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Mechanisms of elimination and substitution reactions. Spontaneous solvolysis reactions via carbanion and carbocation intermediates

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ABSTRACT: The reactions of 4-(4′-nitrophenyl)-4-X-butan-2-one (**1-X;** X = Cl, OTs) with added bases/nucleophiles exhibit second-order kinetics. These substitution and elimination reactions are concluded to be of concerted S_N2 type and irreversible *E*1*cB* type, respectively. The spontaneous formation of alkene from the chloride **1-CI** is suggested to occur by a water-promoted *E*1*cB* reaction. The fraction of elimination product is smaller with the tosylate **1-OTs**. It is plausible that the elimination and substitution reactions of **1-OTs** are carbocation reactions since the Brønsted plot with substituted acetate anion bases shows a tenfold *positive* deviation for the 'water-catalyzed' elimination reaction, and there is a trace of substitution reaction with the acetonitrile component of the solvent yielding **1-NHCOMe**. These results are consistent with a common, very short-lived, carbocation intermediate. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: elimination reactions; substitution reactions; solvolysis reactions; carbanion intermediates; carbocation intermediates

INTRODUCTION

We are interested in mechanistic details of nucleophilic substitution and elimination reactions and the factors which can induce a change in reaction path, or induce a change in reaction mechanism, of a particular reaction. The aim of this work was to investigate the mechanistic details of both the spontaneous and the base-promoted 1,2-elimination reactions of a system having strongly acidic β-hydrogens (Scheme 1). The presence of the acidic hydrogens favors carbanion formation and, accordingly, the base-promoted elimination may occur by an *E*1*cB* reaction mechanism. The corresponding fluoride **1-F** has been employed recently in mechanistic studies of an antibody-catalyzed elimination reaction, which was concluded to have an *E*1*cB* or *E*2 mechanism.[1] Elimination reactions of carbonyl-activated substrates are common in nature. However, it has recently been proposed that enzymes do not catalyze 'simple' *E*1*cB* reactions but involve 1,4-elimination from the enol intermediate.[2]

We are also interested in the mechanism of the spontaneous elimination: does the solvent water abstract the hydron to give the enolate ion which in a subsequent step expels the leaving group, i.e. is the reaction a water-promoted *E*1*cB* reaction? An alternative is a concerted water-promoted *E*2 reaction. Elimination reactions of indenyl and substituted fluorenyl substrates have recently been proposed to occur by *E*1*cB* and *E*2 reaction mechanisms.[3]

The putative carbocation intermediate formed from **1-X** is expected to be extremely shortlived and Richard and Jencks[4] concluded that the closely related 1-(4-nitrophenyl)ethyl carbocation may not have a significant lifetime in aqueous solution. However, we now report results which suggest that the tosylate reacts through an ion pair.

RESULTS

The solvolysis of 4-(4′-nitrophenyl)-4-X-butan-2-one (**1-X**; X = Cl, OTs) in 25 vol.% acetonitrile in water yields the alkene (*E*)-4-(4′-nitrophenyl)-2-oxobut-3-ene and the substitution product 4-hydroxy-4-(4′-nitrophenyl)butan-2-one (**1-OH**) (Scheme 1). The tosylate **1-OTs** gives a small amount of the substitution product 4-acetamido-4-(4′-nitrophenyl)butan-2-one (**1-NHCOMe**). No products other than those shown in Scheme 1 were found. The amide **1-NHCOMe** was not isolated but its identity was inferred from its UV spectrum, the increase in the product ratio [**1-NHCOMe**]/[**1-OH**] with increasing acetonitrile content of the solvent and the failure to observe this product in solvolysis of **1-OTs** in methanol–water. The solvolysis of **1-Cl** in aqueous acetonitrile yields a smaller fraction of alcohol (Table 1) and no traces of **1-NHCOMe** were found.

