Conversion of Aromatic Ketones into π-Arylalkanoic Acids. Oxidation by Thallium(III) and by Halogens

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The mechanism by which thallium(III) nitrate oxidises aromatic ketones to α-arylalkanoic acids has been investigated and the role of additives in the system elucidated. It is found that in the absence of additives an organothallium intermediate, most probably the phenacylthallium species $BzCH_2Tl(NO_3)_2$, persists and that the key to an efficient rearrangement is the ready conversion of this compound into its acetal. Thallium(III) is shown not to be a unique reagent for the oxidation. Other oxidants capable of acting initially as an electrophile and then as a leaving group are equally effective, provided that formation of an acetal is possible. Iodine–silver nitrate in particular offers considerable advantages as a reagent over thallium(III). Higher specificity is achieved, unwanted side-reactions can be avoided, and toxicity problems are eliminated. Bromine may be used instead of iodine, but chlorine proves unsatisfactory as an oxidant.

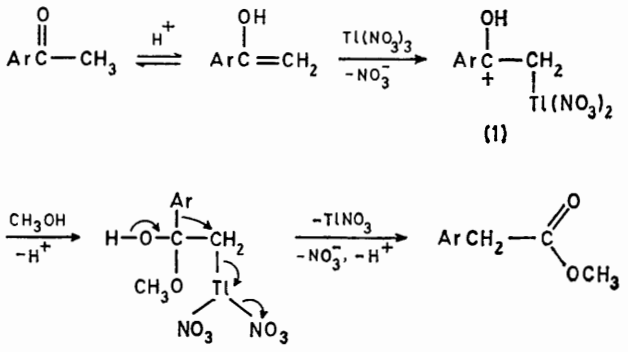
α-ARYLALKANOIC ACIDS have found widespread use as anti-inflammatory agents.[1] Unfortunately, their commercial synthesis has involved either multistep processes or the single-stage Willgerodt–Kindler reaction in which an arylalkanone is converted into the ω-arylalkanoic acid. Among the many drawbacks of this latter reaction is the inability to obtain arylacetic acids with α-alkyl substituents. More recently, McKillop *et al.* have shown that many acetophenones will undergo rearrangement to esters of arylacetic acids at room temperature if thallium(III) nitrate is employed as the oxidant in acidic methanol.[2,‡] Replacement of the acid by trimethyl orthoformate has allowed propiophenone and butyrophenone to be converted, in excellent yields, into the corresponding α-phenylpropanoate and butanoate esters.[3]

However, from the point of view of a reagent for the synthesis of a pharmaceutical product, thallium(III) is far from satisfactory; it is expensive and highly toxic. It is presumably with these points in mind that McKillop has developed a thallium(III) reagent which is permanently bonded to an inert support and which may be regenerated *in situ*.[4] Even so, doubts remain as to whether the regulatory authorities would permit the use of materials manufactured by a thallium-based route.

Now, whilst thallium(III) is an extremely versatile oxidant it is by no means unique. Most of its reactions with unsaturated substrates mirror those of other electrophilic reagents. For instance, in its behaviour towards alkenes and arenes, thallium(III) is intermediate between mercury(II) and lead(IV), all three behaving as typical electrophiles.[5,6] We thought that if the detailed mechanism could be identified by which the first oxidant converts arylalkanones into arylalkanoic acid derivatives, then it might well prove possible to develop more amenable reagents to bring about this reaction. This paper reports some of our attempts to that end.

RESULTS AND DISCUSSION

Two mechanisms have been suggested for the conversion. The original one, proposed by McKillop and his co-workers,[2,7] is shown in Scheme 1. The enol form of acetophenone reacts electrophilically with thallium(III) to give the carbonium ion (1). The hemiacetal, formed by uptake of solvent, then decomposes with migration of the aryl group to form methyl arylacetate. Our disquiet over Scheme 1 centred on two points. First, when



SCHEME 1

other electrophiles, including thallium(III) acetate in acetic acid, were treated with acetophenone the products were the α-substituted acetophenones.[8-11] Presumably, species analogous to the ion (1) underwent rapid proton loss rather than nucleophilic attack by solvent. It is difficult to see why the ion (1) should behave differently. Secondly, perchloric acid appears to play a more fundamental role than solely that of a catalyst for enolisation since, when trimethyl orthoformate was used, the reaction proceeded smoothly in the absence of acid.[3]

More recently, Walker and Pillai have stated that acetophenone dimethyl acetal (2) and α-methoxystyrene (3) mediate in the conversion (Scheme 2).[12] Certainly both compounds, when oxidised in methanol, gave excellent yields of the required ester, but it is implied that higher temperatures are required with the acetal (2) than in direct oxidation of the ketone. We found in ^1H n.m.r. experiments, that neither compounds (2) nor (3) could be detected when acetophenone was dissolved in CD_3OD

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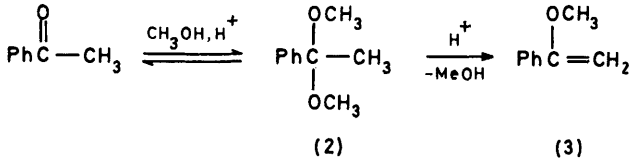
‡ The acid employed is 70% perchloric acid and the thallium(III) nitrate is the trihydrate. A significant quantity of water is, therefore, present in the system.

containing perchloric acid, the only change being the disappearance of the methyl singlet of the ketone through proton exchange. In the presence of orthoformate compound (2) was slowly formed, but no (3) was observed. That propiophenone gives a substantially different product distribution to that shown by the corresponding enol ether [12] also suggests that Scheme 2 cannot be the sole oxidation route.



