Conversion of Aromatic Ketones into α-Arylalkanoic Acids. Part 2.[1] Routes Employing Peracid, Chlorine, or Nitrous Acid

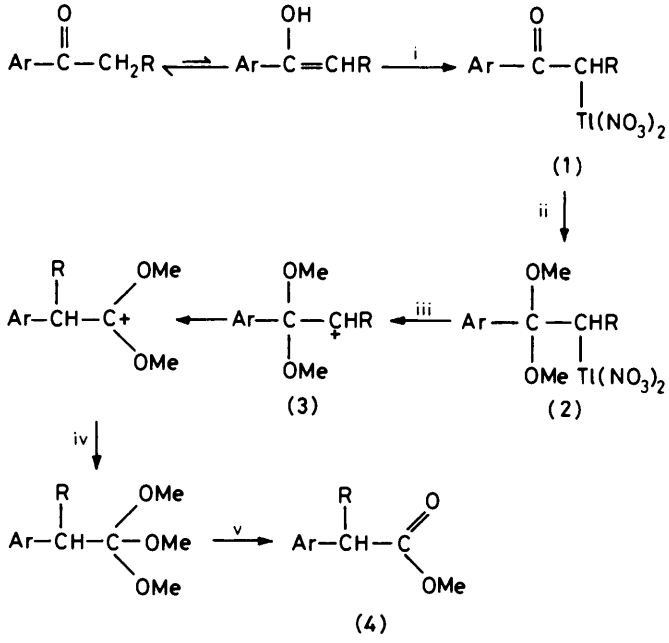
Stanley D. Higgins and C. Barry Thomas *
Department of Chemistry, The University of York, Heslington, York YO1 5DD

Further methods for effecting the oxidative rearrangement of 1-arylalkanones to α-arylalkanoic esters have been investigated. It has been shown that appropriate α-iodoacetals, readily prepared from the ketones, can be converted into esters on treatment either with a peracid or with chlorine. Using the latter reagent, α-chlorination of the ester can be an unwanted side reaction with some substrates and the factors governing by-product formation are discussed. It is demonstrated that, employing chlorine, the process can be made catalytic in iodine. The acetals of 2-amino-1-arylalkanones have also been shown to give high yields of esters under diazotising conditions adding support to the suggestion that the ion, $ArC(OR)_2CHR'^+$, or an incipient version of the ion, is a key intermediate in the process.

α-Arylalkanoic acids have found widespread use as anti-inflammatory agents. The first synthetic routes to these compounds proved somewhat unsatisfactory [2] but a simple one-step process for converting aryl ketones into the methyl esters of the acids using thallium(III) salts has been developed.[3,4] In an earlier paper we elucidated the mechanism of this oxidative rearrangement.[1] We suggested that the process occurred in three discrete stages as shown in Scheme 1. First the electrophilic thallium(III) attacks the enol form of the ketone to give an organothallium species (1) which is too labile to be isolated. Then, under suitable conditions, (1) is converted into the acetal (2). Finally this species undergoes heterolysis to give the carbonium ion (3), or an incipient form of that ion, which then rearranges to give, after uptake of solvent followed by hydrolysis, the methyl ester (4).

We further argued that there was nothing unique about the role of thallium in the reaction. Any other reagent capable of functioning first as an electrophile and then as a good leaving group should be able to bring about a similar transformation. We found that the use of iodine or bromine, in the presence of silver nitrate, could give excellent yields of the ester (4) with less formation of by-products, providing an acetalising solvent was employed.†

There are problems in the use of highly toxic and expensive reagents such as thallium(III) salts for the synthesis of compounds to be used as pharmaceutical preparations.[5] The halogen–silver nitrate system, whilst employing a no less expensive metal salt, avoids the difficulties of toxicity. We have sought alternative, cheaper reagents and the results of these investigations are presented in this paper.



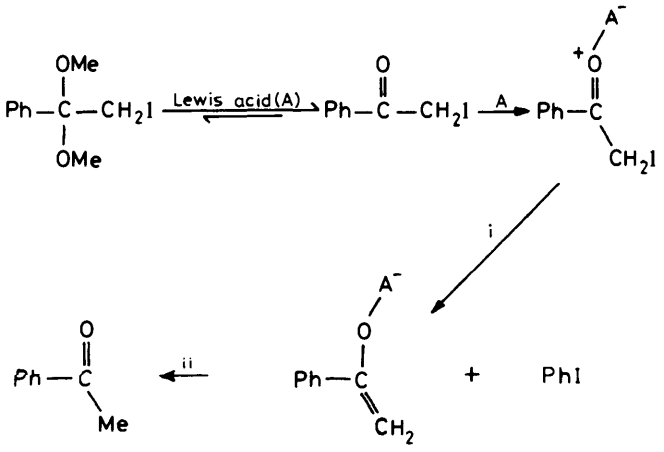
Scheme 1. *Reagents:* i, $Tl(NO_3)_3$; ii, H^+/MeOH or $HC(OMe)_3$; iii, $-TlNO_3$, $-NO_3^-$; iv, MeOH; v, H_2O

