Oxidative Rearrangement of Aryl Ethyl Ketones to Alkyl 2-Arylpropanoates by Lead(IV) Acetate

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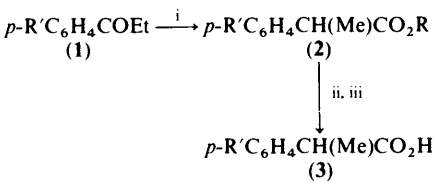
Treatment of the propiophenones *p*-R′$C_6H_4COCH_2Me$ (**1**; R′ = H, Me, Bu^i, Ph, Br) with lead(IV) acetate in trialkyl orthoformate in the presence of acid catalyst is found to give alkyl esters of 2-arylpropanoic acids (**2**) in good to excellent yields *via* 1,2-aryl migration in (**1**). Hydrolysis of (**2**) leads to the corresponding acids, some of which are important pharmaceutical compounds. The rate of aryl migration increases when the substituent R′ is an electron-releasing group such as methyl, isobutyl, or phenyl. The rate of rearrangement of the dimethyl acetals of (**1**; R′ = H, Bu^i, Ph) is nearly the same as that of (**1**). Such rearrangement hardly occurs in the absence of acid catalyst. A reaction pathway involving the formation of a monoalkoxylead(IV) compound, and its decomposition accompanied with aryl migration is discussed.

Some of the 2-arylalkanoic acids are known to be important pharmaceutical agents exhibiting anti-inflammatory and analgesic activity.[1] Many synthetic preparations reported[2] for such acids, involve a useful oxidative rearrangement of alkyl aryl ketones by thallium(III) nitrate trihydrate (TTN).[3-5]

Lead(IV) salts often show similar reactivities to thallium(III) and mercury(II) salts in the oxidation of organic compounds.[6-8] Indeed, Myrboh *et al.*[9] have reported that treatment of acetophenones with lead(IV) acetate and boron trifluoride–diethyl ether in benzene–methanol give methyl arylacetates in high yield *via* the oxidative rearrangement of the aryl group. We now report the application of this rearrangement to propiophenones for the preparation of 2-arylpropanoic acids. Trimethyl orthoformate and perchloric acid used as solvent and acid catalyst, respectively ensure good to excellent yields. Preliminary results have been reported.[10]

Results and Discussion

The reaction was generally carried out by stirring aryl ethyl ketone (**1**) and lead (IV) acetate (LTA) in a suitable solvent in the presence of acid at 25—50 °C for 2—4 h. The major product was the alkyl 2-arylpropanoate (**2**) which is formed *via* the 1,2-migration of the aryl group. Alkaline hydrolysis of (**2**) gave the corresponding acid (**3**) as shown in Scheme 1. By using ethyl 4′-isobutylphenyl ketone (**1**) (R′ = Bu^i) as a substrate the effect of various solvents and acid catalysts upon the yield of organic ester (**2**) was examined. The solvents employed include methanol, ethyl acetate, trimethyl orthoformate (TMOF), triethyl orthoformate (TEOF), triethyl orthoacetate (TEOA), triethyl orthopropionate (TEOP), and diethyl carbonate (DEC), whilst the acids examined include toluene-*p*-sulphonic acid (PTS), boron trifluoride–diethyl ether (BF_3·Et_2O), and perchloric acid ($HClO_4$). Results are summarized in Table 1.



Scheme 1. *Reagents:* i, $Pb(OAc)_4/H^+$, solvent; ii, aq.NaOH; iii, aq. HCl.

Table 1. Oxidative rearrangement of ethyl 4′-isobutylphenyl ketone (**1**) under various reaction conditions[a]

LTA[b] (mmol)	Solvent[c] (ml)	Acid[c] (mmol)	React. temp. (°C)	React. time (h)	Yield[d] (**2**; R′ = Bu^i) (%)	Yield[d] (**1**; R′ = Bu^i) (%)
5	TMOF (55)	70% $HClO_4$ (5)	50	2	85	1
5	TMOF (55)	—	50	2	0	98
5	TMOF (55)	70% $HClO_4$ (10)	50	2	87 (73)[e]	2
10[f]	TMOF (10)	70% $HClO_4$ (10)	25	20	55	29
2[f]	TEOF (55)	70% $HClO_4$ (4)	25	25	1	98
6.1	TMOF (50)	PTS (12.2)	25	4	83	9
5	TMOF (55)	PTS (10)	50	2	42	48
5	TMOF (55)	BF_3·Et_2O (10)	50	2	32	45
5	TEOF (55)	70% $HClO_4$ (10)	50	2	93 (85)[e]	2
5	TEOA (55)	70% $HClO_4$ (10)	50	2	0	96
5	TEOP (55)	70% $HClO_4$ (10)	50	2	0	95
5	DEC (55)	70% $HClO_4$ (10)	50	2	0	95
5	EtOAc (55)	70% $HClO_4$ (10)	50	2	1	95
5	MeOH (55)	70% $HClO_4$ (10)	50	2	0	97

