Methoxide-induced Fragmentation of 2,2,3-Trihalogeno- and 2,2-Dihalogeno-3-methoxy-1,3-diphenylpropanones

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The reaction of 2,2,3-trihalogeno-1,3-diphenylpropanones with sodium methoxide in methanol occurs with exclusive formation of fragmentation products. Kinetic and stereochemical evidence is interpreted in terms of a concerted intramolecular process promoted by initial attack of methoxide anion at the carbonyl carbon. In the case of 2,2-dihalogeno-3-methoxy-1,3-diphenylpropanones the reaction gives fragmentation, rearrangement, and elimination products. The former products are believed to be formed through competing reactions involving an intermediate formed on addition of methoxide to the substrate. For the fragmentation pathway the results are consistent with a carbanionic-intermediate mechanism.

Ketones bearing a nucleofugal substituent in the β position can become fragmentable after the carbonyl group has been converted into an electrofugal group by addition of a base.[1] In an earlier report [2] we described some observations related to the alkoxide-induced reactions of some 2,2-dihalogeno-1,3-diphenylpropanones (**1**).

PhCHXCYZCOPh (**1**)

a X = Br; Y = Z = Br / Y = Br, Z = Cl
a X = Cl; X = Br, Z = Cl / Y = Z = Cl
b X = OMe; Y = Z = Br / Y = Br, Z = Cl / Y = Z = Cl

The reactions of 2,2,3-trihalogeno-1,3-diphenylpropanones (**1a**) with sodium methoxide in methanol at 30 °C were found to afford an equimolecular mixture of β,β-dihalogenostyrenes (**2**) and methyl benzoate (Scheme 1).

$$(\mathbf{1a}) + MeO^- \longrightarrow \underset{(\mathbf{2})}{PhCH{=}CYZ} + PhCO_2Me$$

Scheme 1.

In contrast with the behaviour of the trihalogeno ketones, attempted fragmentation of 2,2-dihalogeno-3-methoxy-1,3-diphenylpropanones (**1b**) under the same conditions showed no indication of reaction.[2] More recently, we have found that when (**1b**) was treated with a tenfold excess of sodium methoxide in methanol at 30 °C an equimolecular mixture of (1-methoxy-2,2-dihalogenoethyl)benzene (**3**) and methyl benzoate was produced along with some amounts of 1,1,3-trimethoxy-1,3-diphenylpropanone (**4**) and the corresponding 2-halogeno-1,3-diphenylpropenone (**5**) (Scheme 2).

$$(\mathbf{1b}) + MeO^- \longrightarrow \underset{(\mathbf{3})}{PhCH(OMe)CHYZ} + PhCO_2Me + \underset{(\mathbf{4})}{PhC(OMe)_2COCH(OMe)Ph} + \underset{(\mathbf{5})}{PhCH{=}CY(Z)COPh}$$

Scheme 2.

Heterolytic fragmentation reactions in water or alcoholic solvents for amines containing a nucleofugal group in the γ position (halogen or ester) are believed to occur by three types of mechanisms according to the order in which the fragments are released.[3]

(*i*) First is a two-stage process involving rate-determining expulsion of the nucleofuge followed by cleavage of the carbenium ion residue to give the corresponding alkene (i_1). The carbenium ion can also react further with the solvent to give substitution (S_N1) (i_2), separate a β electrofuge to give the conventional elimination product (i_3), or react by ring closure (i_4).

(*ii*) Then there is a reaction (ii) wherein the nucleofugal and electrofugal fragments depart simultaneously.

(*iii*) Finally, there is a stepwise reaction where the electrofugal group departs to leave a carbanion which then reacts to give the alkene (iii_1) or stabilises by protonation (iii_2).

We now report the results of a more detailed examination of the reactions of (**1a**) and (**1b**) undertaken in the hope of determining whether any of the above mechanistic models is valid for these fragmentations.

Results

The reaction of (**1a**) with methanolic sodium methoxide led exclusively to fragmentation with formation of β,β-dihalogenostyrene (**2**). Rate constants were measured by g.l.c. analysis by following the increase in styrene relative to an internal standard. Good second-order kinetics, first order in each reactant, were observed. Rate coefficients are shown in Table 1.

