Solvents as phase transfer catalysts. Reaction of trimethylsulfonium iodide and solid potassium hydroxide in acetonitrile leading to an epoxide of benzophenone

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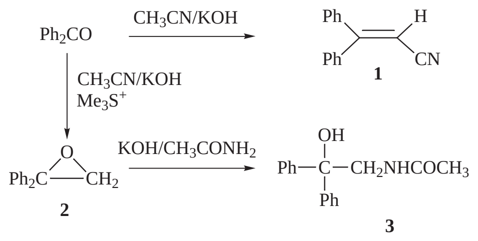
The kinetics of reactions of benzophenone with trimethylsulfonium iodide in acetonitrile in the presence of excess solid potassium hydroxide (KOH) are reported, and the kinetics of formation of products, 2,2-diphenyloxirane, 2,2-diphenylacrylonitrile, and *N*-(2-hydroxy-2,2-diphenyl)acetamide are also monitored. The effects of water, other cosolvents and quaternary ammonium salts are investigated. Initial rates are lower than rates of comparable reactions involving nitrile formation in the absence of sulfonium salts, and the epoxide reaches a concentration maximum before any nitrile forms. The results can be explained by initial formation of the anion $[CH_2CN]^-$, which reacts with the sulfonium salt to give $Me_2S^+CH_2^-$ (ylide, leading to epoxide) before direct reaction of $[CH_2CN]^-$ with benzophenone (leading to nitrile) can occur. Consequently, acetonitrile is acting as a phase transfer catalyst, aiding the transport of base (in a modified form) from the surface of the KOH to form the ylide.

Phase transfer catalysis (PTC), involving quaternary salts (Q^+X^-), has a well-established and important role in many reactions involving strong bases.[1a,2] Cocatalysis by simple primary, secondary and tertiary alcohols often aids PTC involving hydroxide ions, because base can be transported to the organic phase as Q^+/alkoxide.[3] Polyethylene glycols (PEGs) can act similarly as cocatalysts,[4–7] and in some cases PEGs can also act as catalysts in the absence of Q^+X^-.[8] Hence non-ionic molecules such as PEGs, like crown ethers,[1b,9] can act as catalysts rather than just cocatalysts in PTC. We now report evidence that the non-protic solvent, acetonitrile, acts as a phase transfer catalyst in the reaction of trimethylsulfonium iodide (Me_3SI) with solid potassium hydroxide (KOH).[10]

Recently, we reported the kinetics of condensations of benzophenone with acetonitrile initiated by solid KOH, to give diphenylacrylonitrile (**1**).[11] In the presence of Me_3SI, the epoxide (**2**) is formed preferentially *via* a sulfur ylide,[12] and in the later stages of the reaction acetamide (formed by hydrolysis of acetonitrile) may react with the epoxide to give *N*-(2-hydroxy-2,2-diphenyl)acetamide (**3**). Although these reactions are occurring in a complex, heterogeneous reaction mixture, the timing of the onset of formation of the side products (**1** and **3**), and the rate of formation of the nitrile side product, **1**, provide important insights into the reaction mechanism.



Results

A set of standard reaction conditions for kinetic studies, analogous to those used in our investigation of the formation of nitrile (**1**) from benzophenone,[11] was defined. As before,[11] benzophenone (typically 0.5 M in acetonitrile) was reacted in the presence of KOH pellets (two equivs.), water was added to activate the KOH,[12] and reactions were heated at 82–83 °C (usually under reflux) with magnetic stirring at 400 rpm; in addition Me_3SI (1.1 equivs.–only partially soluble) and naphthalene (internal standard) were present in the studies of epoxide formation. A sufficiently large volume of acetonitrile (usually 40 ml at reflux temperatures) was present, so that the withdrawal of small aliquots (*ca.* 20 × 50 µl) of homogeneous solution during sampling did not significantly affect the composition of the heterogeneous reaction mixture. Although reliable analytical data for the epoxide (**2**) could be obtained using liquid chromatography (LC),[13] the availability of equipment was such that almost all of the results were obtained by monitoring the progress of the reactions by gas chromatography (GC). It was established that the GC method gave the expected (based on HPLC[11]) zero order rate constant for nitrile formation in the absence of sulfonium salt.[13]

Although the effects of varying the reaction conditions are emphasised below, experiments under standard conditions were repeated periodically throughout the progress of this work. Under the closely-defined reaction conditions we employed, kinetic results for epoxide formation (determined from changes in the benzophenone concentration) were reproducible within ±10%, but formation of the epoxide is kinetically complex, and 'minor' changes in reaction conditions (*e.g.* rate of magnetic stirring, type of KOH pellets, crushing the KOH) had small but significant effects, in contrast to kinetic results for the nitrile (**1**).[11]

A typical reaction profile under standard epoxidation conditions (Fig. 1) shows a slow initial reaction for about 10 000 s (2.8 h), followed by a faster reaction, producing a maximum yield of *ca.* 40% of epoxide (**2**) after *ca.* 15 000 s; later the epoxide decomposes to the amide (**3**), and the nitrile (**1**) forms. The appearance and disappearance of the four compounds of interest was monitored in all of our kinetic runs, and reliable mass balances of 100 ± 5% were usually obtained.