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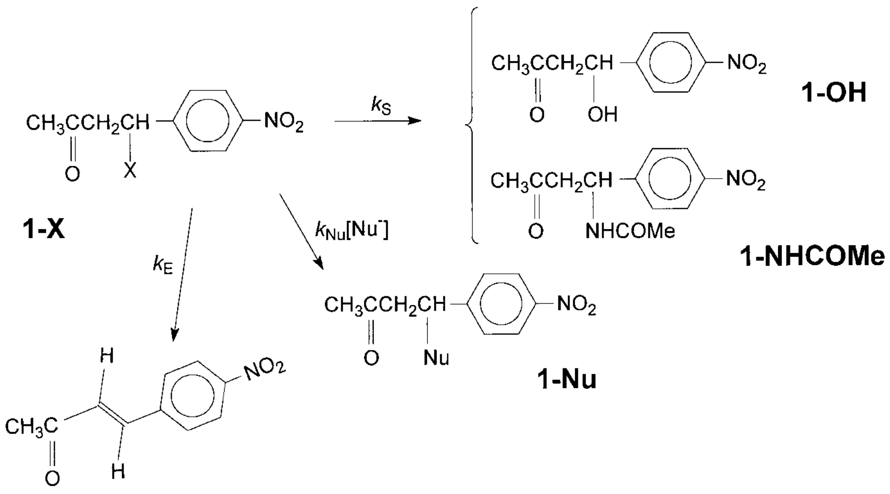


Scheme 1

Table 1. Rate constants for the solvolyses of **1-Cl** and **1-OTs** in 25 vol.% acetonitrile in water

Substrate[a,b]	T (°C)	10^6k_{obs}[c] (s^{-1})	10^6k_E (s^{-1})	10^6k_s (s^{-1})
1-Cl	70	10.9	8.50	2.36
1-OTs	25	140	6.5	133
1-OH	70		0.2	

[a] Substrate concentration 0.01–0.1 mmol dm^{-3}.
[b] $[HClO_4] = 1$ mmol dm^{-3}.
[c] $k_{obs} = k_E + k_s$.

Added bases/nucleophiles give rise to competing bimolecular elimination and substitution reactions as exemplified with azide ion in Fig. 1. The kinetics of the reactions were studied by a sampling high-performance liquid chromatographic procedure. The rate constants and reaction conditions are shown in Table 1. The measured kinetic data for the reactions with added bases and nucleophiles are shown in Table 2. The rate constant for

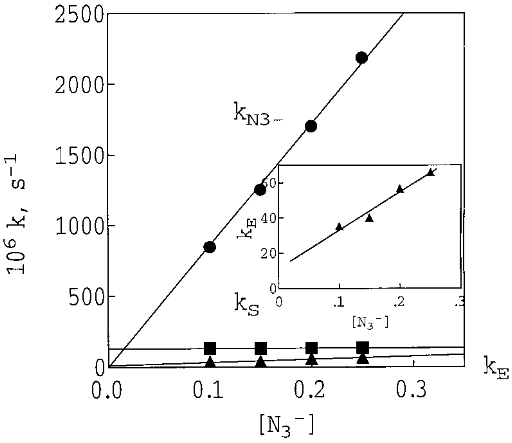


Figure 1. Effect of azide ion concentration on the rate constants k_{N3}, k_S and k_E for the reaction of **1-OTs** in 25 vol.% acetonitrile in water at 25°C. Inset: enlargement of the plot of k_E

Table 2. Rate constants for the reactions of **1-Cl** and **1-OTs** with bases

Solvent	Substrate[a]	Base	T (°C)	10^6k_E (dm^3 mol^{-1} s^{-1})	10^6k_{Nu} (dm^3 mol^{-1} s^{-1})
25 vol.% Acetonitrile in water	**1-OTs**	N_3^-	25	217	8578
		$NCCH_2COO^-$[b]	25	10.3	23.8
		$MeOCH_2COO^-$[c]	25	56.2	28.0
		AcO^-[d]	25	389	
	1-Cl	CF_3COO^-[e]	70	13.2	
		$NCCH_2COO^-$[b]	70	508	
		$MeOCH_2COO^-$[c]	70	2.83×10^3	
		AcO^-[f]	70	1.33×10^4	
Methanol	**1-OTs**	DABCO[g,h]	25	1.46×10^5	
	1-Cl	DABCO[g,h]	25	4.86×10^4	