The g.l.c. analysis of the product of reaction of (**1b**) with a tenfold excess of sodium methoxide in methanol showed the presence of (1-methoxy-2,2-dihalogenoethyl)benzene (**3**). This reaction was accompanied by rearrangement leading to (**4**), and by dehalogenation forming 2-halogeno-1,3-diphenylpropenone (**5**).

The pseudo-first-order kinetics were followed by measuring the ratio [(**3**) + (**4**) + (**5**)]:starting material, by the quenching g.l.c. method. Thus, the second-order rate constants (k_{obs}) calculated as usual from those of first order are composites of fragmentation (k_F), rearrangement (k_R), and elimination (k_E) rate constants. Individual rate coefficients were estimated from

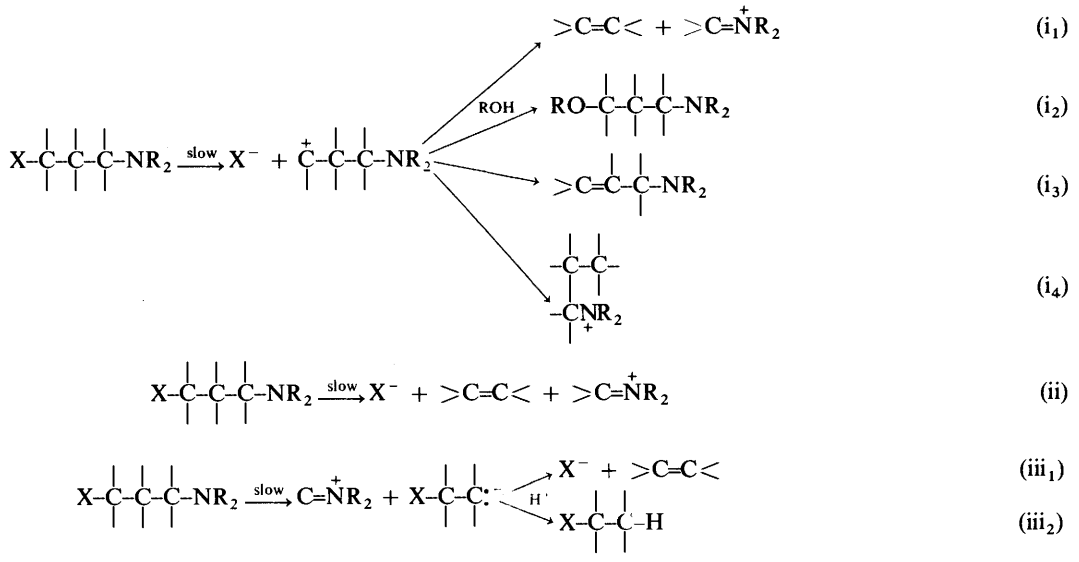


Table 1. Kinetics and isomeric product composition (PhCH=CYZ) for the reaction of PhCHXCYZCOPh with sodium methoxide in methanol at 30 °C.

X	Y	Z	Isomer	k^a	Z:E
Br	Br	Br[b]		2.70	
	Br	Cl[c]	R,S	3.53	96:04
			R,R	1.88	01:99
Cl	Br	Br[c]		1.28	
	Br	Cl[c]	R,S	1.86	97:03
			R,R	1.05	95:05
	Cl	Cl[c]		1.46	

[a] Units $dm^3\ mol^{-1}\ s^{-1}$. [b] [Subst.] 0.0010 mol dm^3; [MeO^-] 0.0016 mol dm^{-3}. [c] [Subst.] 0.0028 mol dm^{-3}, [MeO^-] 0.0032 mol dm^{-3}.

Table 2. Second-order rate coefficients (k_F, k_R, and k_E)[a] for reaction of PhCH(OMe)CYZCOPh [0.0392 mol dm^{-3}] with sodium methoxide [0.392 mol dm^{-3}] in methanol at 30 °C.