Additional detailed Figures will be presented selectively to amplify the discussion. To provide comparisons with other results and to simplify the tabulation of data, the complex shape of the decay curve for benzophenone was approximated

Table 1 Effect of amount of benzophenone on the maximum yield of epoxide and on rates ($k/10^{-5}$ M s^{-1}) for epoxide and nitrile formation[a]

Benzophenone/mol	Epoxide Initial k^b	Epoxide Faster k^c	Nitrile k^d	Maximum yield (%)^e
0.01	0.32	2.1	0.6	>82
0.02^f	0.71	4.2	1.6	41
0.04	0.95	4.8	1.5	16
0.1^g	2.2	0.0^{h,i}	9.1	7

[a] Standard conditions were benzophenone (as tabulated), Me_3SI (0.022 mol), HPLC grade acetonitrile (40 ml) containing 0.03 ml of water, added water (0.1 ml) and pelleted KOH (0.04 mol) containing 0.29 ml of water, heated at 82.5 ± 0.5 °C (usually under reflux) and stirred at 400 rpm; rates with typical errors of 10% were determined from plots of concentration *vs.* time, which were approximately linear over at least 7% of the relevant part of the reaction. [b] From the decrease in benzophenone concentration at the start of the reaction. [c] From the decrease in benzophenone concentration prior to the formation of the maximum yield of epoxide. [d] From the change in concentration of nitrile, which begins to form close to the time when the epoxide yield is at a maximum. [e] Maximum yield of epoxide, based on benzophenone. [f] Average of three experiments carried out throughout the time period of the whole investigation; details of one of the kinetic runs are given in Fig. 1. [g] This result is less directly comparable with the others because the large amount of benzophenone (18.5 g) will affect the reaction medium much more than for the other experiments at lower concentrations, and the reaction temperature was 84 ± 1 °C. [h] Nitrile forms in the faster stage. [i] See Fig. 2.

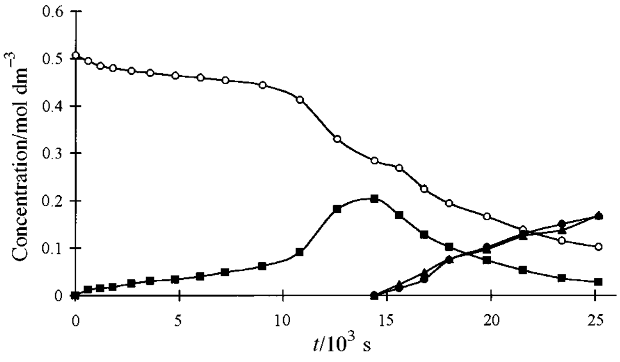


Fig. 1 Reaction profile for epoxide formation from benzophenone [benzophenone (○), nitrile **1** (▲), epoxide **2** (■), amide **3** (●)] under standard conditions—benzophenone (0.02 mol), solid KOH (0.04 mol) and trimethylsulfonium iodide (Me_3SI, 0.022 mol) in acetonitrile (40 ml) containing added water (0.1 ml) at 82.5 ± 0.5 °C

by two straight lines; the first part corresponds to the initial rate under the relatively well-defined reaction conditions at the start of the reaction, and the second part gives the faster rate of epoxide formation just prior to the onset of nitrile formation. The initial rates of nitrile formation and the maximum yields of epoxide (based on benzophenone) are also tabulated; usually, but not always, the epoxide was unstable after a few hours under the reaction conditions, and substantial decomposition to the amide (**3**) could be seen during the later hours of the reaction (as in Fig. 1).

Varying the standard reaction conditions, the effects of changes in concentrations of benzophenone are shown in Table 1 and of Me_3SI are shown in Table 2. Additional details are shown for high benzophenone concentrations (Fig. 2) and low Me_3SI concentrations (Fig. 3). The effects of varying the amounts of added water are shown in Table 3, and the effects of addition of quaternary ammonium salts as cocatalysts are shown in Table 4.