Results and Discussion

In the halogen–silver nitrate system the metal salt serves two functions. First, it polarises the halogen thus assisting electrophilic attack on the enol form of the ketone. This is essential if iodine is to be introduced but bromine is sufficiently reactive not to require a catalyst. Secondly the silver ion assists the solvolysis of the halogenoacetal (5; X = Br or I). In the absence of silver nitrate the halogenoacetals are recovered unchanged. Initially, therefore, we concentrated on alternative ways of effecting the displacement of the halogen.

In the reactions described above the silver ion is simply functioning as a Lewis acid. However, we were unable to effect rearrangement of compound (6), chosen as model substrate, using other Lewis acids in methanol. Neither boron trifluoride nor antimony pentafluoride were effective over long periods of time at room temperature. The only product obtained in both cases was phenacyl iodide. Under reflux, both with and without added trimethyl orthoformate, deiodination occurred to give acetophenone (*ca.* 60%). Similar results were obtained using aluminium trichloride in nitromethane and in benzene. In the latter solvent iodobenzene was produced in 28% yield. These Lewis acids would be expected

† In the experimental procedure given in ref. 1 it is essential that the reaction mixture be heated under reflux *with mechanical stirring*. If stirring is omitted the iodoacetal is not decomposed with rearrangement and complex mixtures of products can be obtained. We thank Prof. R. A. Raphael and Mr. R. Jackson for drawing our attention to this omission.



Scheme 2. *Reagents:* i, PhH, $-H^+$; ii, H_2O

to catalyse the acetalisation-deacetalisation processes but it appears thay they also displace the equilibrium by co-ordinating to the carbonyl oxygen of the ketone. The resultant complex then functions as a source of electrophilic halogen (Scheme 2). A similar displacement of halogen from phenacyl halides has been reported before.[6] Other potential acids proved equally unsuccessful in our hands.*

Our failure to find an alternative Lewis acid to silver ion prompted a different approach to the problem. Whilst this work was in progress Cambie *et al.* reported that iodoalkanes can be solvolysed much more readily in methanol when 3-chloroperbenzoic acid is included in the system.[8] We found that compound (6) undergoes ready rearrangement under these conditions giving methyl phenylacetate (67%), phenacyl iodide (19%), and unchanged starting material (9%). Cambie employed 2.2 equivalents of the peracid but we found much improved yields could be obtained using a greater excess. The use of 4.3 equivalents of peracid led to a 98% conversion of the acetal (6) into the ester (4; Ar = Ph, R = H) in 5 h at room temperature.

Whilst 3-chloroperbenzoic acid is a convenient peracid to use, much cheaper alternatives, notably peracetic acid, are available. Early experiments using 40% commercial peracetic acid were not successful. Deacetalisation of compound (6) to give phenacyl iodide occurred in near quantitative yield. The difficulty here proved to be the presence, in the commercial peracid, of 13% water and 0.7% sulphuric acid. Buffering the peracid with sodium acetate overcame the problem and high yields of rearranged ester were obtained. Representative examples of the rearrangement of iodoacetals are given in Table 1.

The oxidation of aryl iodides by peracids results in the formation of iodine(III) compounds [9] which are significantly more labile than their iodine(I) precursors, decomposing primarily by a heterolytic mechanism.[10] Presumably peracid oxidation of alkyl iodides also results in the formation of iodine(III) species [8,11] which, by analogy with the relative stabilities of aromatic and aliphatic diazonium ions, are likely to undergo spontaneous decomposition with production of a carbonium ion or an incipient version of that ion (Scheme 3).

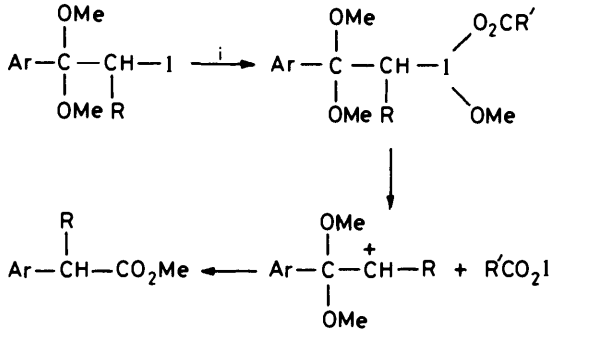
In theory only one equivalent of peracid should be required to oxidise the iodoacetal to the higher oxidation state. The need for a large excess of oxidant is, therefore, rather puzzling.