[a] (**1**; R′ = Bu^i) 5 mmol. [b] $Pb(OAc)_4$. [c] For abbreviation see the text. [d] Determined by g.l.c.; advance DS FFS 0.24 mm × 30 m capillary column at 190 °C. [e] Isolated yield. [f] (**1**; R′ = Bu^i) 10 mmol.

Table 2. Oxidative rearrangement of aryl ethyl ketones (**1**)[a]

Compd. (**1**) R′	Solvent	Yield[b] of (**1**) (%)	Yield[b] of (**2**) (isolated) (%)	B.p. (°C/Torr)	Molecular formula or lit. b.p. (°C/Torr)
H	TMOF	6	78(70)	104—106/18	98—100/12[20]
Bu^i	TMOF	1	73(68)	104—106/1.0	$C_{13}H_{18}O_2$ (206.3)
Bu^i	TEOF	2	88(81)	105—107/0.9	107/1[21]
Ph	TMOF	0	91(88)	142—145/0.3	$C_{16}H_{16}O_2$ (240.3)
Ph	TEOF	3	93(89)	161—162/0.3	$C_{17}H_{18}O_2$ (254.3)
Me	TMOF	3	85(81)	111—112/13	$C_{11}H_{14}O_2$ (178.2)
Br	TMOF	25	68(65)	—	—

[a] (**1**) 50 mmol, LTA 50 mmol, 70% $HClO_4$ 50 mmol, solvent 50 ml; reaction temperature 50 °C, reaction time 2 h. [b] Determined by g.l.c.; 0.6% EGA Chromosorb G(HP), 3 mm × 1 m column at 150 ⟶ 220 °C (5 °C/min); yield based on the starting compound (**1**).

Table 3. Oxidative rearrangement of aryl ethyl ketones (**1**) and their acetals (**6**)

Compound[a] (**1**) or (**6**)	Solvent (ml)	70% $HClO_4$ (mmol)	LTA (mmol)	React. time[b] (h)	Yield[c] of (**2**) (%)	Yield[c] of (**1**) (%)
(**1**; R′ = H)	TMOF (10)	10	10	30	62	25
(**6**; R′ = H)	TMOF (10)	10	10	30	63	18
(**1**; R′ = Bu^i)	TEOF (55)	10	10	25	53	29
(**6**; R′ = Bu^i)	TMOF (10)	10	10	20	60	23
(**6**; R′ = Bu^i)	TEOF (55)	0	10	25	0	97
(**1**; R′ = Ph)	TMOF (10)	10	10	20	72	18
(**6**; R′ = Ph)	TMOF (55)	10	10	20	76	17

[a] (**1**) or (**6**), 10 mmol. [b] Reaction temperature 25 °C. [c] Determined by g.l.c.; 1.5% SE-30 on Chromosorb W (AW, DMCS) 3 mm × 1.1 m (G) column at 150 ⟶ 220 °C (5 °C/min).

As can be seen from Table 1, TMOF or TEOF was the solvent of choice and perchloric acid was the best acid catalyst. However, even in the presence of TMOF or TEOF reaction did not occur without the addition of perchloric acid. Thus, the combination of TMOF or TEOF and perchloric acid was necessary to obtain a high yield of the desired ester (**2**; R′ = Bu^i). The solvent TMOF or TEOF also serves as a source of an alkoxy group, OR (R = Me, Et). Compound (**4**) was formed as a side-product (1—5% yield), and the formation of a trace amount (0.2%) of compound (**5**) was detected by g.l.c. in the

p-Bu^{i}C$_6$H$_4$COCH(Me)OR
(**4**) R = Ac
(**5**) R = Et

oxidation reaction using TMOF as solvent. One reason for the ineffectiveness of solvents other than TMOF and TEOF for oxidative rearrangement is that the solvents themselves are readily oxidized by LTA in the presence of acid catalyst. Thus, almost all the lead(IV) was reduced to lead(II) after 10 min at 50 °C in methanol, TEOA, TEOP, and DEC, although the oxidation products could not be identified.

Myrboh *et al.*[9] obtained high yields of rearrangement products on treating acetophenones with LTA and boron trifluoride–diethyl ether in benzene–methanol. Our work confirms their results, an 88% yield of a rearranged product, thus, being obtained from acetophenone. However, when these reaction conditions were applied to ethyl 4′-isobutylphenyl ketone (**1**; R′ = Bu^i), the expected organic ester was formed in only 5% yield, 29% of the ketone being recovered unchanged.