The effect of replacing the added water by alternative protic solvents such as *tert*-butyl alcohol or polyethylene glycol (PEG) 200 is shown in Table 5—for these experiments, a different grade of KOH pellets was used; although the faster rate of epoxide formation and the rate of nitrile formation agreed satisfactorily with those reported in Tables 1–4 under the standard reaction conditions, the initial rates of epoxide formation (in four experiments under standard conditions) were about double those expected. Initial rates refer to the first 10–20% reaction, when the reactivity of the KOH surface is changing;[11] consequently, the initial rates in Table 5 are not directly comparable with those in Tables 1–4. In contrast, rates for nitrile formation in the absence of sulfonium salt were not dependent on the type of KOH pellets.

Table 2 Effect of amount of trimethylsulfonium iodide (Me_3SI) on the maximum yield of epoxide and on rates ($k/10^{-5}$ M s^{-1}) for epoxide and nitrile formation[a]

Me_3SI/equivs.	Epoxide Initial k^b	Epoxide Faster k^c	Nitrile k^d	Maximum yield (%)^e
0.5	0.61	0.0^{g,h}	4.0	15
1.1^f	0.71	4.2	1.6	41
1.5	0.54	5.3	0.1	54^i
2.0	0.44	2.8	0.03	45^i

[a–f] As for Table 1, except that the standard amount (0.02 mol) of benzophenone was added, and the amount of Me_3SI was varied. [g] Nitrile forms in the faster stage. [h] See Fig. 3. [i] The epoxide was stable under the reaction conditions up to 25 000 s (7 h), and only traces of amide **3** were detected.

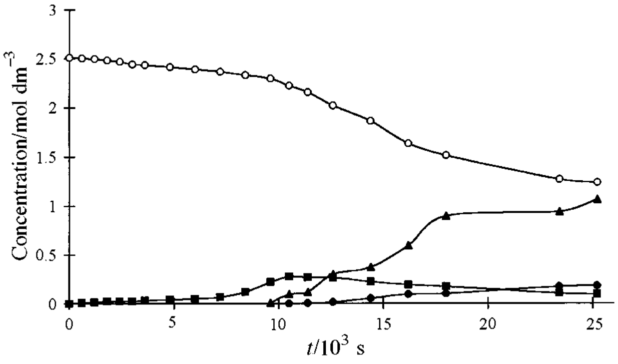


Fig. 2 As for Fig. 1, except that five-fold more benzophenone (0.1 mol) was added and the reaction temperature was 84 ± 1 °C

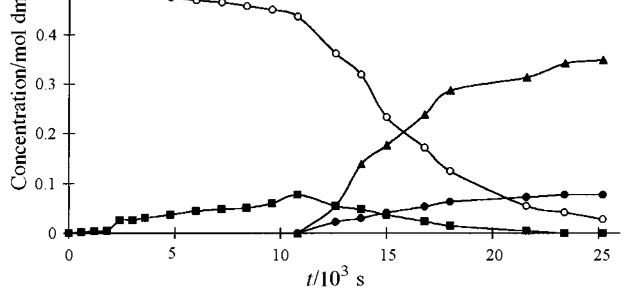


Fig. 3 As for Fig. 1, except that Me_3SI (0.01 mol) was added (half the required amount)

Discussion

Initial rates

Detailed inspection of Figs. 1–3, and the similar plots (not shown) from all of the other kinetic runs,[13] shows that the reaction profiles are complex; even allowing for random errors in sampling and analysing the compositions of the reaction mixtures, the plots are clearly not linear and can only be approximated by the two straight lines used to estimate the initial and faster rates of formation of epoxide shown in Tables 1–5. Hence, the rates shown are approximate, but useful compar-

Table 3 Effect of varying amounts of water on the maximum yield of epoxide and on rates ($k/10^{-5}$ M s^{-1}) for epoxide and nitrile formation[a]

	Epoxide		Nitrile	
Water/ml	Initial k^b	Faster k^c	k^d	Maximum yield (%)[e]
0.0	0.8	2.3	3.0	51
0.1[f]	0.71	4.2	1.6	41
0.2	0.76[g]	4.3	0.67	40
0.3	0.64[g]	5.1	0.15	40[h]
0.5	0.48[g]	2.7	0.0	17[i]

[a–f] As for Table 1, except that the amount of added water was varied, and benzophenone (0.02 mol) was used. [g] Based on only 2–5% reaction. [h] The epoxide was stable under the reaction conditions up to 25 000 s (7 h), and only 1% of amide **3** was detected. [i] No epoxide decomposition product **3** was detected even after 7 h.