[a] Substrate concentration 0.01–0.1 mmol dm^{-3}.
[b] Measured with 0.10–0.40 mol dm^{-3} buffer, $[NCCH_2COO^-]/[NCCH_2COOH] = 10$.
[c] Measured with 0.10–0.40 mol dm^{-3} buffer, $[MeOCH_2COO^-]/[MeOCH_2COOH] = 1$.
[d] Measured with 0.10–0.40 mol dm^{-3} $[AcO^-]/[HOAc] = 4$.
[e] Measured with CF_3COO^-, 0.25–0.75 mol dm^{-3}.
[f] Measured with 0.025–0.100 mol dm^{-3} acetate buffer, $[AcO^-]/[HOAc] = 4$.
[g] Diazabicyclo[2.2.2]octane.
[h] Measured with 0.01 mol dm^{-3} base, $[Base]/[BaseH^+] = 1$.

Table 3. Kinetic deuterium isotope effects for the reactions of **1-Cl** and **1-OTs** in 25 vol.% acetonitrile in water

Substrate[a]	Base	T (°C)	k_{obs}^H/k_{obs}^D	k_E^H/k_E^D	k_S^H/k_S^D
1-Cl[b]	Solvent	70	2.0	2.4	1.26
1-Cl	AcO^-[c]	25	4.2	4.2	
1-Cl	DABCO[d,e]	25	3.2	3.2	
1-OTs[b]	Solvent	25	1.2	2.8	1.18
1-OTs	DABCO[d,e]	25	4.6	4.6	

[a] Substrate concentration 0.01–0.1 mmol dm^{-3}.
[b] $[HClO_4] = 1$ mmol dm^{-3}.
[c] Measured with 0.75 mol dm^{-3} acetate buffer, $[AcO^-]/[HOAc] = 100$.
[d] Diazabicyclo[2.2.2]octane.
[e] Measured with 0.01 mol dm^{-3} base in methanol, $[Base]/[BaseH^+] = 1$.

the substitution reaction of **1-OTs** with acetate ion is difficult to measure owing to the large amount of elimination with this base.

The corresponding deuterated compounds [1,1,1,3,3-$^2H_5$]-4-(4′-nitrophenyl)-4-X-butan-2-one (**d-1-X**) react slower to give alkene. The measured kinetic deuterium isotope effects for solvolysis and base-promoted reactions are shown in Table 3.

DISCUSSION

Base-promoted elimination reactions

The following experimental results show that the base-promoted elimination reactions of **1-Cl** and **1-OTs** do not occur via carbocation intermediates but rather are *E*2 and/or *E*1*cB* type reactions.

The large Brønsted parameters for **1-Cl** and **1-OTs**, $\beta = 0.67$ and 0.68, respectively, measured with substituted acetate anions (Fig. 2), indicate that the reactions have either a one-step mechanism (*E*2) or an irreversible carbanion mechanism ($E1cB_I$). A very small β value is expected for a mechanism in which a reversibly formed unstable carbocationic intermediate is dehydronated in the rate-limiting step.[5,6] Accordingly, these substantial β values exclude reactions through ion pairs but are consistent with *E*2 and $E1cB_I$ reaction mechanisms. Moreover, only a low concentration of added strong base is required to give elimination exclusively. It is unreasonable that a short-lived ion pair would show such large selectivity.