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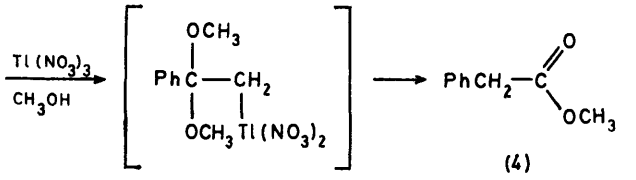
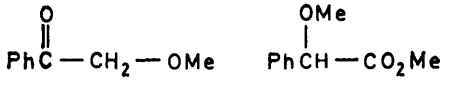


(4)

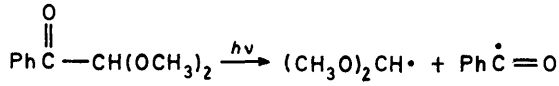
SCHEME 2

We suspect that this route is never significant. Compound (3) should react readily with any electrophile. Indeed, we found it to be converted rapidly into methyl phenylacetate even by the poorly electrophilic [5,13] lead(IV) acetate. However, the oxidation of the acetal is probably an artefact. In acidic methanol the acetal (2) rapidly reverted to acetophenone and, even without added acid, sufficient water of crystallisation was present from the thallium(III) salts to lead to some hydrolysis, acid inevitably being formed during their reduction. The species that is oxidised is, therefore, likely to be acetophenone.



(5) (6)

Oxidation of acetophenone with thallium(III) nitrate in acidic methanol by McKillop's procedure gave the product distribution shown in experiment 1 (Table 1). Besides unchanged starting material and the two products (4) and (5), reported earlier, we found two minor products, α,α-dimethoxyacetophenone (7) and methyl benzoate (8). Compound (7) is the product of further oxidation of (5) (experiment 2), but the formation of methyl benzoate puzzled us. However, experiments 3 and 4 demonstrate that, whilst compound (8) results from further reaction of compound (7), the process is light induced. α,α-Dimethoxyacetophenone has been employed as a photo-initiator in polymerization processes [14] and the benzoyl radicals so formed presumably undergo a one-electron oxidation followed by uptake of solvent (Scheme 3).



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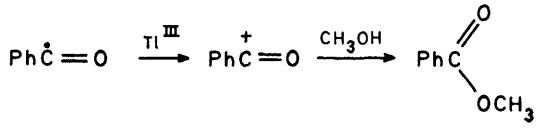


(8)

SCHEME 3

Experiment 5 demonstrates that the acid does not simply serve as a catalyst for enolisation. Acetophenone disappeared as rapidly as in the presence of acid, yet the yield of rearranged ester was much reduced. Of greatest significance, however, was the low accountability, by gas chromatography, of products from this experiment: only 65% of the acetophenone was converted into volatile components. Yet the *weight* of crude product was greater than expected. With time, this colourless oil slowly turned brown and a white precipitate was deposited which gave the characteristic green flame test for thallium.

We believe that, under these conditions, an organothallium intermediate survives the reaction. It would be too involatile to be detected by gas chromatography and is unstable over any length of time at room temperature. Unfortunately, all attempts to isolate the compound failed, but the ^{1}H n.m.r. spectrum of the crude product recorded immediately after reaction confirms the presence of a component additional to those identified by chromatography.

Of the products given in Table 1 the only one to have an unsplit aromatic signal in its ^{1}H n.m.r. spectrum is

TABLE 1

Products from oxidations by thallium(III) nitrate in methanol in the presence of 70% $HClO_4$ at 20 °C

			Products (%)						
Expt.	Substrate	Time/h	(17; X = H)	(4)	(5)	(6)	(7)	(8)	Total
1	(17; X = H)	5	8	71	8		2	2	91
2	(5)	5			8	11	80		99
3	(7)	96					44	55	99
4 [a]	(7)	96					93		93
5	(17; X = H)	5 [b]	7	36	8		13	1	65