Table 4 Effect of quaternary ammonium salts (10 mol%) on the maximum yield of epoxide and on rates ($k/10^{-5}$ M s^{-1}) for epoxide and nitrile formation[a]

	Epoxide		Nitrile	
Catalyst	Initial k^b	Faster k^c	k^d	Maximum yield (%)[e]
None[f]	0.71	4.2	1.6	41[g]
Me_4NBr	1.0	3.8	1.5	52[g]
$(Bu^n)_4NBr$	0.52	3.7	2.4	41[g]
$(Bu^n)_4NF$	1.2	5.3	1.1	48[g]
$(Bu^n)_4NHSO_4$	3.3	9.0	0.6	53[g]

[a–f] As for Table 1, using benzophenone (0.02 mol). [g] The epoxide was unstable under the reaction conditions decomposing to give 20–50% of amide **3** after 7 h.

Table 5 Effect of small amounts of cosolvents on the maximum yield of epoxide and on rates ($k/10^{-5}$ M s^{-1}) for epoxide and nitrile formation[a]

	Epoxide		Nitrile	
Cosolvent	Initial k^b	Faster k^c	k^d	Maximum yield (%)[e]
Water[f]	1.6[g]	4.5	1.5	43[h]
Bu^tOH	0.9[g]	2.8	1.3	46[h]
PEG 200	5.3[g]	(5.3)	1.5	31[h]

[a–e] As for Table 1, using benzophenone (0.02 mol), except that the added water (0.1 ml) was replaced by an equimolar amount (0.0055 mol) of cosolvent, and the KOH pellets contained 15% water (0.34 ml), as in our previous work (ref. 11). [f] Average of four experiments carried out towards the end of the investigation. [g] Rate constants (compared with the corresponding reaction in the absence of sulfonium salt leading to nitrile **1** see ref. 11) are as follows: $k/10^5$ M s^{-1}; water, 1.6 (3.1); Bu^tOH, 0.9 (1.9); PEG 200, 5.3 (*ca.* 10). [h] The epoxide was unstable under the reaction conditions, decomposing to give 20–40% of amide **3** after 7 h

isons can be made between the initial rates of epoxide formation (Tables 1–4) and the rates of nitrile formation reported previously.[11]

Although the rates (Tables 1–5) are quoted as if the reactions were of zero kinetic order, the observed rates were found to be approximately proportional to the initial concentration of benzophenone (Table 1). Hence, the kinetic order in benzophenone is approximately 1, as observed for nitrile formation.[11] Also, the decrease in benzophenone concentration during the faster stage of epoxide formation and the later stages of the reactions, when taken together, fits approximate first order kinetics.[13] The complexity of the kinetics is due in part to changes in the reactivity of the KOH, caused by absorbtion of water produced during the reaction.[11]

The small dependence of initial rates for a four-fold variation in the amount of sulfonium salt is explained by its low solubility in acetonitrile. The rates (Table 2) refer to reactions in which not all of the Me_3SI dissolves initially, and at the start of the reaction there is probably a saturated solution of Me_3SI in acetonitrile in all four cases.

The effect of added water on initial rates is also small (Table 3), and the decreasing trend is the opposite of that reported[11] for nitrile formation in the absence of sulfonium salt. The faster rates of epoxide formation (Table 3) reach a maximum at *ca.* 0.3 ml of added water, as observed previously for the nitrile reaction.[11] As more water is added, the yield of epoxide decreases, and when 0.5 ml of water is added, only 17% epoxide is formed and there is no decomposition to the amide (**3**) and no nitrile is formed. It appears that the added water accelerates decomposition of the Me_3SI and so formation of the epoxide ceases prematurely. An independent experiment showed that even under standard conditions (0.1 ml water), 5% of the Me_3SI was destroyed in only 3 h at 60 °C, supporting published data on the base hydrolysis of sulfonium salts.[14]

Quaternary ammonium salts (Q^+X^-), acting as phase transfer catalyts, should help to increase the transport of base away from the KOH surface, and so increase the rates (Table 4).[11] However, lipophilic counteranions are known to interfere with phase transfer catalysis of less lipophilic anions (*e.g.* HO^-, $[CH_2CN]^-$) and the expected order of efficiencies of the catalysts is $F^- > Cl^- > Br^- > I^-$.[15–17] Iodide is present in the reaction (initially as Me_3SI), and it may suppress catalysis by tetrabutylammonium bromide (TBAB); however tetramethylammonium bromide is not retarded (Table 4). The less lipophilic fluoride and hydrogen sulfate catalysts are effective (Table 4), although the rate enhancements are less than those observed previously for nitrile formation.[11] Hence, suppression of rates by iodide is not a major effect; it also seems likely that the cation in Me_3SI, the trimethylsulfonium ion, is an adequate alternative to a quaternary ammonium salt,[17–19] and so the addition of extra catalysts (Q^+X^-) usually exerts a smaller additional effect on rates.