* A recent patent application [7] suggests that rearrangement may be achieved using weak Lewis acids such as copper oxide or zinc salts.

Table 1. The rearrangement of iodoacetals (5; X = I) to methyl α-arylalkanoates (4) by peracids in methanol

Substrate (5; X = I)		Peracid [a] (mol	Time	Temp.	Yield of (4)
Ar	R	equiv.)	(h)	(°C)	(%)
Ph	H	B (4.3)	5	20	98
Ph	H	A (4.2)	72	20	73
Ph	H	A (6.2)	48	20	95
Ph	H	A (6.2)	18	50	98
Ph	Me	A (6.2)	18	20	95
2-(2,4-$Cl_2C_6H_3O$)C_6H_4	H	B (4.2)	18	20	95
2-(2,4-$Cl_2C_6H_3O$)C_6H_4	H	A (6.2)	48	50	94

[a] A is 40% peracetic acid containing 1.5% sodium acetate; B is 3-chloroperbenzoic acid.



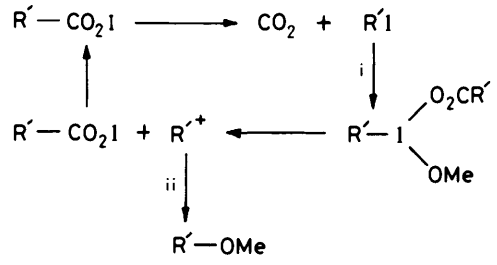
Scheme 3. *Reagents:* i, $R'CO_3H$, MeOH

It cannot be that alternative modes of reaction occur on the substrate or we should not obtain such high conversions. It is possible that the peracid may react with methanol, though similar results were obtained when the solvent was changed to dichloromethane. This excessive consumption of peracid has been noted before [8,12,13] and the suggestion made, in the case of peracetic acid, that iodomethane resulting from homolytic decomposition of the co-product, iodine acetate (7), reacts with the oxidant [11] (Scheme 4). In attempting to reduce the amount of oxidant required we tried replacing the peracid by hydrogen peroxide but found that no reaction occurred, the acetal (6) being recovered unchanged.

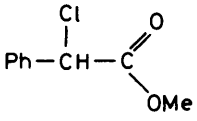
The relative labilities of organic diacetoxyiodosyl compounds (alkyl > alkenyl > aryl) [9,14,15] is mirrored by their dichloroiodosyl analogues.[9] Dichloroiodosylbenzenes can readily be made by passing chlorine through an ice-cold solution of an aryl iodide in an inert solvent.[16] Stable dichlorides of iodoalkenes have been prepared in a similar way,[14] but the only saturated analogue reported is that from iodomethane, synthesised at -196 °C. At -30 °C it decomposed to give chloromethane. We therefore investigated the feasibility of employing chlorine as the oxidant.

Passing chlorine through ice-cold solutions of the acetal (6) in methanol or chlorinated solvents resulted in trivial amounts of methyl phenylacetate. Instead two products, (8) and (9), predominated. Typically, in chloroform, these were formed in 74 and 22% yield, respectively. The production of phenacyl chloride implies that deacetalisation is occurring during the course of the reaction. This was avoided by adding trimethyl orthoformate to the solvent, when the ester (8) was obtained in 94% yield.

In forming compound (8), rearrangement has certainly been effected but α-chlorination has also occurred. In attempts to limit this unwanted side-reaction, different conditions were



Scheme 4. *Reagents:* i, $R'CO_3H$, MeOH; ii, MeOH



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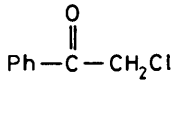