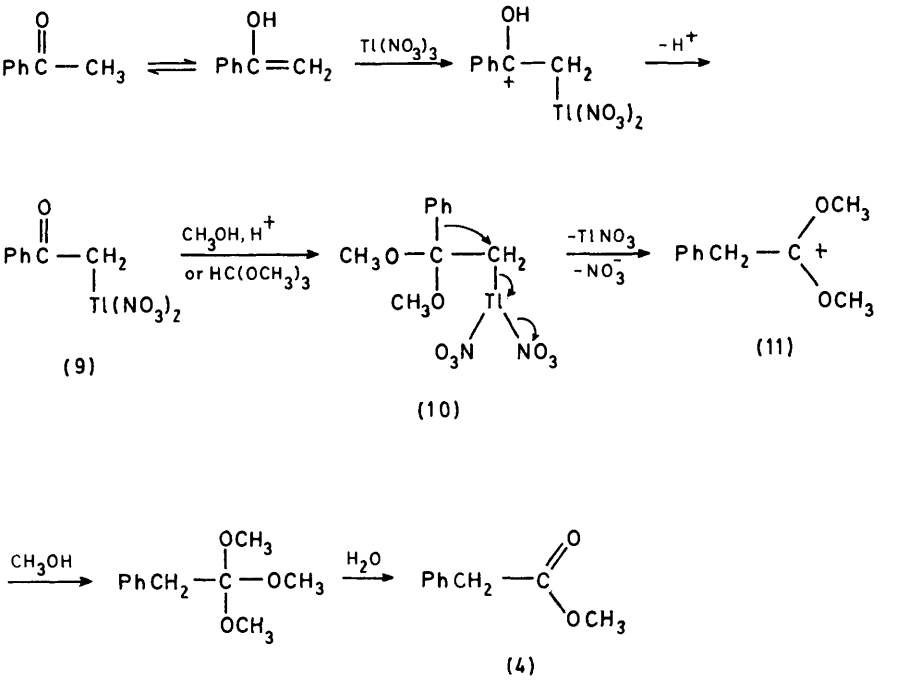
[a] The reaction was carried out in the dark. [b] No $HClO_4$ present.

methyl phenylacetate. This shows a broadened singlet at τ 2.85 whereas the other compounds have the complex deshielded aromatic multiplets typical of a benzoyl function. The spectrum of the crude product contains only the one singlet at τ 2.85: all other signals due to aromatic protons occur below τ 2.75, *i.e.* are deshielded, and appear to be multiplets. Assuming that the τ 2.85 signal corresponds to the 36% of methyl phenylacetate present, integration of the aromatic region suggests that the remaining resonances correspond to *ca.* 65% of the substrate, in excellent agreement with quantitative recovery. Since the other identified products only account for 29% we believe the remainder to be an organothallium compound of which the most likely, in view of the deshielded nature of the aromatic protons, is the phenacyl thallium compound (9). No signal attributable to the methylene group in compound (9) could be positively identified, but two unassigned signals of equal intensity were observed at τ 5.10 and 8.87. These might be the methylene signal split by a large thallium coupling (J 226 Hz), but we were unable to find any references to the spectra of suitable model compounds.

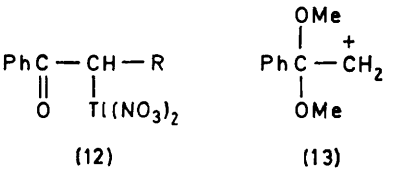
We can, then, explain the marked effect of solvent on the course of thallium(III) oxidations. Compound (9) is comparatively stable for an organothallium(III) species and only slowly undergoes solvolysis to give α-methoxyacetophenone (5). The solvolysis of phenacyl halides in aqueous alcohol leads solely to unrearranged products.[15] Similarly, both lead(IV) [9,10] and thallium(III) [11] in acetic acid oxidise acetophenone to phenacyl acetate, presumably *via* an intermediate analogous to compound (9).

However, under acetalising conditions, *i.e.* in acidic methanol or trimethyl orthoformate, compound (9) is in equilibrium with its dimethyl acetal (10), which must be much more labile. Indeed, there is a strong driving force for decomposition since loss of the thallium group with concomitant aryl migration leads to the very stable carbonium ion (11) (Scheme 4). Solvolysis of this ion and hydrolysis of the resultant ortho-ester gives methyl phenylacetate (4).

In support of our view that acetalisation of intermediates, such as (9), is necessary if acceptable yields of rearranged esters are to be obtained it is significant that, in acidic methanol, propiophenone and butyrophenone undergo only mediocre conversion into the corresponding esters.[2,3] We would anticipate that compound (12; R = Me or Et) would be more labile than compound (9) and increased steric crowding might displace the equilibrium for acetalisation towards the α-thalliated ketone, thus inhibiting rearrangement. If, however, the equilibrium is displaced the other way by the use of trimethyl orthoformate, rearrangement will proceed readily, as has been observed.[3]



SCHEME 4

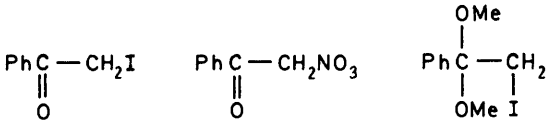


If Scheme 4 is a correct representation of the mechanism of oxidation of aromatic ketones there would seem to be little special about the role of thallium(III). It simply serves initially as a good electrophile and then

as an acceptable leaving group. Other reagents should be capable of effecting the conversion providing conditions favour acetal formation. The critical feature to rearrangement would appear to be the formation of the carbonium ion (13) or an incipient version of this ion.

The Woodward–Prévost reaction closely resembles the thallium(III) oxidation in that electrophilic iodine reacts with an alkene and the resultant adduct then undergoes silver-ion catalysed solvation.[16,17] Iodine itself is not sufficiently electropositive to react directly with the alkene and the positive iodine, the precise nature of which is uncertain (but see ref. 18), is generated *in situ* by the action of silver salts on the halogen.