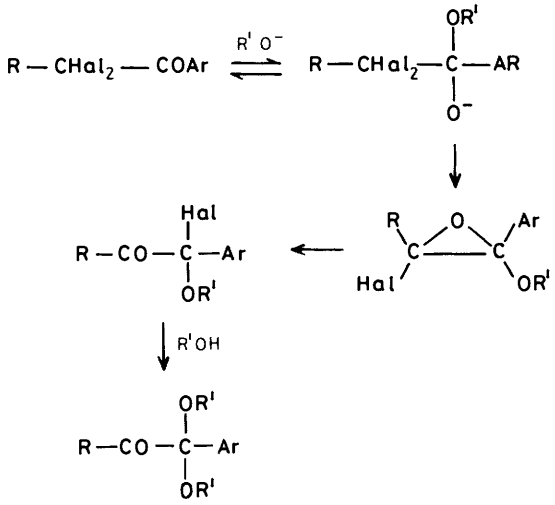
Y	Z	Isomer	10^3k_F	10^3k_R	10^3k_E
Cl	Cl		0.33	0.025 ± 0.025	0.02 ± 0.015
Br	Cl	*R,R*	1.12	0.89	0.16
		R,S	1.57	0.49	0.18
Br	Br		6.73	0.05 ± 0.04	2.85

[a] In $dm^3\ mol^{-1}\ s^{-1}$. F indicates fragmentation, R rearrangement, and E elimination.

a combination of k_{obs} with product ratios and are listed in Table 2.

Discussion

The carbenium-ion mechanism (i) may be dismissed at once for the fragmentation of the 2,2-dihalogeno-3-methoxy-substrates (**1b**) by structural considerations and on the basis that the nucleofugal group is present in the fragmentation product. These fragmentations are accompanied by rearrangement leading to 1,1,3-trimethoxy-1,3-diphenylacetone (**4**), and are also subject to competing dehalogenation. Similar rearranged products have been observed when α,α-dihalogenated alkyl aryl ketones reacted with alkoxides in the corresponding alcohol. The reaction was interpreted [4] in terms of the intermediacy of an



Scheme 3.

anion formed by nucleophilic addition of the base on the carbonyl. The α-halogeno-α′-alkoxy epoxide resulting from intramolecular halide displacement rearranges spontaneously to the corresponding 1-alkoxy-1-halogenoalkan-2-one, which is then converted into 1-aryl-1,1-dialkoxy-2-alkanone *via* either another epoxide formation or solvolysis (Scheme 3).

From Table 2 it is evident that the relative rates of the rearrangement process (k_R) are not determined by the influence of the 2-halogens on the affinity of the carbonyl to add methoxide. This fact can be rationalised on the grounds that the tetrahedral intermediate is formed in a fast step. Moreover, the relative magnitude of the halogen effect is inconsistent with a mechanism which involves epoxide rearrangement or solvolysis in the rate-determining step. The enhanced kinetic significance of the rearrangement of 2-bromo-2-chloro-3-methoxy-1,3-diphenylpropanone (**1b**; Y = Br, Z = Cl) is reconcilable if one considers that the rate of formation of the α-alkoxy-α′-halogeno-epoxide is a composite of contributions from the leaving group ability of the departing halogen and the efficiency of the other one to polarise positively the 2-carbon atom and so enhance the susceptibility of the latter to nucleophilic attack by the adjacent anion. It seems reasonable to assume that in the case of the 2,2-

dichloro and 2,2-dibromo compounds the increase of one of these effects is compensated by the decrease of the other. For the intermediate case (**1b**; Y = Br, Z = Cl) epoxide formation might be favoured by both influences. Thus, the above observations seem to indicate that the rearrangement pathway follows a mechanism in which the anionic intermediate undergoes rate-determining formation of epoxide which is rapidly converted into the trimethoxyacetone.

In line with the tetrahedral intermediate proposed for hydrolysis of chloral[5] it is tempting to suggest the involvement of a related species in the competitive fragmentation of the present systems. Therefore, formation of (**3**) can be envisaged as a process induced by rapid addition of methoxide anion on the carbonyl carbon. However, a mechanism involving methoxide attack during the cleavage step cannot be excluded. Though no intermediate could be shown experimentally, and while the available evidence does not allow unambiguous distinction between these two possibilities, we feel that this reaction may also proceed through the tetrahedral intermediate. Since this process competes favourably with the rearrangement reaction, a one-step cleavage will require that the rate of fragmention is greater than that of formation of the anionic intermediate which was assumed to occur in a fast step. However, the fact that the fragmentation of *R,R*-(**1b**; Y = Br, Z = Cl) only just exceeds the corresponding rate of rearrangement (Table 2) renders this possibility less likely.