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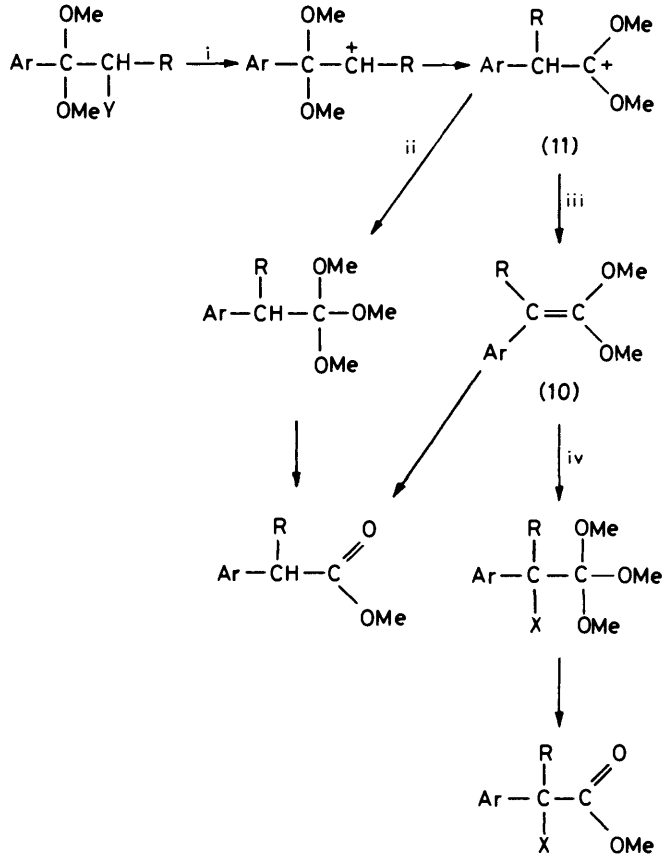
employed. Reduction of the amount of chlorine used, the exclusion of light from the system, and variations in the temperature had no effect upon the product distribution. Further chlorination of methyl phenylacetate is not the cause of the problem. This ester was unaffected by chlorine, iodine monochloride, or iodine trichloride under the reaction conditions.

The problem clearly resembles that of the α-methoxylation encountered in thallium(III) and iodine–silver nitrate oxidations of acetophenone. In the former process the intermediate leading to α-substitution has been suggested to be the keten acetal (10; Ar = Ph) (Scheme 5). Whether or not this side reaction can be controlled appears to depend on the relative rates of oxidation of the starting ketone and decomposition of the intermediate acetal [5; X = halogen or $Tl(NO_3)_2$]. In the iodine–silver nitrate system the latter process is always the slower and the side reaction can be eliminated by ensuring that no more than one equivalent of oxidant is employed. With thallium(III) the first step is often rate determining and α-substitution cannot, therefore, be controlled. When chlorine oxidises the acetal (6) it would appear that either halogen attack on (6) is slower than on the keten acetal (10; Ar = Ph, R = H) and the rearranged carbonium ion (11; Ar = Ph, R = H) reacts solely by loss of a proton, or, possibly, that the orthoformate is in equilibrium with the keten acetal.

This problem of α-substitution is not experienced in thallium(III) reactions when propiophenone or isobutyrophenone are the starting materials, a result which McKillop ascribed to increased steric hindrance in the second electrophilic attack by thallium(III).[4] We found that similar results were obtained in the chlorine oxidation of (5; X = I). Providing R ≠ H, rearrangement occurs to give the unsubstituted ester (4) in high yield. Representative examples of this conversion are shown in Table 2.

The chlorine route, limited as it is by the failure of acetophenones to give simple products, nevertheless has one very attractive feature. The conversion of arylalkanones into α-arylalkanoic esters can be made catalytic in iodine, chlorine being the effective oxidant (Scheme 6). The iodine is eliminated from (5; X = I) as iodine monochloride and this reagent is sufficiently polarised to iodinate arylalkanones. Thus excellent yields of ester have been obtained by warming suitable ketones for 1 h with iodine monochloride in methanol containing trimethyl orthoformate, cooling to 0 °C, and adding chlorine either as a gas or predissolved in a solvent, the latter procedure having the considerable advantage that



Scheme 5. *Reagents:* i, $-Y^-$; ii, MeOH, $-H^+$; iii, $-H^+$; iv, 'X^+'/MeOH

Table 2. The conversion of iodoacetals (5; X = I) and ketones ($ArCOCH_2R$) to methyl α-arylalkanoates by chlorine or iodine–chlorine in methanol–trimethyl orthoformate at 0 °C

Substrate		Time	Yield of (4)
Ar	R	(min)	(%)
Ph	H[a]	10	94[c]
Ph	Me[a]	10	92
Ph	Et[b]	10	93
4-Bu^{t}C$_6$H$_4$	Me[b]	5	98
4-(2-FC$_6$H$_4$)C$_6$H$_4$	Me[b]	5	87
2-(4-ClC$_6$H$_4$)-benzoxazol-5-yl	Me[b]	10	97

[a] Starting material:iodoacetal. [b] Starting material: ketone. [c] Product: methyl α-chlorophenylacetate.

the amount of chlorine employed can be controlled. Iodine can be recovered from the system or, alternatively, providing excess of chlorine has not been employed, fresh ketone can be added.