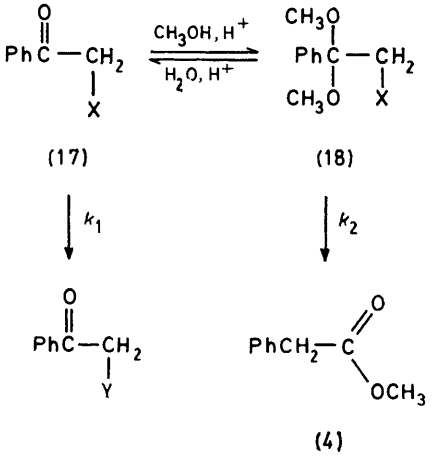
Acetophenone, when heated with iodine and silver nitrate (1 equiv.) in refluxing methanol for 1 h, gave a 94% yield of α-iodoacetophenone (14). Other ring-substituted acetophenones [2-methyl-, 4-chloro-, 4-methoxy-, 4-trifluoromethyl-, and 2-(2′,4′-dichlorophenoxy)-] were also iodinated in yields of 84—99%, which suggests that this method is as useful for synthesising 1-aryl-2-iodoethanones as the closely analogous thallium(I)–iodine route.[19] The solvolysis of phenacyl halides in methanol results in no products of rearrangement [15] and the inclusion of perchloric acid to encourage acetalisation and of extra silver ions (1 equiv.) to catalyse the displacement of the iodide was little more successful (experiment 6, Table 2). Only a small amount of methyl phenylacetate was obtained, the majority of the products stemming from direct substitution of the iodine in compound (14) or from further oxidation. Surprisingly, the yield of rearranged ester was higher if perchloric acid was omitted from the system (experiment 7).



(14) (15) (16)

When we subjected α-methoxystyrene to the Prévost conditions (two equivalents of $AgNO_3$) we were equally surprised to find that, at room temperature, the iodoacetal (16) was obtained in a yield of 84%, contaminated with a small amount of compound (14). It appears that (16) is relatively resistant to solvolysis.

We can then ascribe the anomalous results in Table 2 and the differences between the Prévost and the thallium(III) oxidations to the different rates of the reactions shown in Scheme 5. With the metal oxidant, the



(17) (18) (4)

SCHEME 5

acetal [18; X = $Tl(NO_3)_2$] decomposes very much faster than its precursor [17; X = $Tl(NO_3)_2$] so that, irrespective of the position of equilibrium, the major product is the rearranged ester (4). However, when X = I the rates k_1 and k_2 are not substantially different and the position of equilibrium becomes critical. With perchloric acid present, whilst the rate of acetalisation should be increased, the water content of the acid displaces the equilibrium towards compound (17; X = I). In the absence of added acid the proportion of compound (18; X = I) is increased, acetalisation still being possible as nitric acid is generated during initial iodination.

The secret to obtaining high yields of compound (4) using iodine as oxidant must then lie in displacing the equilibrium well to the right. Certainly, the iodoacetal (16) can be solvolysed by refluxing in methanol in the presence of silver nitrate. The reaction took *ca.* 4 h for completion and, as expected, the major product was methyl phenylacetate in 98% yield. Using phenacyl iodide as the starting material and adding to the solvent trimethyl orthoformate together with a trace of acid,*

TABLE 2

Products from the oxidation of acetophenone by iodine (1.2 equiv.) and silver nitrate (2 equiv.) in refluxing methanol for 5 h

		Products (%)								
Experiment	Additive	(17; X = H)	(4)	(5)	(6)	(7)	(8)	(14) [a]	(15) [a]	Total
6	70% $HClO_4$	2	5	43		9	3	6	12	80
7		8	18			11	1	12	20	70
8	$HC(OMe)_3$		76		18					94
9	$HC(OMe)_3$ [b]		90							90

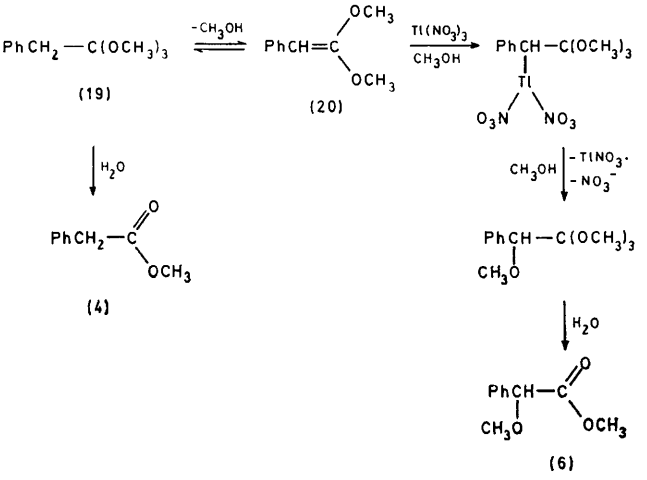
[a] Yield determined by ^1H n.m.r. spectroscopy from the intensity of the methylene signal using compound (4) as the standard. [b] 1.0 Equiv. of I_2 used.

* The yield was significantly lower if acid was omitted; presumably acetalisation requires catalysis.

to encourage the formation of compound (16), was equally successful. Under the same conditions a 99% yield of the ester was obtained.