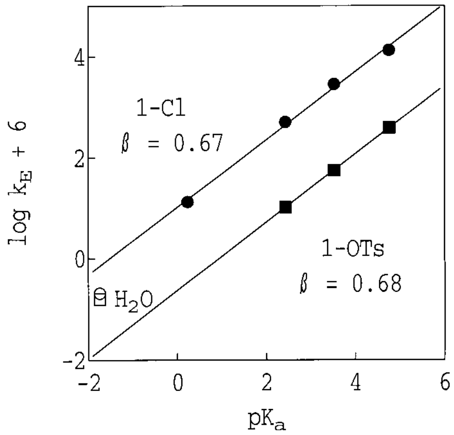


Figure 2. Brønsted plots for the elimination reactions of **1-Cl** (●) and **1-OTs** (■) with substituted acetate anions in 25 vol.% acetonitrile in water at 70 and 25 °C, respectively

Several studies of base-promoted 1,2-elimination reactions of carbonyl-activated substrates have been reported.[7] With poor leaving groups the elimination occurs through the reversibly formed enolate ion, which in the rate-limiting step expels the leaving group. Accordingly, the elimination reaction exhibits specific base catalysis. An example is the elimination of MeOH from $CH_3COCH_2CH_2OMe$.[7a] It was shown that the reaction mechanism changes to an irreversible *E*1*cB* mechanism if the leaving group is a more efficient one, e.g. $ArCOO^-$.[7b] It is difficult, of course, rigorously to exclude the possibility of a concerted *E*2 mechanism since the two mechanisms show very similar characteristics such as bimolecular kinetics and general base catalysis. However, the $E1cB_I$ mechanism is indicated by the low sensitivity of the reaction rate toward the change of *para* substituent in the aromatic moiety of the leaving group, i.e. a small Hammett parameter ρ was measured.[7b] This small sensitivity is attributable to a stepwise reaction in which the first step, the ionization to the enolate anion, is rate-limiting. Moreover, the departure of a carboxylate leaving group from the carbanion intermediate is expected to have a small but significant barrier.[8]

With more efficient leaving groups, such as halide ions and aromatic sulfonates, the mechanism may change to the concerted *E*2 type owing to the disappearance of the barrier for departure of the leaving group and/or to a significant stabilization of the concerted *E*2 transition state by a partial bond-breaking to the leaving group. However, the mechanistic assignment is not very simple since also the transition state of the hydron-transfer step to give the putative carbanion intermediate is stabilized by hyperconjugative interactions with the leaving group.[8–10]

The measured Brønsted parameters for elimination of **1-Cl** and **1-OTs** with substituted acetate ions of $\beta = 0.67$ and 0.68, respectively, show that the hydron is transferred to the oxygen base to a large extent in the transition state. A proton transfer of 38% corresponds to the isotope effect maximum for reaction of an oxygen base with a carbon acid.[11] The moderate values of the kinetic deuterium isotope effects (Table 3) are consistent with a large amount of hydron transfer in the transition state. The very similar β values for the two substrates and the similar rates of second-order elimination suggest that the reactions are of $E1cB_I$ type [the measured elimination rate constant for **1-Cl** with $CNCH_2COO^-$ ion as base at 70 °C using a factor of 2.5 for a decrease in temperature of 10 °C yields $k_E \approx 8 \times 10^{-6}$ M^{-1} s^{-1} at 25 °C compared with 10.3×10^{-6} M^{-1} s^{-1} for **1-OTs** (Table 2)]. This is in accord with the high acidity of the β-hydrogens; the pK_a should be close to that of acetone, which has been measured as 19.3.[12]

Only one elimination product, the *trans* isomer (Scheme 1), is produced. This is in accord with the results of Shokat *et al.*,[1] who showed that an antibody-catalyzed elimination of HF from **1-F** gave exclusive formation of the *trans*-alkene. Experiments using specifically deuterated substrates showed both *anti* and *syn* elimination modes. The kinetic deuterium isotope effect on the acetate-catalyzed background reaction of **1-F** was measured as $k^H/k^D = 3.7$ at 25 °C,[1] which is smaller than that of the acetate-catalyzed reaction of **1-Cl** ($k_E^H/k_E^D = 4.2$; Table 3).