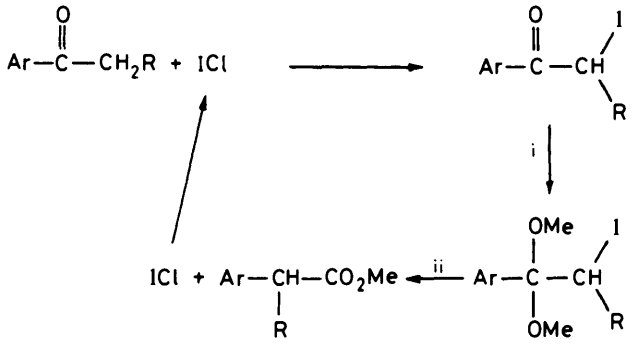
One further method of generating the critical carbonium ion (3) was investigated. Aliphatic diazonium ions, which may be made from the corresponding amines, decompose spontaneously, the products being typical of those expected from a carbonium ion.[17] We argued that treatment of an aminoacetal such as (12) with nitrite ions under acidic conditions ought to lead to methyl phenylacetate. The problem proved to be the synthesis of (12). All attempts at acetalising α-aminoacetophenone were ineffective. Under acid conditions the aminoketone was recovered unchanged, whilst under

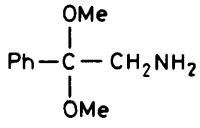
neutral conditions the self-condensation product (13) was obtained.[18,19]

For most substrates the Neber rearrangement of oxime toluene-*p*-sulphonates to aminoacetals is unsatisfactory since, with electron-donating groups such as phenyl, Beckmann rearrangement is a competitive process.[19] The Gabriel synthesis [20] from phenacyl bromide, however, proved to be a satisfactory route to compound (12) and a number of its analogues. Reaction with potassium phthalimide and acetalisation followed by reduction with hydrazine hydrate in methanol gave an 81% yield of (12) overall.[21] This method failed at the acetalisation stage with one or two substrates, notably the ketone (14), presumably for steric reasons. Support is provided for this hypothesis by the fact that the acetal (15) was eventually synthesised by catalytic hydrogenation of the azide (16) (Scheme 7), no difficulty being experienced in acetalizing the azidoketone. However we believe that the most attractive route industrially to aminoacetals such as (17) is *via* high pressure amination of halogenoacetals [22] (Scheme 8, X = halogen).

Initial experiments aimed at diazotising the acetal (15) by passing dry hydrogen chloride through cold solutions of the amine and isopentyl nitrite in methanol or methanol–trimethyl orthoformate proved disappointing. A range of products were obtained of which rearranged esters made up a very small proportion (<8%). When the hydroxylic solvents were omitted from the system a violent reaction occurred and an 83% yield of methyl and isopentyl phenylacetates was obtained (ratio *ca.* 1 : 2). The reaction could be moderated by dilution with dichloromethane and by cooling to 0 °C, and even higher yields of ester then resulted (96% in the ratio 5 : 4).

Alkyl nitrites, whilst valuable sources of *in situ* nitrosonium ions, are relatively expensive reagents. The preferred source of the ion is sodium nitrite. Whilst this salt is insoluble in most organic solvents it will dissolve in acetic acid. The earlier work with peracids had shown that acetic acid is too weak an acid to cause significant deacetalisation. Thus, when compound (12) was added to 1.2 equivalents of sodium nitrite in cold acetic acid, a 91% yield of ester (4) was obtained. That the reaction is general is shown by the similar yield of rearranged ester obtained when the acetal (15) was employed as substrate.





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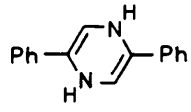

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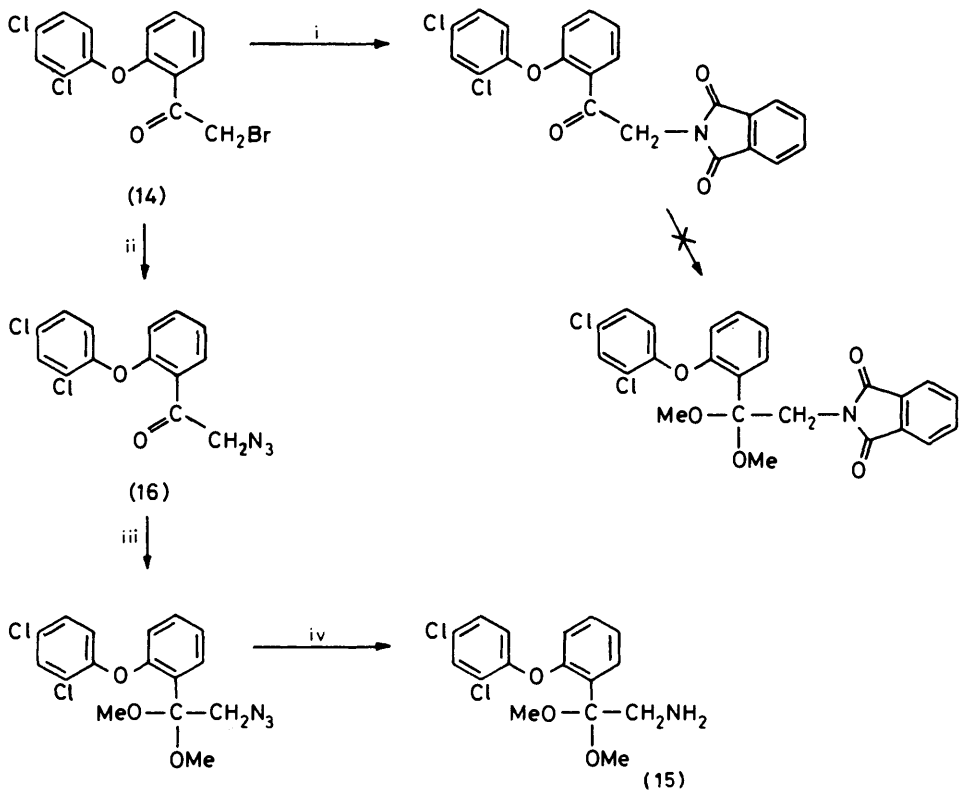
Scheme 6. *Reagents:* i, $HC(OMe)_3$; ii, Cl_2