Since the oxidation of (**1**) proceeded well to give (**2**) in TMOF or TEOF in the presence of perchloric acid at 50 °C for 2 h, this oxidation system was applied to various propiophenones; the results of these reactions are summarized in Table 2. The yields of rearranged products were generally very high, especially when the substituent R′ is an electron-releasing group such as methyl, isobutyl, or phenyl. This tendency is similar to that observed in silver salt-mediated[11,12] and thallium(III) nitrate-mediated[5] synthesis of alkyl esters of 2-arylpropanoic acids from aryl 1-halogenoethyl ketones.

Table 4. Oxidative rearrangement of acetophenones (**7**)[a]

Compd. (**7**) R′	Solvent	React. temp. (°C)	React. time (h)	Yield (%)[b] (**8**)	Yield (%)[b] (**7**)
H	TMOF	50	2	46	0
H	TMOF	−12	20	46	20
H	MeOH	50	2	1	93
Me	TMOF	50	2	46	0
OMe	TMOF	50	2	52	0
Br	TMOF	50	2	41	0

[a] (**7**) 5 mmol, LTA 5 mmol, 70% $HClO_4$ 10 mmol, solvent 55 ml. [b] Determined by g.l.c.; 3% FFAP on Chromosorb W (AW, DMCS) 3 mm × 2 m column at 100 ⟶ 200 °C (5 °C/min): yield based on the starting compound (**7**).

Similar, acid-catalysed rearrangements also occurred with the dimethyl acetals of the propiophenones (**6**) (Scheme 2, Table 3). As shown in the Table, use of the acetals failed to increase the product yields which are almost identical with those from the ketones (**1**).

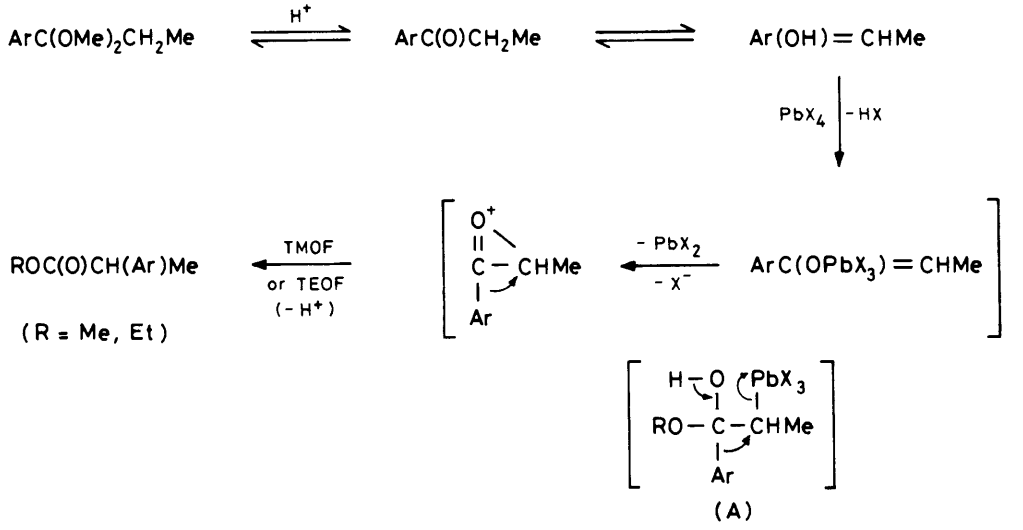
(**1**) or *p*-R′C$_6$H$_4$C(OMe)$_2$Et (**6**) $\xrightarrow[\text{in TMOF or TEOF}]{Pb(OAc)_4/H^+}$ *p*-R′C$_6$H$_4$CH(Me)CO$_2$R (**2**)

Scheme 2.

This oxidative rearrangement system can also be applied to other acetophenones (**7**), but yields of the corresponding methyl arylacetates (**8**) are lower (40—57%) than with the propiophenones (Scheme 3, Table 4). In methanol almost no reaction was observed.

p-R′C$_6$H$_4$Ac (**7**) $\xrightarrow[\text{TMOF}]{Pb(OAc)_4, H^+}$ *p*-R′C$_6$H$_4$CH$_2$CO$_2$Me (**8**)

Scheme 3.



Scheme 4.