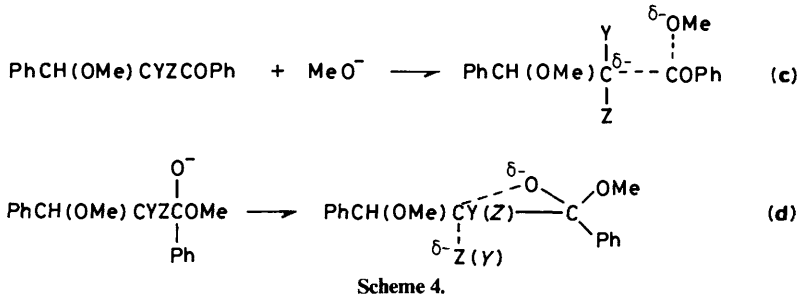
The hypothesis that competing pathways involving a common anionic addition intermediate are operative is strengthened by the fact that control experiments showed that the fragmentation–rearrangement product distribution was not significantly influenced by addition of increasing proportions of dimethyl sulphoxide to the reaction medium. If the assumption that methoxide-promoted cleavage leading to fragmention is a one-step process were correct, then methoxide anion would be a reactant in the rate-controlling stage. Stabilisation of anions through hydrogen-bonding solvation becomes stronger as the negative charge is more concentrated.[6] Thus, it is likely that the expected decrease in solvation on going from MeOH to MeOH–DMSO solvent, arising from the strong hydrogen-bond-accepting properties of DMSO, will be more important and the reactivity increased to a greater extent in the case of methoxide anion than in that of the tetrahedral intermediate involved in the rearrangement reaction. On the other hand, one would expect that dispersion of the negative charge in a one-step cleavage transition state (**c**) should be similar to that corresponding to rearrangement (**d**).

2-halogens from chlorine to bromine, in accord with the expectation that an increased ability of the 2-halogen to stabilise the incipient negative charge[7] will be required to achieve C(2)–CO bond breaking.[8] It was also observed that the fragmentation produces nearly the same mixture of *R,R*- and *R,S*-(2-bromo-2-chloro-1-methoxyethyl)benzenes (*ca.* 1:1.2) from either *R,R* or a mixture of *R,R*- and *R,S*-2-bromo-2-chloro-3-methoxy-1,3-diphenylpropanone. This result requires that the isomeric methoxy ketones become equivalent at some stage in the fragmentation pathway. In accord with this observation and on the basis that separation of the electrofugal group would leave a stabilised carbanion possessing a reluctant nucleofuge (OMe) it seems reasonable to infer that the reaction with these compounds proceeds through the carbanion fragmentation mechanism (iii_2).

For the reactions with the 2,2,3-trihalogeno ketones (**1a**), the absence of competing solvolytic substitution and of 1,2-dehalogenation can be taken as evidence against carbenium ion intermediate formation. Additional support for this conclusion is provided by the observation that the reactions with (**1a**; X = Y = Br, Z = Cl) and (**1a**; X = Z = Cl, Y = Br) occur with marked (≥95%) stereospecificity (Table 1). If reaction (i) does indeed represent the mechanism for fragmentation of (**1a**) one would expect a different stereochemical result.

Comparison of the data in Tables 1 and 2 indicates that the increase in reaction rates in passing from the 3-methoxy (**1b**) to the 3-halogeno (**1a**) ketones exceeds significantly that anticipated simply from the different electron-attracting stabilising effect of the 3-substituent on rate-determining carbanion formation. Such kinetic evidence considered in conjunction with the stereochemical results for fragmentation of (**1a**; X = Y = Br, Z = Cl) and (**1a**; X = Z = Cl, Y = Br) is difficult to reconcile with a carbanion pathway for the reactions with the 3-halogeno ketones and can be best rationalised in terms of a concerted process.

Compared with the relative rates of fragmentation of the 3-methoxy ketones, the reactions with the 3-halogeno ketones exhibit a much lesser sensitivity as the 2-bromine atoms are successively substituted by chlorine. If the relative rates of the reactions with the latter compounds were to reflect only the different C(2)–CO bond cleavage energy values, then the relative effect of the change of 2-halogens should be comparable to magnitude and direction to that for the reactions with the 3-methoxy substrates. The observed kinetic evidence could be accounted for on the basis of a concerted fragmention transition state where some degree of double-bond formation reduces



Scheme 4.

Consequently a different response to the presence of dimethyl sulphoxide might be expected for rearrangement compared with the one-step cleavage mechanism. A reasonable interpretation of these results is that the ground state in the rate-controlling stage leading to fragmentation should not differ from that of the rearrangement.