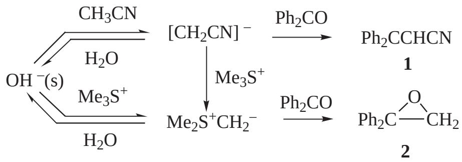
The rate of the standard reaction was slightly suppressed if the added water was replaced by *tert*-butyl alcohol but PEG 200 accelerated the reaction (Table 5); for comparison *tert*-butyl alcohol had no effect on the rate of nitrile formation, but PEG 200 was an effective cosolvent/cocatalyst.[11]

Mechanistic implications

For the results discussed above, trends in initial rates of epoxide formation were not unexpected in comparison with previous studies of nitrile formation in the absence of Me_3SI.[11] The presence of Me_3SI could accelerate epoxide formation because Me_3SI could act as a PT catalyst and hydrolysis of Me_3SI would give methanol, which may also be catalytic.[11] In agreement with the expected rate enhancements when Me_3SI is present, only epoxide forms in the initial and faster stages of these reactions (Tables 1–5, Figs. 1–3)—the nitrile (**1**) is undetectable.

Surprisingly however, the initial rate of epoxide formation is two-fold slower than the rate of nitrile formation (under the same conditions, but in the absence of Me_3SI[11]—see Table 5, footnote *g*). Potassium iodide is formed as a by-product of epoxide formation, but parallel studies of furfural have shown that added KI does not affect the rate of epoxide formation.[10] If formation of epoxide and nitrile were parallel independent reactions, and the presence of Me_3SI (acting as a PT catalyst) accelerated formation of the nitrile (or even if Me_3SI had no kinetic effect), then the rate of nitrile formation in the presence of Me_3SI should be much greater than the rate of epoxide formation (*i.e.* the nitrile should form preferentially). To explain the exclusive formation of epoxide in the early stages of the reactions, we propose that there is a crossover between the two reactions (Scheme 1); instead of proceeding to nitrile (**1**), the acetonitrile anion $[CH_2CN]^-$ reacts with the trimethylsulfonium ion to give the sulfur ylide.

The above evidence about relative rates of formation of epoxide and nitrile can be supported by the following more direct comparisons. When, after an hour or more, reactions reach the stage corresponding to the faster rates of epoxidations (Tables 1–5), the exact reaction conditions are less well



Scheme 1 Possible routes to the S-ylide (the reverse reactions with water form either CH_3CN or Me_3S^+)

defined than at the start of the reaction. In addition to the reactions of benzophenone, some of the sulfonium salt will have been hydrolysed to methanol and dimethyl sulfide,[14] and some of the acetonitrile will have been hydrolysed to acetamide;[11] also the condition and reactivity of the KOH will have been altered by the water generated during the reaction.[11] However, the rates tabulated for the faster epoxidation stage are obtained from data immediately before the nitrile begins to form *in the same reaction mixture*.

Consequently, the reaction conditions during the faster stage of epoxide formation and the stage for nitrile formation are expected to be similar, and meaningful comparisons can be made between these two rates. Results (Tables 1–5) show that the rates of nitrile formation are typically about half of the faster rates for epoxide formation, probably because of the approximately first order dependence of the rate on the concentration of benzophenone in the later part of the reaction (as in Figs. 1–3). However, when the benzophenone is in excess, either because more has been added (Fig. 2, entry row 4 in Table 1) or because less Me_3SI has been added (Fig. 3, first entry in Table 2), the rates of nitrile formation are four- to seven-fold higher than the corresponding rates of formation of epoxide, yet formation of nitrile is delayed for about 2 h (presumably until almost all the Me_3SI has reacted).

An alternative explanation of the unexpectedly low rates of nitrile formation in the presence of Me_3SI is that formation of nitrile is inhibited because the ylide forms on the surface of the KOH;[12] this proposal is supported by spectroscopic evidence in the case of highly-stablised S-ylides (*e.g.* by a CO_2Et group[12]), but it is not clear whether the presence of an ylide could prevent formation of $[CH_2CN]^-$. Also $Me_2S^+CH_2^-$ is highly reactive,[20] and could form and react very differently from a stabilised ylide. Furthermore, rates of formation of both epoxide and nitrile respond almost identically to changes in the solid base,[10] suggesting a link between the two reactions (formation of $[CH_2CN]^-$). As discussed above for examples when KOH is the base, the two reactions respond similarly to changes in reaction conditions, and it would not be expected that Q^+ salts (*e.g.* $NBu_4^+HSO_4^-$, Table 4) would catalyse a reaction involving formation of a neutral ylide on the surface of a solid. Also, a surface reaction does not readily explain the small dependence of the reaction rate on the surface area of the KOH or the approximately linear dependence of the reaction rate on the concentration of benzophenone (Table 1).