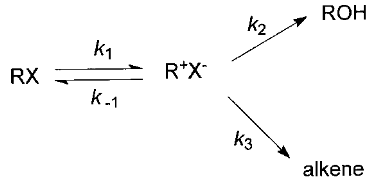
Spontaneous elimination: solvent-promoted *E*1*cB* elimination reaction and elimination through ion-pair intermediate

Solvolytic elimination reactions are generally thought to occur through carbocation ion pairs and free carbocation intermediates.[6] The following experimental results show that the solvolytic elimination reaction of **1-Cl** does not occur via such intermediates but is an *E*2 or *E*1*cB* type reaction:

(i) Irreversible formation of an ion pair which in competing subsequent steps undergoes elimination and substitution (Scheme 2, $k_{-1} \ll k_2, k_3$) is not consistent with the measured isotope effect of $k_{obs}^H/k_{obs}^D = 2.0$. A maximum secondary kinetic deuterium isotope effect of about 1.3 is expected for such a mechanism.[13]

(ii) A similar mechanism but with reversible formation of the ion pair (Scheme 2, $k_{-1} \gg k_2, k_3$) might account for the results. However, unreasonable isotope effect values, e.g. a very small kinetic isotope effect on the elimination step (k_3), are required to account for the measured isotope effects.

(iii) The catalytic constants for water as the base falls below the Brønsted lines by a factor of about 4 (see Fig. 2), which is in accord with what has been observed previously for water-promoted *E*1*cB*/*E*2 reactions.



if $k_{-1} > k_2, k_3$

$k_S = Kk_2$ where $K = k_1/k_{-1}$

$k_E = Kk_3$

$$k_{obs} = k_S + k_E = K(k_2 + k_3)$$

$$k_S^H/k_S^D = (K^H/K^D)(k_2^H/k_2^D)$$

$$k_E^H/k_E^D = (K^H/K^D)(k_3^H/k_3^D)$$

$$k_{obs}^H/k_{obs}^D = (K^H/K^D)(k_2^H + k_3^H)/(k_2^D + k_3^D)$$

Scheme 2

We therefore conclude that water abstracts a hydron from **1-Cl** in a concerted *E*2 reaction or in an irreversible *E*1*cB* process. This conclusion is in accord with our results for other halides having an acidic β-hydrogen which have been proposed to react with solvent water by *E*2 and $E1cB_I$ mechanisms.[3] The acidities of these indene and substituted fluorene substrates are within the pK_a interval of 17.9–22.5. The pK_a of **1-Cl** is similar since it should be close to that of acetone (pK_a = 19.3).[12] The isotope effect on the elimination is smaller than that with

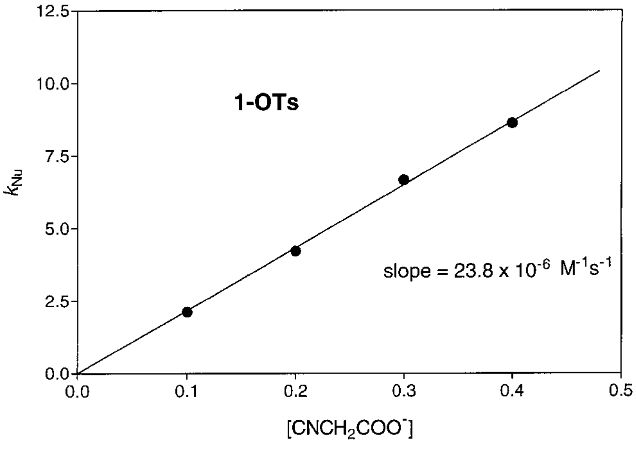


Figure 3. Effect of [$CNCH_2COO^-$] on the substitution rate constant k_S for the reaction of **1-OTs** in 25 vol.% acetonitrile in water at 25 °C

added stronger base which is expected for *E*1c*B* reactions, and may suggest that both the water- and the base-promoted elimination of **1-Cl** and *E*1c*B*$_I$ reactions.