Table 5. Preparation of 2-arylpropanoic acids (**3**)

Compound (**2**)		Yield of (**3**) (%)		M.p. (°C)	Molecular formula or lit. m.p. (°C)
R′	R	By g.l.c.[a]	Isolated		
H	Me	96	75	15—16	15—16.5[22]
Bu^i	Me	93	87	75—76	75—77[5]
Bu^i	Et	95	88		
Ph	Me	85	76	146—146.5	146—146.5[5]
Ph	Et	84	75		
Me	Me	96	76	36—37	36—37[5]
Br	Me	95	75	72—72.5	$C_9H_9BrO_2$ (229.1)[b]

[a] See Experimental section. [b] Found: C, 47.2; H, 3.9. Calc. for: C, 47.2; H, 4.0%.

To conclude, the following points can be stated (i) a strong acid, such as perchloric acid, is required for the rearrangement reaction of propiophenones or their acetals. The acid functions as a catalyst for the rapid enolization of the ketone and as a reagent responsible for the formation of the strong electrophilic lead species $Pb(OAc)_{4-n}(ClO_4)_n$.[7,13] (ii) Solvents of low dielectric constant such as TMOF or TEOF are favoured for the reaction.[14,15] Their ability to induce acetalization, however, plays no part in the reaction since product yields could not be improved appreciably by the use of acetals as starting materials. The solvents TMOF or TEOF also act as a source of an alkoxy group. (iii) Lead(IV) salt was reduced completely to lead(II) salt. Thus we can deduce from these observations that lead(IV) oxidizes the enol to give the product ester and lead(II) species. By analogy with the rearrangement of arylmethanols with $Pb(OAc)_4$,[13,16,17] we propose a reaction pathway *via* a monoalkoxylead(IV) compound which decomposes with aryl migration as shown in Scheme 4. However, the pathway *via* alkoxyplumbiation of the enol to give an unstable organolead intermediate such as (**A**) cannot be ruled out. The alkoxyplumbiation mechanism has previously been proposed for the oxidation of alkenes.[7,13]

Experimental

^{1}H N.m.r. spectra were recorded with a JEOL FX-90Q (90 MHz) instrument and refer to solutions in $CDCl_3$ with Me_4Si as an internal standard. Gas chromatography were carried out with a Shimadzu GC-7AS apparatus using biphenyl, triphenylmethane, or benzyl benzoate as internal standard.

Propiophenones (**1**; R′ = H, Me, Br), solvents, and inorganic materials were commercial products of the purest standard. Compounds (**1**; R′ = Ph),[18] (**1**; R′ = Bu^i),[19] and (**6**; R′ = H, Bu^i, Ph)[10] were prepared by reported methods.

General Procedure for Oxidation of the Propiophenones (**1**) *with Lead*(IV) *Acetate.*—Lead(IV) acetate (2.47 g, 10 mmol; purity 89.7%) was added to an homogeneous solution of each propiophenone (**1**) (5 or 10 mmol) in a mixture of solvent (10—15 ml) and 70% perchloric acid (10 mmol). The mixture was stirred at 25—50 °C for 2—30 h after which the solvent was distilled off under reduced pressure and chloroform (60 ml) was added to the residue. The precipitated solid of lead(II) acetate was filtered off and the filtrate was washed with water (20 ml × 2), dried (Na_2SO_4), and evaporated under reduced pressure. The yield of (**2**) was determined by g.l.c. analysis using an internal standard; triphenylmethane or biphenyl for (**1**; R′ = H, Me, Bu^i, Br) and benzyl benzoate for (**1**; R′ = Ph) (see Tables 1 and 2). To isolate (**2**) the reaction was scaled up five times; distillation afforded the product as a colourless liquid.

Oxidation of (**6**) and acetophenones was similarly carried out.

The stability of LTA in a solvent was examined as follows. LTA (10 mmol) was added all at once to a mixture of solvent (55 ml) and 70% perchloric acid (10 mmol) and the mixture was stirred at an appropriate temperature for an appropriate time. The amount of lead(IV) salt in the mixture was determined by iodimetry at appropriate time intervals.

Alkaline Hydrolysis of Alkyl 2-Arylpropanoates (**3**).—The alkaline hydrolysis of (**2**) to free acids (**3**) was carried out following the procedure described in reference 10 (Table 5). The yield and purity of the acid were determined by g.l.c. analysis after the sample has been trimethylsilylated using bis(trimethylsilyl)trifluoroacetamide (BSTFA); as usual (for R′ = H, Me, Bu^i, Br; 5% SE-52 on Chromosorb W, 3 mm × 2 m column at 150 or 170 °C: for R′ = Ph; 2% OV-17 on Gas Chrom Q, 3 mm × 2 m column at 210 °C). The purity was found to be 99.5% in all cases.

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