From Table 2 it is seen that there is a trend for the rate of the fragmentation reaction to increase with changing the location of the partial negative charge on the 2-carbon atom formed during C(2)–CO bond breaking. Moreover, it is conceivable that due to their small magnitude, the polar effect differences may be overshadowed by a possible counterbalancing influence of conformational nature.

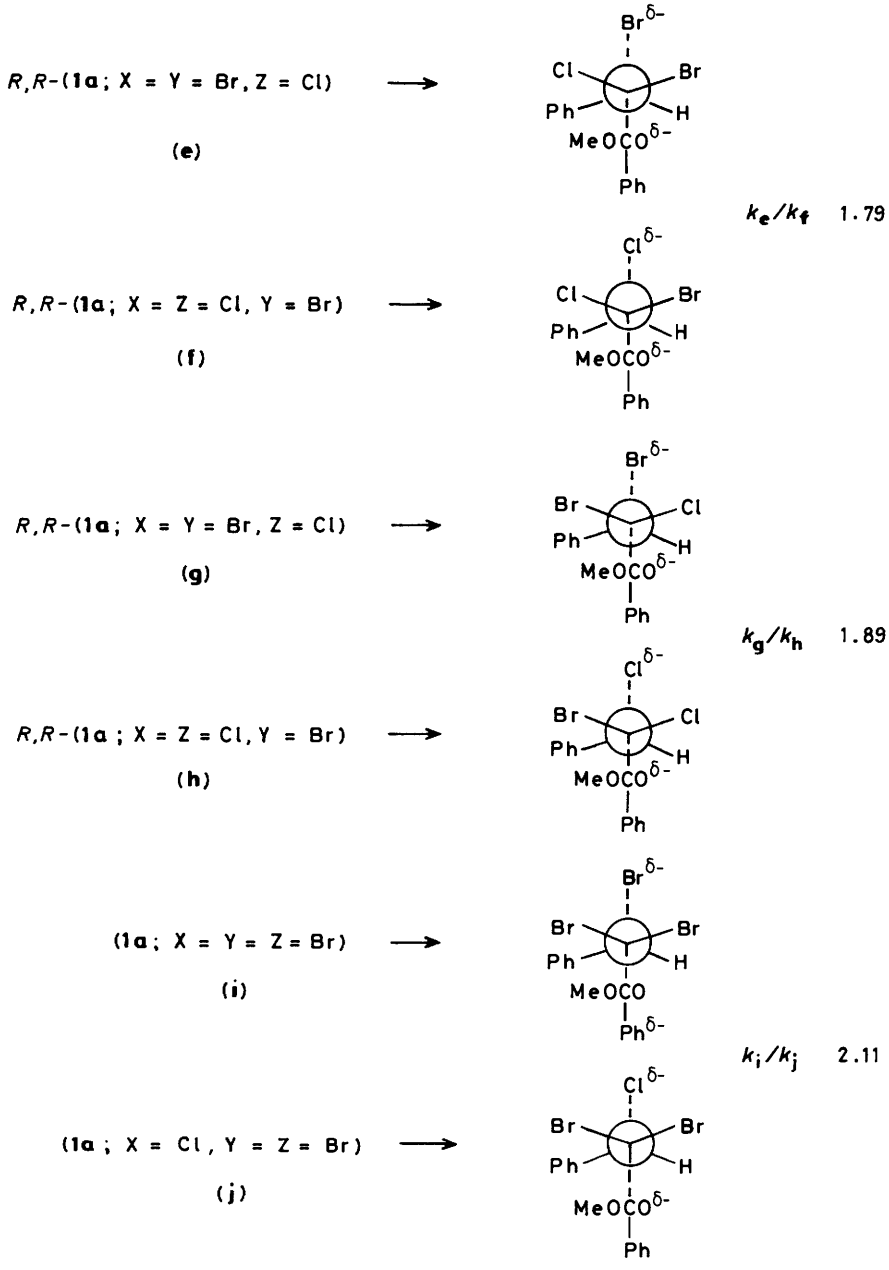
Additional support for the proposed intramolecular concerted fragmentation is provided by the observed effect of changing the nucleofuge from chlorine to bromine. Although the variation in

rate is not large the relative magnitude of the 3-halogen influence falls in the sequence of leaving-group reactivity* and is consistent with a mechanism which involves partial bond breaking to the nucleofuge in the rate-determining pathway.