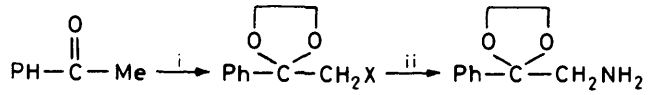


Scheme 7. *Reagents:* i, phthalimide; ii, N_3^-; iii, $HC(OMe)_3/H^+$; iv, H_2–Pd

Table 3. Analytical data for some 1-aryl-2-iodo-1,1-dimethoxyalkanes [$XC_6H_4C(OMe)_2CHIR$]

			^1H N.m.r. (δ)			
X	R	B.p. or m.p. (°C)	ArH	OMe	CHI	R
H	Me	80—85 at 0.09 mmHg [a]	7.17—7.63	3.15 and 3.31	4.60 (q)	1.76 (d)
2-(2,4-$Cl_2C_6H_3O$)	H	87—88.5 [b]	6.58—7.98	3.32	3.94	

a Found: C, 43.0; H, 5.1. $C_{11}H_{15}IO_2$ requires C, 43.15; H, 4.94%. [b] Found: C, 43.1; H, 3.25. $C_{16}H_{15}Cl_2IO_3$ requires C, 42.38; H, 3.31%.



Scheme 8. *Reagents:* i, X_2, $HOCH_2CH_2OH$; ii, NH_3, pressure

Conclusions

All three of the routes to α-arylalkanoate esters reported in this paper offer advantages over the original thallium(III) method. The reagents are very much cheaper and less toxic than thallium(III) but are somewhat less convenient than the 'single-pot' reaction. The iodine–chlorine route comes closest to this ideal in that, whilst it is a two-stage process, isolation of an intermediate is not required. It also has the extra advantage that the iodine can be employed catalytically. The main drawback is that, like thallium(III) oxidations, some substrates result in products in which α-substitution has occurred.

Experimental

The analytical procedures and many of the authentic materials have been described previously.[1] 3-Chloroperbenzoic acid (Aldrich) and peracetic acid (Laporte) were commercial samples whose purity was checked before use by the method of McDonald *et al.*[22]

Methyl Chloro(phenyl)ethanoate (8).—This was prepared by the method of Eliel *et al.*[23] and had b.p. 102—104 °C at 2 mmHg (lit.,[23] 134—136 °C at 15 mmHg); δ 3.73 (3 H, s, OMe), 5.37 (1 H, s, CHCl), and 7.21—7.66 (5 H, m, ArH).

1,1-*Dimethoxy*-2-*iodo*-1-*arylalkanes*.—These were prepared from the corresponding ketones by the method previously employed.[1] Analytical data on these compounds is given in Table 3.