Modifying a Prévost oxidation by including trimethyl orthoformate in the solvent,* whilst giving acceptable yields of rearranged ester from acetophenone (experiment 8), also resulted in the formation of the α-methoxylated ester (6). Traditionally Prévost reactions are carried out using a slight excess of iodine (typically 20%) [16,17] and this appears to be the cause of the difficulty. The use of exactly one equivalent of halogen enabled acetophenone to be converted into compound (4) without the concomitant formation of compound (6) (experiment 9).

This problem of α-methoxylation was encountered by McKillop *et al.* in the thallium(III) oxidation of acetophenones to arylacetate esters when trimethyl orthoformate was incorporated in the solvent.[3] It is not that the methyl phenylacetate is itself susceptible to further oxidation, but its presumed precursor, the orthoester (19), is in equilibrium with the keten acetal (20), and it is this alkene which is further oxidised to compound (6) (Scheme 6).



SCHEME 6

Whilst further oxidation appears to be uncontrollable with thallium(III), since the organothallium adduct (9) is so labile as to decompose before thalliation of acetophenone is complete, in the iodine-based reactions the halogen can be completely consumed before solvolytic displacement occurs. Providing, therefore, that oxidant is not present in excess, α-methoxylation can be eliminated.

It is possible to replace iodine as the oxidant by bromine, though reaction times are lengthened as compound (18; X = Br) undergoes solvolysis more slowly than its iodo-analogue: 108 h were required to give a 96% yield of compound (4). Chlorine, however, proved ineffective since compound (18; X = Cl) decomposes at a negligible rate in boiling methanol–trimethyl orthoformate. The longer reaction times using bromine can be offset by employing higher boiling alcoholic solvents. For instance, use of ethanol–triethyl orthoformate reduced the time required for complete solvolysis by a factor of four.

* The addition of acid to the system is unnecessary in this case. Nitric acid is formed during iodination of the ketone.

The oxidative rearrangement is not confined to acetophenone. A range of higher homologues and ring-substituted analogues can be converted, in good yield, into the corresponding esters. Representative examples are listed in Table 3. The presence of electron-withdrawing substituents in the aromatic ring inhibits rearrangement and leads to isolation of the intermediate acetal. In some cases, *e.g.* 2-chloroacetophenone, longer reaction time resulted in much increased yields of the rearranged ester, but no variation of conditions induced successful reaction with the most electron-deficient aromatic rings. Arylalkanones with branched side chains are less amenable to oxidative rearrangement than their straight-chain analogues.

TABLE 3

Conversion of arylalkanones (Ar·CO·R) into methyl arylalkanoates by oxidation with iodine and silver nitrate (2 equiv.) in refluxing methanol containing trimethyl orthoformate

Substrate		Products (%)	
Ar	R	ester	Ar·C(OMe)$_2$·CHI·R′
Ph	Me	90	
2-MeO·C$_6$H$_4$	Me	91	
2-Me·C$_6$H$_4$	Me	90	
1-Naphthyl	Me	94	
2-Naphthyl	Me	92	
4-Cl·C$_6$H$_4$	Me	93	
4-Br·C$_6$H$_4$	Me	73	20
2-Cl·C$_6$H$_4$	Me	23	73
4-CF$_3$·C$_6$H$_4$	Me		99
2-NO$_2$·C$_6$H$_4$	Me		92
Ph	CH_2Ph	65	28 [a]
Ph	Et	96	
Ph	Pr^n	94	
Ph	Pr^i	17	[b]

[a] PhC(OMe)$_2$·CHOMe·Ph. [b] The only other material present was unchanged starting material. Iodination of this ketone is slow.

The critical factor in obtaining phenylacetic acid derivatives on oxidation of acetophenone appears to be that conditions should favour the formation of the incipient carbonium ion (13). Thallium(III), the preferred reagent to date, is a relatively expensive and potentially toxic reagent. The halogen–silver nitrate route is, therefore, an attractive substitute, since, although the reagents are certainly no cheaper, the toxicity problem is eliminated. The reaction conditions are as convenient as with thallium(III) and the specificity is higher. Most notably, the drawback of concomitant α-methoxylation of the desired product from acetophenones can be eliminated. Work is in progress to find cheaper alternatives to silver nitrate.

EXPERIMENTAL

^{1}H and ^{13}C N.m.r. spectra were recorded on Varian A-60A and Jeol FX60 instruments, respectively, using deuteriochloroform as solvent unless stated otherwise. Gas chromatography was carried out on Pye 104 instruments

fitted with columns (6 ft × ¼ in) packed with 10% Carbowax 20M, 10% diethyleneglycol adipate, 10% Apiezon-L, or 10% silicone oil (SE 30), each coated on Celite. 4-Nitrotoluene or, where this was inappropriate, benzophenone were employed as internal standards. Preparative-scale gas chromatography was effected on a Pye 105 instrument fitted with similar columns (⅜ in diameter). Mass spectra were recorded on an AEI MS 30 spectrometer which was coupled *via* a heated capillary and a jet separator to a gas chromatograph: all spectra were recorded at 70 eV and the source temperature was held at 150—180 °C. Melting points were determined on a Kofler microhot-stage and are uncorrected. Elemental analyses were by Butterworth Micro-analytical Services (Teddington).