The spontaneous elimination of **1-OTs** is much less favored and solvolytic substitution to give **1-OH** is the predominant reaction. However, k_E for **1-OTs** at 25 °C is about 50 times larger than the corresponding estimated rate constant for **1-Cl** (asumming a factor of about 2.5 for a change in temperature of 10 °C; Table 1). The large 10-fold positive deviation of the uncatalyzed elimination reaction from the Brønsted plot with added bases (open square in Fig. 2) is different to what is observed for **1-Cl** (a fourfold negative deviation; open circle in Fig. 2) and suggests another mechanism. The second-order rate constant plotted in the diagram is obtained by dividing the observed first-order rate constant for the spontaneous elimination with the concentration of water in the aqueous solution. However, if an elimination reaction through a carbocation intermediate is much faster than a water-promoted *E*1c*B* or *E*2 reaction, a positive deviation such as that shown in Fig. 2 is expected. We consider this as a strong indication for a carbocation reaction mechanism for the spontaneous elimination of **1-OTs**.

The small kinetic deuterium isotope effect of $k_E{}^H/k_E{}^D = 2.8$ for the spontaneous elimination of **1-OTs**, together with the predominant solvolytic substitution reaction having a secondary isotope effect as large as $k_S{}^H/k_S{}^D = 1.18$ (Table 3), indicates that the carbocation intermediate is formed reversibly (Scheme 2, $k_{-1} \gg k_2$, k_3).

We have previously found a similar behavior for some other acidic substrates, i.e. the bromides react with water through an *E*2 or *E*1c*B* reaction mechanism but the corresponding brosylates and tosylates react through the ion pair.[3a–c,e] For example, it was concluded, based upon the 14-fold positive deviation for the spontaneous elimination rate constant from the Brønsted plot with substituted acetate anions, that 9-({[(4′-bromophenyl)-sulfonyl]oxy}methyl)fluorene reacts through the ion pair.[3e] A change in leaving group to bromide ion changes the mechanism to *E*2 or *E*1c*B*$_I$. A similar change in mechanism was also observed by decreasing the pK_a of the substrate without changing the brosylate leaving group.[3e]

Substitution reactions

Both **1-Cl** and **1-OTs** show bimolecular substitution reactions with added good nucleophiles, which is exemplified in Fig. 1 for the reaction of **1-OTs** with azide ion. Basic nucleophiles give rise to competing bimolecular elimination (Table 2), but the amount of elimination with the strongly nucleophilic azide ion (pK_a = 4.8) is not large (Fig. 1). The tosylate also yields second-order substitution with substituted acetate ions, as shown in Fig. 3 for reaction with $CNCH_2COO^-$. The substitution with these acetate ions shows a low sensitivity toward the pK_a of the nucleophile of $\beta_{nuc} \approx 0.06$ (based upon data for $CNCH_2COO^-$ and $MeOCH_2COO^-$, Table 2). The acetonitrile component of the solvent yields some substitution product **1-NHCOMe**; water is about a 50 times better nucleophile than acetonitrile, i.e. $k_{MeCN}/k_{HOH} \approx 0.02$ (ratio of second-order rate constants). More stable carbocations do not react with acetonitrile under neutral conditions in aqueous solvent mixtures.[3b]

The chloride shows a larger elimination-to-substitution ratio with nucleophiles/bases and therefore its sensitivity toward nucleophilicity is more difficult to study. Chlorides have been found to interact much more strongly with nucleophiles than tosylates in S_N2 reactions of 1-phenylethyl derivatives.[4] No traces of **1-NHCOMe** were found in the solvolysis of **1-Cl**.