Experimental

G.l.c. analyses were performed in all cases using a 20% SE-30 on Chrom W glass column (100 cm × 0.125 in) with a Varian 3700 instrument equipped with a flame-ionisation detector and a CDS 111 integrator. ^{1}H N.m.r. spectra were recorded with a Varian EM 360 60 MHz spectrometer. Reaction products were identified by comparison of their ^{1}H n.m.r. spectra and retention times with those of authentic samples. Individual calibration detector response factors were used for quantitative determinations. Blank experiments showed that the products could not be formed during work-up or analysis. G.l.c. conditions were carefully checked for each isomeric pair to assure that isomerisation did not occur during analysis.

Materials.—Methanol was purified according to the described procedure[9] and stored under nitrogen. Sodium methoxide solutions were prepared under nitrogen and stored



Scheme 5.

* Based on antiperiplanar concerted fragmentations steric differences can be anticipated for the reactions with the 3-halogeno ketones due to the relief of the interaction between the 2-halogens and the nucleofuge, and to the increased *gauche* interactions of one of the former with the phenyl group on going from the appropriate conformations to the corresponding transition states. However, the stereochemical contributions of the members of each of the pairs in Scheme 5 to *anti* fragmentation are constant. Thus, we might safely say that the present comparison between rates of reaction will lead to direct evaluation of relative leaving-group effects.

Table 3. ^{1}H N.m.r. spectra and m.p.s of $C_6H_5CHXCYZCOC_6H_5$.

X	Y	Z	Isomer	Chemical shift (δ)[a] 3-H	OCH_3	M.p./°C[b]
	Br	Br		5.02	3.21	89–90
OCH_3	Br	Cl	*R,R*	5.04	3.34	88.5–90
			R,S	5.18	3.24	
	Cl	Cl		5.15	3.18	95–96
	Br	Br		5.84		100–101.5
Br			*R,R*	5.78		
			R,S	5.92		94–95
	Br	Br		5.67		99.5–100
Cl	Br	Cl	*R,R*	5.82		
			R,S	5.70		83–84
	Cl	Cl		5.70		95.5–96

[a] In CCl_4. [b] From methanol.

in H_2O- and CO_2-free conditions. Solutions containing the required concentrations of reagents were prepared immediately before use by suitable dilution of stock solutions. To minimise contact with air all containers were reflushed with nitrogen. 2,2-Dibromo- and 2,2-dichloro-3-methoxy-1,3-diphenylpropanones were prepared as described.[2] The 2-bromo-2-chloro-3-methoxy substrate was obtained according to the reported procedure[2] as a mixture of the *R,R* and *R,S* isomers in the ratio 7:4. Since attempted separation of the diastereoisomers by recrystallisation or chromatography failed, the mixture was subject to partial reaction with sodium methoxide in methanol. After reaction of the *R,S* isomer was complete, the *R,R* unchanged compound was isolated from the resulting mixture by column chromatography on silica gel and elution with light petroleum (b.p. 30–60 °C). The configurational assignment followed from stability considerations.[10] and comparisons of the 3-H chemical shifts with those of the dibromo- and dichloro-analogues (Table 3). 2,2,3-Tribromo- and 2,2,3-trichloro-1,3-diphenylpropanones were prepared as reported.[2] (*RS*)-2,3-Dibromo-2-chloro-1,3-diphenylpropanone was obtained contaminated with the *R,R* isomer (9%) by bromination of 2-chloro-1,3-diphenylpropenone (0.002 mol) with bromine (0.0035 mol) in dichloromethane (100 cm^3). Purification of this crude by elution chromatography using a silica gel column with pentane as eluant afforded the pure *R,S* compound. After repeated silica gel column chromatography and recrystallisations the *R,R* isomer could not be separated from the *R,S* compound and the mixture was used as such.