All inorganic reagents were available commercially as were all the substituted acetophenones employed in this study. Methyl benzoate, methyl phenylacetate, 2-chloro-1-phenylethanone, propiophenone, butyrophenone, isobutyrophenone, deoxybenzoin, methanol, and trimethyl orthoformate were also purchased.

1-*Methoxy*-1-*phenylethene* (3).—Styrene (10 g), silver acetate (24 g), and iodine (24.5 g) were stirred at room temperature in methanol (200 ml) for 20 min. The mixture was filtered, poured into water (1 l), and extracted with diethyl ether. The extracts were washed with 10% aqueous sodium thiosulphate, dried ($MgSO_4$), and the solvent distilled off. Distillation, in the dark, of the residue gave 2-iodo-1-methoxy-1-phenylethane (22.4 g, 89%) an an oil, b.p. 80—81 °C at 0.4 mmHg (lit.,[20] 107—108 °C at 5 mmHg); δ 3.25 (s, OCH_3) and 3.26 (d, *J* 7 Hz, CH_2I) (total 5 H), 4.23 (1 H, t, *J* 7 Hz, CH), and 7.25 (5 H, s, ArH). 1-Methoxy-1-phenylethene (3) was prepared from this compound by the method of Winstein and Ingraham,[20] b.p. 91—92 °C at 21 mmHg (lit.,[20] 88—89 °C at 20 mmHg); δ 3.48 (3 H, s, OCH_3), 4.12 and 4.78 (1 H, each, 2d, *J* 2.5 Hz, $=CH_2$), and 7.10—7.83 (5 H, m, ArH).

2-*Methoxy*-1-*phenylethanone* (5).—Compound (5) was prepared from phenyl magnesium bromide and methoxyacetonitrile by the method of Moffett and Shriner,[21] b.p. 80—81 °C at 3.0 mmHg (lit.,[21] 110—112 °C at 9 mmHg); δ 3.49 (3 H, s, OCH_3), 4.68 (2 H, s, $COCH_2$), and 7.30—8.10 (5 H, m, ArH).

2,2-*Dimethoxy*-1-*phenylethanone* (7).—Redistilled phenylglyoxal (5 g) was added to a mixture of methanol (30 ml) and trimethyl orthoformate (15 ml) containing concentrated sulphuric acid (0.5 ml); after 1 h at room temperature the mixture was poured into water and extracted with diethyl ether. The extract was dried ($MgSO_4$), the solvent removed, and the product distilled to give 2,2-dimethoxy-1-phenylethanone (7) (4.7 g, 70%) as an oil, b.p. 90—92 °C at 0.9 mmHg (lit.,[22] 85—86 °C at 0.25 mmHg); δ 3.47 (6 H, s, OCH_3), 5.20 (1 H, s, CH), and 7.25—8.25 (5 H, m, ArH).

Methyl 2-*Methoxy*-2-*phenylacetate* (6).—2-Hydroxy-2-phenylacetic acid (5 g) and methanol (30 ml) containing dry hydrogen chloride (5 g) were refluxed for 18 h, the cooled solution poured into water, and the aqueous phase made alkaline with saturated aqueous sodium carbonate. The ether extract was dried ($MgSO_4$) and the solvent removed to give crude methyl 2-hydroxy-2-phenylacetate (5.3 g); δ 3.70 (3 H, s, OCH_3), 3.79 (1 H, s, OH, removed by D_2O), 5.21 (1 H, s, CH), and 7.44br (5 H, s, ArH). This material was heated under reflux with thionyl chloride (4.8 g) for 30 min, after which the excess of thionyl chloride was removed and the reaction mixture poured into water. The diethyl ether extracts were dried ($MgSO_4$) and the solvent removed to give crude methyl 2-chloro-2-phenylacetate (4.9 g); δ 3.79 (3 H, s, OCH_3), 5.42 (1 H, s, CH), and 7.32—7.77 (5 H, m, ArH). This material was added to a solution of sodium (2 g) in methanol (50 ml) and the solution refluxed for 18 h; it was then poured into water and the diethyl ether extract dried ($MgSO_4$). Evaporation of the solvent and distillation of the residue gave methyl 2-methoxy-2-phenylacetate (6) (3.8 g, 66%) as an oil, b.p. 98 °C at 1.5 mmHg (lit.,[23] 119 °C at 11 mmHg); δ_H 3.36 (3 H, s, OCH_3), 3.68 (3 H, s, CO_2CH_3), 4.75 (1 H, s, CH), and 7.08—7.58 (5 H, m, ArH); δ_C [$(CD_3)_2SO$], 51.74 (CO_2CH_3), 56.69 ($CHOCH_3$), 81.38 ($CHOCH_3$), 127.91, 128.40, and 136.52 (ArC), and 170.72 (C=O).

1,1-*Dimethoxy*-1-*phenylethane*.—This compound was prepared from acetophenone by the method of Bogert and Herrera,[24] b.p. 79 °C at 15 mmHg (lit.,[24] 90 °C at 20 mmHg); δ 1.49 (3 H, s, CH_3), 3.10 (6 H, s, OCH_3), and 7.06—7.67 (5 H, m, ArH).