2-*Amino*-1,1-*dimethoxy*-1-*phenylethane* (12).—1-Phenyl-2-phthalimidoethanone was prepared by the method of Sheehan and Bolhofer[20] and had m.p. 166—166.5 °C (lit.,[21] 165—167 °C); δ 5.17 (2 H, s, CH_2) and 7.29—8.20 (9 H, m, ArH). This compound (15 g) was acetalised by heating under reflux for 18 h in methanol (150 ml) containing trimethyl orthoformate (20 ml) and toluene-*p*-sulphonic acid (1 g). The resultant solution was poured into 10% sodium carbonate solution, extracted with chloroform, and dried ($MgSO_4$). Removal of the solvent gave 1,1-*dimethoxy*-1-*phenyl*-2-*phthalimidoethane* (17 g, 88%) as a white solid, m.p. 139—141 °C (from chloroform–trimethyl orthoformate); δ_H 3.37 (6 H, s, OMe), 4.10 (2 H, s, CH_2), 7.15—7.60 (5 H, m, ArH), and 7.72 (4 H, s, phthalimido ArH); δ_C 42.36 (CH_2), 49.35 (OMe), 102.18 [Ar*C*$(OMe)_2$], 122.96, 127.34, 127.66, 128.15, 131.56, 133.67, 138.06 (ArC), and 167.20 p.p.m. (CO); *m/z* 311 (2%, $M^{+\cdot}$), 280 (12, *M* − OMe), 248 (9, *M* − OMe − MeOH), 236 (7), 160 [9, *M* − $PhC(OMe)_2$], 151 [100, $PhC(OMe)_2^+$], 105 (44, $PhCO^+$), 91 (15, $PhCH_2$), and 77 (30, $C_6H_5^+$) (Found: C, 69.25; H, 5.4; N, 4.45. $C_{18}H_{17}NO_4$ requires C, 69.45; H, 5.46; N, 4.50%).

When subjected to reduction with hydrazine following the method of Bornstein *et al.*[21] 1,1-dimethoxy-1-phenyl-2-phthalimidoethane (5 g) gave 2-*amino*-1,1-*dimethoxy*-1-*phenylethane* (3.1 g, 93%) as a colourless liquid, b.p. 66—68 °C at 0.3 mmHg; δ_H 0.93 (2 H, s, removed by D_2O, NH_2), 2.99 (2 H, s, CH_2), 3.22 (6 H, OMe), and 7.32—7.75 (5H, m, ArH); δ_C 46.91 (CH_2), 48.78 (OMe), 103.56 [Ar*C*$(OMe)_2$], 127.18, 127.91, 128.08, and 130.28 p.p.m. (ArC); *m/z* 151 (100% $M - CH_2NH_2$), 134 (10, $PhCOCHNH_2$), 118 (23, *M* − MeO − MeOH), 105 (60, $PhCO^+$), 91 (38, $PhCH_2^+$), and 77 (67, $C_6H_5^+$) (Found: C, 66.1; H, 3.4. $C_{10}H_{15}NO_2$ requires C, 66.27; H, 3.43%).

2-*Amino*-1-[2-(2,4-*dichlorophenoxy*)*phenyl*]-1,1-*dimethoxyethane* (15).—2-Bromo-1-[2-(2,4-dichlorophenoxy)phenyl]-ethanone (14) (30 g) was converted into 2-*azido*-1-[2-(2,4-*dichlorophenoxy*)*phenyl*]*ethanone* (16) (19.5 g, 72.8%) following the method of Hromatka and Skopalik.[24] The white solid had m.p. 79.5—80 °C (from ethanol); δ_H 4.66 (2 H, s, CH_2N_3) and 6.66—8.19 (7 H, m, ArH); δ_C 59.17 (CH_2N_3), 115.98, 122.72, 123.69, 125.56, 127.26, 128.56, 130.91, 131.32, 134.80, 148.85, 156.40 (ArC), and 193.49 p.p.m. (CO) (Found: C, 52.05; H, 2.8; N, 12.9. $C_{14}H_9Cl_2N_3O_2$ requires C, 52.20; H, 2.82; N, 13.04%).

Acetalisation of this azide in the same way as for the preparation of halogenoacetals[1] gave 2-azido-1-[2-(2,4-dichlorophenoxy)phenyl)]-1,1-dimethoxyethane (43.5%) after purification of the crude product by column chromatography [silica gel 60, diethyl ether–light petroleum (b.p. 40—60 °C) (1 : 8) as eluant]; δ 3.25 (6 H, s, OMe), 3.94 (2 H, s, CH_2), and 6.63—8.02 (7 H, m, ArH); *m/z* 343/341/339 (0.1/0.5/1%, $M - N_2$) and 315/313/311 (10/66/100, $M - CH_2N_3$). The acetalised azide (1.3 g) and 10% palladium-on-charcoal (0.5 g) were shaken in methanol (15 ml) under hydrogen (1 atm) for 18 h. The resulting mixture was filtered, poured into 5% aqueous sodium carbonate, extracted with diethyl ether and dried ($MgSO_4$). Removal of the solvent gave a yellow oil which was purified by column chromatography [silica gel 60, methanol–dichloromethane (1 : 9) as eluant] to give 2-*amino*-1,1-*dimethoxy*-1-[2-(2,4-*dichlorophenoxy*)*phenyl*]*ethane* (0.67 g, 56%) as a viscous oil; δ 1.10 (2 H, br s removed by D_2O, NH_2), 3.19 (2 H, s, CH_2NH_2), and 3.21 (s, OMe) (total 8 H), and 6.60—7.93 (7 H, m, ArH); *m/z* 315/313/311 (1/6/10%, $M - CH_2NH_2$), 279/277 (30/100, $M - CH_2NH_2 - Cl$ (Found: C, 56.0; H, 4.9; N, 4.0. $C_{16}H_{17}Cl_2NO_3$ requires C, 56.16; H, 5.00; N, 4.09%).