What is the mechanism for the nucleophilic substitution reactions with the solvent components? It was concluded that the spontaneous elimination reaction of **1-OTs** occurs by a carbocation mechanism (see above). This suggests that the substitution also occurs stepwise (Scheme 2), through a very unstable carbocation ion pair. The reactivity of the closely related 1-(4-nitrophenyl)-ethyl carbocation with solvent water has been estimated to be roughly of the order of 10^{13} s^{-1} by extrapolation of rate constants for less reactive 1-phenylethyl derivatives.[4]

In summary, the results for the substitution reactions of **1-OTs** with weak nucleophiles (such as the solvent components) are consistent with a dissociative mechanism with little or no assistance. Bimolecular S_N2 substitution becomes important with stronger nucleophiles.

EXPERIMENTAL

General procedures. NMR spectra were recorded at 25 °C with a Varian Unity 400 spectrometer, at 400 MHz for ^{1}H and at 100.6 MHz for ^{13}C. Chemical shifts are indirectly referenced to TMS via the solvent signal (chloroform-d_1 7.26 and 77.0 ppm). High-performance liquid chromatographic analyses were carried out on a C_8 reversed-phase column (5 μm, 100 × 3 mm i.d.) using a Hewlett-Packard Model 1090 liquid chromatograph equipped with a diode-array detector. The mobile phase was a solution of acetonitrile in water. The reactions were studied at constant temperature in a HETO 01 PT 623 thermostated bath. The pH was measured using a Radiometer PHM82 pH meter equipped with an Ingold micro glass electrode.

Materials. Merck silica gel 60 (240–400 mesh) was used for flash chromatography. Diethyl ether was distilled under nitrogen from sodium and benzophenone. Pyridine and dichloromethane were distilled under nitrogen from calcium hydride. Methanol and acetonitrile were of

HPLC grade. All other chemicals were of reagent grade and used without further purification.

4-Hydroxy-4-(4′-nitrophenyl)butan-2-one (**1-OH**) was synthesized from 4-nitrobenzaldehyde and acetone by a published procedure.[1] The product was purified by flash chromatography on silica gel with 40–50% ethyl acetate in pentane and recrystallization from toluene–pentane to give pure alcohol.

[1,1,1,3,3-$^2H_5$]-4-Hydroxy-4-(4′-nitrophenyl)butan-2-one (**d-1-OH**) was synthesized as described above using acetone-d_6 (99.8% ^{2}H). The deuterium contents were measured by ^{1}H NMR spectroscopy to be >98 at% ^{2}H in the 1-and 3-positions.

(E)-4-(4′-Nitrophenyl)-2-oxobut-3-ene was synthesized by a published procedure.[1]

4-Chloro-4-(4′-nitrophenyl)butan-2-one (**1-Cl**) was synthesized by two methods. *Method 1.* The alcohol **1-OH** (0.5 g) was added to a stirred solution of phosphorus pentachloride (1 g) in dry diethyl ether (10 cm^3) at 0 °C. The reaction mixture was stirred at room temperature for about 1 h. The mixture was then hydrolyzed by slow addition of ice. The ether layer was separated and the aqueous layer was extracted twice with diethyl ether. The combined ether solution was washed with brine and dried over sodium sulfate. The solvent was removed and the residue oil was purified by flash chromatography on silica gel with 15% ethyl acetate in pentane as eluent to give the chloride **1-Cl** containing 10% of alkene, but otherwise free from impurities. *Method 2.* Dry hydrogen chloride gas was bubbled through a solution of **1-OH** in dry dichloromethane at 0 °C for 1 h.

^{1}H NMR, δ 8.21 (m, 2 H), 7.61 (m, 2 H), 5.42 (dd, J = 7.8, 6.2 Hz, 1 H), 3.36 (dd, J = 17.6, 7.8 Hz, 1 H), 3.12 (dd, J = 17.6, 6.2 Hz, 1 H), 2.19 (s, 3 H).