1-*Aryl*-2-*iodoethanones*.—2-Bromo-1-phenylethanone, prepared by the method of Cowper and Davidson,[8] was converted into 2-iodo-1-phenylethanone (14) by the method of Pasto and Garves,[15] m.p. 35—36 °C (lit.,[15] 35 °C). Ring-substituted 2-iodo-1-phenylethanones were prepared by the oxidation at room temperature of the appropriate acetophenone by iodine–silver nitrate (*q.v.*) and had the following physical data: 2-*iodo*-1-(2′-*methylphenyl*)*ethanone*, m.p. 29—32 °C; δ 7.75—7.00 (4 H, m, ArH), 4.26 (2 H, s, CH_2), and 2.42 (3 H, s, Me); too labile for microanalysis; 2-iodo-1-(3-nitrophenyl)ethanone, m.p. 85—88 °C (lit.,[25] 92—93 °C); δ 8.88—7.80 (4 H, m, ArH) and 4.41 (2 H, s, CH_2); 1-(4-chlorophenyl)-2-iodoethanone, m.p. 71—73 °C (lit.,[26] 75.5 °C); δ 8.07—7.22 (4 H, m, ArH) and 4.34 (2 H, s, CH_2); 2-iodo-1-(4-methoxyphenyl)ethanone, m.p. 59—61 °C (lit.,[27] 61 °C); δ 8.12—6.95 (4 H, m, ArH), 4.29 (2 H, s, CH_2), and 3.85 (3 H, s, OCH_3); 2-*iodo*-1-(4-*trifluoromethylphenyl*)-*ethanone*, m.p. 55—56 °C; δ 8.25—7.60 (4 H, m, ArH) and 4.38 (2 H, s, CH_2) (Found: C, 34.3; H, 1.8%. $C_9H_6F_3IO$ requires C, 34.3; H, 1.9%).

1-*Aryl*-2-*halogeno*-1,1-*dimethoxyethanones*.—These compounds were prepared in a manner akin to that of Marquet *et al.*[28] The halogenoketone (10 g), dissolved in methanol (10 ml) and trimethyl orthoformate (20 ml), was heated under reflux for 1 h in the presence of toluene-*p*-sulphonic acid (0.5 g). The solution was made alkaline with sodium methoxide in methanol and poured into 5% sodium carbonate solution; the diethyl ether extracts were washed with dilute sodium thiosulphate, dried ($MgSO_4$), and the solvent removed by distillation. Recrystallisation or distillation of the crude product gave the halogenoacetals, the physical parameters of which are listed in Table 4.

Methyl 2-*Arylalkanoates*.—These were isolated either by distillation or by preparative gas chromatography from the oxidation of the appropriate 1-arylalkanone with iodine–silver nitrate in methanol–trimethyl orthoformate under reflux (*q.v.*). The physical parameters of these compounds are set out in Table 5.

1,1,2-*Trimethoxy*-1,2-*diphenylethane*.—Benzoin (10 g) was heated under reflux in methanol (150 ml) saturated with hydrogen chloride for 18 h. After cooling, trimethyl orthoformate (50 ml) was added and the mixture was heated under reflux for a further 2 h. The cooled solution was made alkaline with methanolic sodium methoxide, poured into water, and extracted with diethyl ether. The extracts were dried ($MgSO_4$) and the solvent removed to give 1,1,2-*trimethoxy*-1,2-*diphenylethane* (9.66 g, 75%) as white crystals,

TABLE 4

Analytical data on 1-aryl-2-halogeno-1,1-dimethoxyethanes [X·C_6H_4·C(OMe)$_2$$CH_2$Y]

X	Y	B.p. or m.p. (°C)	^{1}H N.m.r. (δ) OMe	CH_2	ArH
H	Cl	25—26 [a]	3.19	3.65	7.13—7.60
H	Br	45.5—46.5 [f]	3.27	3.54	7.13—7.60
H	I	96—98 at 2 mmHg [c]	3.23	3.52	7.25—7.72
2-Cl	I	*d*	3.23	3.84	7.05—7.60
4-Br	I	*d*	3.21	3.68	7.10—7.70
3-NO_2	I	72.5—73.5 [e]	3.27	3.53	7.46—8.52
4-CF_3	I	57—60 [f]	3.20	3.48	7.61

[a] Found: C, 59.7; H 6.5. $C_{10}H_{13}ClO_2$ requires C, 59.9; H, 6.5%. [b] Lit., m.p. 46—47 °C (ref. 29). [c] Compound (16) Found: C, 41.3; H, 5.5. $C_{10}H_{13}IO_2$ requires C, 41.1; H, 5.5%.) [d] Isolated by preparative chromatography. [e] Found: C, 35.7; H, 3.6; N, 4.0. $C_{10}H_{12}INO_4$ requires C, 35.6; H, 3.6; N, 4.2%. [f] Found: C, 36.7; H, 3.4. $C_{11}H_{12}F_3IO_2$ requires C, 36.8; H, 3.4%.

m.p. 56—57.5 °C (from hexane); δ 3.16 and 3.20 [total 6 H, 2 s, C(OCH_3)$_2$], 3.47 (3 H, s, CHOCH_3), 4.56 (1 H, s, CH), and 6.67—7.34 (10 H, m, ArH) (Found: C, 75.0; H, 7.3%. $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.4%).

