents, the reaction proceeds through a zwitterionic intermediate. Thus, besides the relationship of the nucleophile–nucleofuge pair, the nature of the solvent plays a fundamental role in the mechanism of this particular reaction.

EXPERIMENTAL

Melting points were recorded on Koffler hot-stage apparatus (Microquímica APF-301) and were not corrected. IR spectra were obtained with a Perkin-Elmer Model 781 spectrophotometer, ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AW-200 instrument, using tetramethylsilane as internal reference. The kinetic runs were followed spectrophotometrically utilizing a Shimadzu UV-201A spectrophotometer.

1,1,1-Trichloro-4-methoxy-3-penten-2-one was a gift from Dr Marcos Martins, prepared according a described procedure.[9]

All solvents and amines were analytically pure (Merck) and were further purified by standard methods prior to use. Aqueous solutions were prepared with deionized water.

Product characterization. The substrate 1,1,1-trichloro-4-methoxy-3-penten-2-one (1·0 g, 4·56 mmol) was made to react with benzylamine (0·54 g, 5·0 mmol) in hexane (10 mmol) at 25 C. After 10 min, the resulting 1,1,1-trichloro-4-benzylamino-3-penten-2-one separated in the form of a white precipitate, which was filtered and dried (1·23 g, 90% yield). The product was recrystallized from acetone–hexane, m.p. 90 °C; elemental analysis, C 49·11, H 4·05, N 4·95; $C_{12}H_{12}NO$ requires C 42·23, H 4·1, N 4·79%; IR, λ_{max} 3060, 3030, 2950, 1620, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ2·13 (s, 3H, CH_3), 4·48 (d, 2H, $J = 6{\cdot}00$ Hz), 5·47 (s, 1H, CH=C), 7·32 (m, 5H, C_6H_5), 10·88 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$), δ19·70 (CH_3), 47·40 (CH_2), 86·70 (HC=), 97·08 (CCl_3), 126·92 (C_6H_5, *m*-C), 127·82 (C_6H_5, *p*-C), 128·85 (C_6H_5, *o*-C), 135·98 (C_6H_5, *ipso*-C), 168·72 (=CCH_3), 180·15 (C=O).

Kinetic runs. The kinetics runs were carried out under pseudo-first-order conditions by adding 30 μl of a 10^{-2} M solution of the substrate to 3 ml of a solution of the amine (0·01–1·0 M) in a thermostated cell (25 ± 0·1 °C) and following the appearance of the products at 326 nm. Reactions in water were carried out with buffered solutions.

All runs were followed for at least 3–4 half-lives. In every run a total of 250 absorbance readings were acquired by a microcomputer interfaced with the spectrophotometer and processed by a Microquímica kinetics data acquisition program, which yielded rate constants with errors smaller than 1·0%.

ACKNOWLEDGEMENTS

Thanks are due to FINEP for supporting this work through the PADCT-II Program. We are also grateful to Dr Marcos Martins for the kind gift of the substrate for our studies.

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