[1,1,1,3,3-$^2H_5$]-4-Chloro-4-(4′-nitrophenyl)butan-2-one (**d-1-CI**) was synthesized using Method 1 above. The deuterium contents were measured by ^{1}H NMR to be >98 at% ^{2}H in the 1-and 3-positions.

4-[(4′-Methylbenzenesulfonyl)oxy]-4-(4″-nitrophenyl)butan-2-one (**1-OTs**) was synthesized by stirring a mixture of **1-OH** (1 g), 4-methylbenzenesulfonyl chloride (3 g), dry dichloromethane (5 cm^3) and dry pyridine (2.5 cm^3) at room temperature. The reaction was quenched after 10 h (about 50% reaction) by addition of 2 mol dm^{-3} hydrochloric acid. The aqueous phase was extracted twice with dichloromethane. The combined organic phases were washed with water and brine and dried with sodium sulfate. Evaporation of the solvent and separation by flash chromatography on silica gel with 35–40% ethyl acetate in pentane, followed by recrystallization from ethanol–dichloromethane–pentane, gave pure **1-OTs**, m.p. 66–67 °C; ^{1}H NMR, δ 7.20–8.09 (m, 8 H), 5.92 (dd, J = 6.7, 6.5 Hz, 1 H), 3.26 (dd, J = 17.5, 6.5 Hz, 1 H), 2.93 (dd, J = 17.5, 6.7 Hz, 1 H), 2.40 (s, 3 H), 2.10 (s, 3 H).

[1,1,1,3,3-$^2H_5$]-4-[(4′-Methylbenzenesulfonyl)oxy]-4-(4″-nitrophenyl)butan-2-one (**d-1-OTs**) was synthesized using the method described above. The deuterium contents were measured by ^{1}H NMR spectroscopy to be >98 at% ^{2}H in the 1- and 3-positions.

Kinetics and product studies. For reaction at 70 °C, the reaction solutions were prepared by mixing acetonitrile with water at room temperature (*ca* 22 °C). A few microliters of substrate dissolved in acetonitrile were added. Aliquots of this reaction mixture (0.5 cm^3) were transferred to several 2 cm^3 HPLC flasks, which were sealed with gas-tight PTFE septa and placed in an aluminum block in the thermostated water-bath. The concentration of the substrate in the reaction solution was 0.01–0.1 mmol dm^{-3}. At appropriate intervals, samples were removed and analysed using the HPLC apparatus. For reaction at 25 °C, a 2 cm^3 HPLC flask, sealed with a gas-tight PTFE septum, was placed in the aluminum block of the HPLC apparatus thermostated by the water-bath. The reactions were initiated by fast addition, by means of a syringe, of a few microliters of the substrate dissolved in acetonitrile. The rate constants for the disappearance of the substrates were calculated from plots of substrate peak area versus time by means of a non-linear regression computer program. Very good pseudo-first-order behavior was seen for all the reactions studied. The separate rate constants for the elimination and substitution reactions were calculated by combination of product composition data, obtained from the peak areas and the relative response factors determined in separate experiments, with the observed rate constants.

The relative response factors of **1-OH** and alkene were determined by analyzing a mixture of the two components, prepared by weighing, using HPLC. The relative response factor for **1-Cl** to alkene was determined in the following way: **1-Cl** (about 10% alkene) in ethanol (in the presence of 1 mmol dm^{-3} perchloric acid) was analyzed at least five times. A volume of 0.5 cm^3 of this solution was transferred in to a 2 cm^3 measuring flask and 0.5 mol dm^{-3} HMTA solution (0.5 cm^3 in methanol) was then added. After the reaction was finished, the reaction mixture was re-analyzed. The results were used to calculate the relative response factors for **1-Cl** and the corresponding alkene product. The estimated errors are considered as maximum errors derived from maximum systematic errors and random errors.

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