2-Nitrato-1-phenylethanone (15).—2-Iodo-1-phenylethanone (1.0 g) and silver nitrate (0.7 g) were stirred in tetrahydrofuran (50 ml) for 18 h at ambient temperature and then for 3 h under reflux. The cold solution was poured into water, extracted with diethyl ether, the extracts dried ($MgSO_4$), and the solvent removed. The resultant oil (0.56 g) was subjected to preparative gas chromatography to give 2-nitrato-1-phenylethanone (15) (0.37 g, 57%) as a colourless liquid; δ 5.67 (2 H, s, CH_2NO_3) and 7.30—8.10 (5 H, m, ArH): *m/e* 105 (77%, $PhCO^+$) and 77 (100, $C_6H_5^+$).

Oxidations by Thallium(III) *Nitrate*.—A typical oxidation was carried out in the following manner. Thallium(III) nitrate trihydrate (94% Tl^{3+} as estimated by iodometry, 0.01 mol) was added to a stirred solution of the substrate (0.01 mol) in methanol (25 ml) containing perchloric acid (5 ml; 70%, w/w). After 5 h at room temperature the precipitate of thallium(I) nitrate was filtered off and the filtrate poured into water (250 ml). Extraction with diethyl ether (3 × 50 ml), drying of the extracts ($MgSO_4$), and removal of the solvent gave a crude product which was analysed by comparison with authentic samples by g.c.–m.s. and by ^{1}H n.m.r. spectroscopy. Quantification was carried out on the diethyleneglycol adipate column at 150—180 °C.

In one experiment using acetophenone as the substrate the perchloric acid was omitted. The colourless oil (1.79 g) obtained slowly turned brown on standing and deposited a white precipitate which gave the characteristic green colour of thallium when subjected to a flame test. The analysis of this oil is described in the text.

In those experiments where trimethyl orthoformate replaced the perchloric acid the volume of solvent was not changed, methanol (15 ml) and trimethyl orthoformate (15 ml) being employed. When the course of the reaction was monitored by ^{1}H n.m.r. spectroscopy, solutions were made up on a smaller scale in an n.m.r. tube.

In two experiments the thallium(III) salt was replaced by lead(IV) acetate, but otherwise the reaction was conducted as above.

Oxidation of 1-Arylalkanones by Iodine–Silver Nitrate.—In a typical experiment iodine (10.5 mmol) was added to a suspension of silver nitrate (21.0 mmol) in a mixture of methanol (45 ml) and trimethyl orthoformate (15 ml), containing the appropriate ketone (10 mmol); the mixture was then heated under reflux for 5 h. After the solution had been cooled, the silver salts were filtered off, and the filtrate worked up in the same way as in the thallium(III) oxidations. In some reactions the temperature was maintained at *ca.* 20 °C throughout and in others the solvent was replaced by ethanol and triethyl orthoformate to obtain higher temperatures. In a few cases iodine was replaced by bromine as the oxidant. Larger scale reactions were carried out when it was desired to isolate pure samples of the rearranged ester.

TABLE 5

Analytical data on methyl 2-arylalkanoates (Ar·CR^1R^2·CO_2Me)

R^1	R^2	Ar	M.p. or b.p. (°C) [mmHg]	lit. m.p. or b.p. (°C) [mmHg]	^{1}H N.m.r. (multiplicity) (δ) R^2	C*H*R^1	CO_2Me	ArH	Other
H	H	2-MeC_6H_4	72—74 [0.85]	*a*		3.66 (s)	3.70 (s)	7.18 (s)	2.30 (s)
H	H	2-MeOC_6H_4	119—121	119—120 [2]		3.62 (s)	3.64 (s)	6.67—7.45 (m)	3.78(s)
H	H	2-ClC_6H_4	77—78 [1.8]	125—128 [23] [30]		3.80 (s)	3.68 (s)	7.05—7.50 (m)	
H	H	4-BrC_6H_4	113—114	113—114 [3]		3.55 (s)	3.67 (s)	7.03—7.57 (m)	
H	H	1-naphthyl	112—116 [0.06]	162—165 [11] [2]		3.66 (s)	3.61 (s)	7.25—8.00 (m)	
H	H	2-naphthyl	134—136	138—140 [2]		3.70 (s)	3.61 (s)	7.25—7.98 (m)	
H	H	2-(2,4-Cl_2·C_6H_3O)C_6H_4	154—156 [0.8]	*b*		3.72 (s)	3.59 (s)	6.70—7.50 (m)	
H	Me	Ph	62—65 [0.5]	92—96 [9] [2]	1.45 (d)	3.72 (q)	3.57 (s)	7.28 (s)	
H	Et	Ph	97—98 [2.0]	225—226 [760] [31]	0.91 (t), 1.96 (m)	3.54 (t)	3.64 (s)	7.27(s)	
H	Ph	Ph	59—60	59 [32]		5.02 (s)	3.65 (s)	7.28 (s)	
Me	Me	Ph	70 [1.5]	81—86 [5] [33]	1.55 (s)		3.55 (s)	7.27br (s)	

[a] Found: C, 73.0; H 7.3. $C_{10}H_{12}O_2$ requires C, 73.2; H, 7.4%. [b] Found: C, 57.7; H 3.8. $C_{15}H_{12}O_3$ requires C, 57.9; H, 3.9%.

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