2,2-*Dibromo*-3-*chloro*-1,3-*diphenylpropanone* was similarly obtained by reaction of 2-bromo-1,3-diphenylpropenone (0.002 mol) with BrCl (0.004 mol) in dichloromethane (100 cm^3) (Found: C, 45.1; H, 2.6; Cl, 8.5. $C_{15}H_{11}Br_2ClO$ requires C, 44.8; H, 2.8; Cl, 8.8%). 2-Bromo-2,3-dichloro-1,3-diphenylpropanone was obtained as reported[2] as a mixture of the *R,R* and *R,S* isomers in the ratio 2:3. Repeated silica gel column chromatography using pentane as the eluant afforded the diastereoisomerically pure *R,S* compound. Attempted separation of the *R,R* compound from its *R,S* isomer by column chromatography or recrystallisation failed and the mixture was used as such. As before, the assignment of configurations was based on stability grounds. The ^{1}H n.m.r. and m.p. data are summarised in Table 3. The structure of 1,1,3-*trimethoxy*-1,3-*diphenylacetone* (**4**), m.p. 93–94 °C, δ 6.9–7.3 (10 H, ArH, s), 5.02 (1 H, s), 3.02 (3 H, s), 2.94 (3 H, s), and 2.88 (3 H, s) (Found: C, 71.9; H, 6.8. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7%), was assigned on the basis of its ^{1}H n.m.r. spectrum and by comparison of the aromatic signals with those of $PhC(OMe)_2COCH_3$ and $PhCOC(OMe)_2CH_3$.[4]

Rate Measurements.—Kinetics were studied at 30 ± 0.03 °C. Rate constants were evaluated employing the approximation least-squares method. Each determination was repeated in triplicate and were estimated to be accurate to within ±3% unless noted otherwise in the Tables.

The reaction with the 3-halogeno ketones (**1a**) were started by mixing a solution of the appropriate substrate in methanol (10 cm^3, 0.056 mmol) with methanolic sodium methoxide solution (10 cm^3, 0.064 mmol) with maximum precautions to exclude atmospheric carbon dioxide. Aliquot portions (3 cm^3) were periodically removed with an automatic pipette and quenched by shaking with a mixture of aqueous hydrochloric acid (3 cm^3, 0.0372 mmol) and CCl_4 (1 cm^3) containing acenaphthene (internal standard for g.l.c. analysis; 0.0063 mol). The mixture was centrifuged and the organic layer analysed by g.l.c. The temperature program used was 130 °C for 3 min followed by heating at 40 min^{-1} to 250 °C which was maintained until the end of the run. The peak area ratios of product to internal standard were converted into molar ratios by detector response calibration charts constructed by using authentic samples. Since *R,R*-(**1b**; X = Z = Cl, Y = Br) and *R,R*-(**1b**; X = Y = Br, Z = Cl) could not be separated from their corresponding *R,S* isomers, an estimation of the relative reactivities was made by the competition method by g.l.c. analysis. The rate coefficients for the *R,R* substrates were obtained by combination of the diastereoisomeric coefficient ratio ($k_{R,S}/k_{R,R}$ = $\log[R,S]/[R,S]_o/\log[R,R]/[R,R]_o$ where $[R,S]_o$ and $[R,R]_o$ refer to initial concentrations and $[R,S]$ and $[R,S]$ to concentrations at time t) with the known rate constant of the *R,S* substrate ($k_{R,S}$).

The reactions of the 3-methoxy ketones (**1b**) were carried out in pseudo-first-order conditions. Sample solutions (5 cm^3) of the appropriate substrate (0.392 mmol) in methanol were transferred into a flask containing methanolic sodium methoxide (5 cm^3, 3.92 mmol). Samples (0.8 cm^3) were withdrawn with a Hamilton syringe and injected directly into the g.l.c. column, using temperature programming from 160 to 200 °C at 20 min^{-1}. Then the temperature was maintained at 200 °C for 13 min. Quantitative determinations were performed by converting the peak area ratios of products to starting material into molar ratios. The observed rate coefficient for *R,S*-(**1b**; Y = Br, Z = Cl) was determined by combination of the rate constant corresponding to the diastereoisomeric mixture with that of the *R,R* isomer. The individual rate cofficients were calculated from equations (iv).

$$k_F = k_{obs}/1 + \frac{\%\ \text{elim.} + \%\ \text{rearrang.}}{\text{frag.}} \quad \text{(iva)}$$

$$k_R = k_F \frac{\%\ \text{rearrang.}}{\%\ \text{frag.}} \quad \text{(ivb)}$$

$$k_E = k_F \frac{\%\ \text{elim.}}{\%\ \text{frag.}} \quad \text{(ivc)}$$

Acknowledgements

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