Reversibility of ylide formation (as in Scheme 1) has been proposed previously for aqueous media,[21] and for ylides formed from KOH in DMSO;[22] protonation of $Me_2S^+CH_2^-$ would reduce its concentration, and so reduce the occurrence of dimerisation to ethylene observed in DMSO.[20] Attack by iodide on Me_3SI^+ could produce MeI in equilibrium,[23] but no products of methylation were observed.

Applications to syntheses

Liquid–liquid PTC is well established for the base-induced reactions of sulfonium salts with aldehydes to give epoxides;[21,24,25] reactions are particularly favourable for aldehydes such as *p*-nitrobenzaldehyde, which reacts relatively rapidly to give a stable epoxide.[12,26] As would be expected, lipophilic sulfonium salts such as lauryldimethylsulfonium are more effective catalysts than trimethylsulfonium,[27] and reactions are also favoured by the presence of less lipophilic ('hard') counter-anions.[25,28] The selection of an effective catalyst is more important for ketones, which react more slowly than aldehydes.[11,28]

Additional catalytic cycles involving sulfides are being developed as routes to chiral epoxides.[29,30] One of these involves solid–liquid PTC using solid KOH in acetonitrile at room temperature, with benzyl bromide and camphoryl sulfide leading to addition of 'PhCH' to benzaldehyde or *p*-chlorobenzaldehyde; no additional PTC was required and acetonitrile was found to be a much more effective 'solvent' than THF,[30] consistent with our proposal that acetonitrile also acts as a catalyst.

For epoxidation of benzophenone, the mechanistically-informative side reactions leading to **1** and **3**, when acetonitrile is used as solvent, are a major drawback in synthetic applications. Also, reactions are usually slower under heterogeneous conditions, and the relatively high temperatures required for acceptable rates led to decomposition of sulfonium salt[14] and possibly of the ylide. A convenient synthesis of epoxide **2** in good yield was carried out using *tert*-butyl alcohol as solvent to improve the phase transfer from solid KOH to Me_3SI; we did not observe any major side products, so there does not appear to be a strong tendency for hydroxide or butoxide ion to attack the epoxide.

Conventional reaction conditions, *via* sulfur ylides for the synthesis of **2**, utilise sodium hydride in dry DMSO.[20] Other workers have used hydroxide bases (including solid KOH[12,22]) to obtain S-ylides under reaction conditions which are not anhydrous, and may even include water as solvent.[21,24] The sulfoxonium ylide (Me_2SOCH_2) is more stable than $Me_2S^+CH_2^-$. In preparative experiments monitored by NMR spectroscopy, we observed the formation of **2** in very good yields after only 1.5 h using the more reactive trimethylsulfoxonium iodide at 60 °C in dry NaH–DMSO (as reported[20]); yields were lower (70%) using NaOH–DMSO or NaOH–acetonitrile at 50 °C for 90 min, rising to over 80% after 18 h. Reactions in NaOH–DMSO gave similar yields when 0.3 or 2.8% water was added to the reaction mixture.[31] Epoxide **2** has also been synthesised *via* a sulfonium ylide on an insoluble resin—the ylide was generated from the sulfonium fluorosulfate using *tert*-butoxide in DMSO.[32]

Conclusions

For the heterogeneous reaction conditions used in our kinetic studies, we propose that the initial formation of epoxide (**2**) from benzophenone proceeds without competition from the formation of the nitrile **1** because the available base/nucleophile reacts preferentially with Me_3SI (Scheme 1). When the Me_3SI has almost all reacted (*e.g.* by epoxide formation or by hydrolysis), the concentrations of the two anions, $[CH_2CN]^-$ (leading to nitrile **1**) and $[CH_3CONH]^-$ (leading to amide **3**), increase (Figs. 1–3). In the absence of Me_3SI, the rate of nitrile formation is faster than that for epoxide, so the major route to the sulfur ylide (leading to epoxide **2**) is *via* $[CH_2CN]^-$. The Me_3S^+ ion probably also acts as a PT catalyst to enhance the transport of $[CH_2CN]^-$ away from the surface of the KOH, but the rate of epoxide formation is lower because formation of the ylide, $Me_2S^+CH_2^-$, is reversible (Scheme 1). According to this mechanism (Scheme 1), acetonitrile is deprotonated by the solid KOH to give $[CH_2CN]^-$, which reacts in solution with Me_3S^+ to give the sulfur ylide $Me_2S^+CH_2^-$, regenerating acetonitrile. Hence, the acetonitrile solvent is acting as a phase transfer catalyst, and DMSO may behave similarly.[10,11]

Experimental

Materials

Benzophenone, the nitrile (**1**), pelleted KOH for data in Table 5, solvents and catalysts were available from earlier work,[11] except that the HPLC grade acetonitrile was from Rathburn and the pelleted KOH (Fluka) for data in Tables 1–4 contained 13 wt% water; trimethylsulfonium iodide (Me_3SI) was obtained from Aldrich and the internal standard was naphthalene (scintillation grade, Aldrich).