3-*Methylbutyl Phenylethanoate*.—Phenylethanoic acid (10 g) was heated under reflux in 3-methylbutan-1-ol (50 ml) containing dry hydrogen chloride (5 g) for 18 h. The mixture was poured into saturated sodium carbonate solution, extracted with diethyl ether, and dried ($MgSO_4$). Removal of the

solvent followed by distillation of the residue gave 3-methylbutyl phenylethanoate (11.3 g, 73.5%) as a colourless liquid, b.p. 94—95 °C at 0.6 mmHg, δ 0.9 (d, *J* 6 Hz, Me) and 1.1—1.9 (m, CH_2CHMe_2) (total 9 H), 3.60 (2 H, s, $PhCH_2$), 4.17 (2 H, t, *J* 6 Hz, OCH_2), and 7.31 (5 H, s, ArH).

Oxidation of Iodoacetals with Peracids.—The general procedure for peracid oxidations was as follows. The 1-aryl-2-iodo-1,1-dimethoxyalkane (1 g) and the desired amount of 3-chloroperbenzoic acid were dissolved in methanol or in dichloromethane (30 ml) and left at room temperature for the appropriate period of time. The mixture was poured into 10% sodium carbonate solution, the organic layer separated or the solution extracted with dichloromethane (methanol systems), washed with sodium thiosulphate solution and dried ($MgSO_4$). The solvent was evaporated and the product analysed in the manner described previously.[1] When peracetic acid was employed the system was buffered with sodium acetate (1.5% of peracid).

Oxidation of Iodoacetals with Chlorine.—The following general procedure was adopted. 2-Iodo-1,1-dimethoxy-2-phenylalkane (1 g) in chloroform or methanol–trimethyl orthoformate (30 ml) was cooled in a darkened reaction vessel. Chlorine gas was passed through the solution for up to 15 min or a predetermined amount of chlorine dissolved in an appropriate solvent was added, the solution poured into water, extracted with diethyl ether or dichloromethane and dried ($MgSO_4$). The solvent was removed and the products analysed in the usual way.

In some experiments the starting material was the ketone rather than the iodoacetals. The ketone was refluxed with iodine monochloride (1.00 g) in methanol containing trimethyl orthoformate, cooled to 0 °C, and chlorine added to the solution either as a gas or a solution in dichloromethane. Analysis then proceeded normally.

Diazotisation of 2-Amino-1-phenylethanone Hydrochloride.—2-Amino-1-phenylethanone hydrochloride (1.3 g) in methanol (20 ml) and trimethyl orthoformate (10 ml) was cooled to −5 °C and dry hydrogen chloride passed in for 10 min. 3-Methylbutyl nitrite (2.5 ml) was added to the solution in a dropwise manner, left for 1 h, and allowed to warm to room temperature. After 18 h the solution was poured into water, extracted with diethyl ether, the extracts dried ($MgSO_4$), and the solvent removed to give 1,4-dihydro-2,5-diphenylpyrazine (0.16 g) as a solid, m.p. 162—164 °C (lit.,[25] 164 °C). A further 0.79 g was isolated from the aqueous solution on basification.

Diazotisation of 2-Amino-1-aryl-1,1-dimethoxyethanes with 3-Methylbutyl Nitrite and Hydrogen Chloride.—The 2-amino-1-aryl-1,1-dimethoxyethane (1 g) and 3-methylbutyl nitrite (3 equiv.), either with or without a solvent (20 ml), were cooled to −5 °C, then **with great caution** dry hydrogen chloride was passed into the mixture for 20 min, and the mixture left for 18 h at room temperature. The solution was poured into water, extracted with dichloromethane, the extracts dried ($MgSO_4$), and the solvent removed. Analysis was then effected in the usual manner.

Diazotisation of 2-Amino-1-aryl-1,1-dimethoxyethanes with Sodium Nitrite in Acetic Acid.—Sodium nitrite (1.2 equiv.) was added during 45 min to a stirred solution of the 2-amino-1-aryl-1,1-dialkoxyethane (1 g) in acetic acid (20 ml). After 18 h the mixture was poured into water, extracted with diethyl ether, the extracts dried ($MgSO_4$), and the solvent removed. The crude product was analysed in the usual manner.

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