2,2-Diphenyloxirane (**2**) was obtained by reacting Me_3SI (5.7 g, 0.028 mol) and benzophenone (4.6 g, 0.025 mol) in *tert*-butyl alcohol (25 ml) at 40 °C with KOH (4.2 g, 0.075 mol) in a magnetically-stirred three-necked flask, fitted with a condenser and an exit tube to a gas scrubber (a Dreschel bottle containing bleach to oxidise Me_2S). After 11 h, when 80% reaction had occurred, the reaction mixture was cooled, and the *tert*-butyl alcohol was removed by rotary evaporation at 25 °C; the residue was treated with a solution of water (90 ml) and sodium hypochlorite or bleach (12 ml), and the product **2** was isolated by diethyl ether extraction to give an off-white solid, which was recrystallised from ethanol; mp 55–56 °C, lit.[33] 55.5–56 °C.

N-(2-Hydroxy-2,2-diphenylethyl)amide **3** was isolated from a reaction of the epoxide **2** (3.92 g, 0.02 mol) and KOH (2.244 g, 0.02 mol) in refluxing acetonitrile (40 ml) containing water (0.1 ml) for 7 h. A crude product (1.0 g), isolated by extraction with dichloromethane (DCM), was purified by column chromatography on silica eluted with 1 : 1 DCM : petroleum spirit (30–40 °C) to give **3** (0.29 g); mp 140.6–142 °C, lit.[34] 143 °C. Another sample of **3** was prepared by repeating the above preparation adding acetamide (1.1 equivs.);[35] **3** could then be isolated in 80% yield without chromatography as white crystals, mp 142.5–143.5 °C; $\delta_H(CDCl_3)$ 1.78 (3H, s), 4.01 (2H, s), 4.34 (1H, s, exchanged in D_2O–TFA), 6.17 (1H, br s, exchanged in D_2O–TFA), 7.20–7.41 (10H, m); δ_C 23.1, 49.5, 78.4, 126.1, 127.3, 128.4, 144.7 and 171.7.

Analytical methods

HPLC analyses were carried out as described earlier.[11] GC analyses were made on HP5880 or 5890 (series II) chromatographs, with FID detection at 275 °C; the column was a WCOT fused silica 25 m × 0.25 mm capillary column, coated with CP-SIL 19CB (Chrompack), further treated with pyridine to remove acidic sites, and it was eluted with helium carrier gas. Small (1–2 μl) volumes of samples were injected *via* a split injection system into the injection port at 250 °C. The oven program began at 100 °C for 1 min, followed by a 20 °C min^{-1} ramp to 180 °C, then held for 5 min before a second 20 °C min^{-1} ramp to 250 °C, and finally held for 5 min; retention times (in min) were: DCM (1.00), the internal standard naphthalene (2.41), benzophenone (5.62), epoxide (**2**, 5.98), nitrile (**1**, 9.08) and amide (**3**, 13.96). Response calibrations were made by analysing *ca.* 10^{-3} M mixtures of the internal standard and one of the compounds of interest; the average of five injections was used to obtain response factors and agreement was within ±5%.

Kinetic methods

Standard reaction conditions. To a 100 ml three-necked flask, fitted with a Liebig condenser and an exit tube to a gas scrubber as above, was added benzophenone (3.69 g, 0.020 mol), acetonitrile (40 ml), water (usually 0.1 ml), and naphthalene (1.00 g, 0.008 mol). The mixture was warmed and stirred magnetically (usually at a speed of 400 rpm) until homogeneous; Me_3SI (4.57 g, 0.022 mol) was then added, and the heterogeneous mixture was heated to reflux, using an oil bath thermostatted to 84 ± 1 °C (temperatures inside the flask were typically 82.5 ± 0.5 °C). The first sample of the reaction mixture was removed (see below) before KOH pellets (2.24 g, 0.04 mol) were added, and the reaction was then sampled at regular intervals whilst heating and stirring continued. Sampling, usually over a period of 7 h, involved using a 1 ml syringe with a 3″ needle to transfer 2 or 3 drops of reaction mixture into a sample bottle; the reaction mixture was washed with water (2 ml), extracted with DCM (3 ml), dried over $MgSO_4$ and filtered through cotton wool. Samples were analysed at least in duplicate consecutively by GC within a few hours. After 4 h, the reaction solution became yellow, corresponding to the onset of nitrile formation (Fig. 1).

For other kinetic runs, one of the reaction variables was altered to the reaction conditions described in Tables 1–5, and the rate of formation of **2** in the absence of Me_3SI was monitored similarly by GC.

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References

1 C. M. Starks, C. L. Liotta and M. Halpern, *Phase Transfer Catalysis, Fundamentals, Applications and Industrial Perspectives*, Chapman and Hall, New York, 1994 (*a*) ch. 8; (*b*) pp. 153–159.
2 M. Rabinovitz, Y. Cohen and M. Halpern, *Angew. Chem., Int. Edn. Engl.*, 1986, **25**, 960.
3 J. de la Zerda and Y. Sasson, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1147.
4 E. V. Dehmlow and J. Schmidt, *Tetrahedron Lett.*, 1976, 95.
5 J. M. Harris, N. H. Hundley, T. G. Shannon and E. C. Struck, *J. Org. Chem.*, 1982, **47**, 4789.
6 R. Neumann and Y. Sasson, *J. Org. Chem.*, 1984, **49**, 1282.
7 Y. Kimura and S. L. Regen, *J. Org. Chem.*, 1982, **47**, 2493.
8 E. V. Dehmlow, R. Thieser, Y. Sasson and E. Pross, *Tetrahedron*, 1985, **41**, 2927.
9 E. V. Dehmlow and S. S. Dehmlow, *Phase Transfer Catalysis*, VCH, Weinheim, 3rd edn., 1993, p. 54.
10 Preliminary communication: T. W. Bentley, R. V. H. Jones, A. H. Larder and S. J. Lock, *J. Chem. Soc., Chem. Commun.*, 1994, 2309.
11 T. W. Bentley, R. V. H. Jones, A. H. Larder and S. J. Lock, *J. Chem. Soc., Perkin Trans. 2*, 1998, 89.
12 E. Borredon, F. Clavellinas, M. Delmas, A. Gaset and J. V. Sinisterra, *J. Org. Chem.*, 1990, **55**, 501.
13 A. H. Larder, Ph.D. Thesis, University of Wales, 1997.
14 C. G. Swain and E. R. Thornton, *J. Org. Chem.*, 1961, **28**, 4808.
15 Y. Sasson and N. Bilman, *J. Chem. Soc., Perkin Trans.* 2, 1989, 2029.
16 E. V. Dehmlow, *Tetrahedron Lett.*, 1976, **2**, 91.
17 S. Kondo, Y. Takeda and K. Tsuda, *Synthesis*, 1989, 862.
18 J. B. Campbell, US patent, 3639492 (1972); *Chem. Abs.*, 1972, **77**, 21 156.
19 S. Kondo, Y. Takeda and K. Tsuda, *Synthesis*, 1988, 403.
20 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.
21 M. Yoshimine and M. J. Hatch, *J. Am. Chem. Soc.*, 1967, **89**, 5831.
22 B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 1971, **93**, 3773.
23 B. A. McCortney, B. M. Jacobson, M. Vreeke and E. S. Lewis, *J. Am. Chem. Soc.*, 1990, **112**, 3554.
24 M. J. Hatch, *J. Org. Chem.*, 1969, **34**, 2133.
25 (*a*) P. Mosset and R. Gree, *Synth. Commun.*, 1985, **15**, 749; (*b*) J. Forrester, R. V. H. Jones, P. N. Preston and E. S. C. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1937.
26 K. Rafizadeh and K. Yates, *Org. Prep. Proced. Int.*, 1985, **17**, 140.
27 Y. Yano, T. Okonogi, M. Sunaga and W. Tagaki, *J. Chem. Soc., Chem. Commun.*, 1973, 527.
28 (*a*) A. Merz and G. Markl, *Angew. Chem., Int. Edn. Engl.*, 1973, **12**, 845; (*b*) M. Rosenberger, W. Jackson and G. Saucy, *Helv. Chim. Acta*, 1980, **63**, 1665.
29 V. K. Aggarwal, H. Abdel-Rahman, R. V. H. Jones, H. Y. Lee and B. D. Reid, *J. Am. Chem. Soc.*, 1994, **116**, 5973.
30 N. Furukawa, Y. Sugihara and H. Fujihara, *J. Org. Chem.*, 1989, **54**, 4222.
31 S. J. Lock, Ph.D. Thesis, University of Wales, 1993.
32 M. J. Farrall, T. Durst and J. M. J. Frechet, *Tetrahedron Lett.*, 1979, 203.
33 S. J. Cristol, J. R. Douglass and J. S. Meek, *J. Am. Chem. Soc.*, 1951, **73**, 816.
34 J. Meisenheimer and L.-H. Chou, *Justus Liebigs Ann. Chem.*, 1939, **539**, 70.
35 Carried out by M. Boras, Swansea, 1997.

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