Thallium(III) Nitrate-mediated Efficient Synthesis of 2-Arylpropionic Acids from 1-Halogenoethyl Aryl Ketones

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Treatment of 1-halogenoethyl aryl ketones [4'-$RC_6H_4COCH(X)Me$] (**1**; R = H, Bu^i, OMe, Me, Ph, or Br; X = Br or Cl) with $Tl(NO_3)_3 \cdot 3H_2O$ and perchloric acid in a trialkyl orthoformate at 25—50 °C affords alkyl esters (**3**) of 2-arylpropionic acid in good-to-excellent yields *via* 1,2-aryl migration in substrates (**1**). The hydrolysis of esters (**3**) leads to the corresponding acids, some of which are pharmaceutically important compounds. The reaction hardly occurs in methanol. The key step of the reaction is the *in situ* acetal formation of the starting ketone. The thallium(III) salt acts as an effective Lewis acid catalyst for both acetal formation and halide abstraction.

Several α-arylalkanoic acids have been used as important pharmaceuticals exhibiting anti-inflammatory and analgesic activities,[1] various methods for preparing these compounds having hitherto been developed. A method using 1,2-aryl migration in alkyl aryl ketones and their derivatives is one of them,[2] the most useful example of which being a direct oxidation of alkyl aryl ketones with thallium(III) nitrate trihydrate (TTN).[3-6] Other methods are the oxidation by (diacetoxyiodo)benzene[7] or iodine–silver nitrate[6] and the treatment of the enamines with diphenyl phosphorazidate.[8]

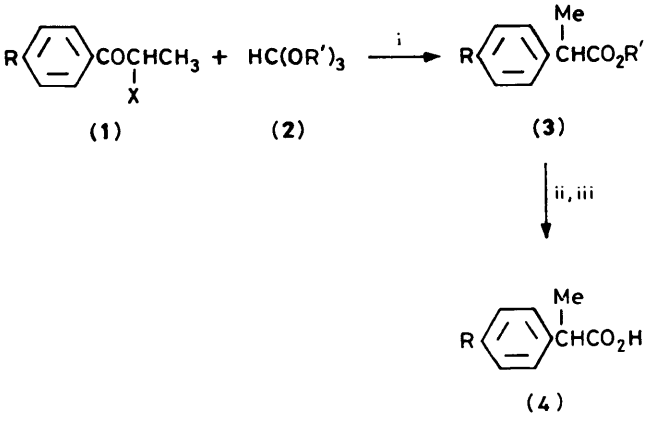
The same compounds were also produced from α-halogenoalkyl aryl ketones or their acetals by 1,2-aryl shift assisted by silver salts[9,10] or Lewis acids such as $ZnBr_2$, $SnCl_2$, and $CoCl_2$,[11] respectively. Similar reaction with the corresponding tosyl ester proceeds even thermally in the presence of calcium carbonate.[12,13] We report herein another efficient synthetic method of preparing alkyl esters of 2-arylpropionic acids by the interaction of TTN with 1-halogenoethyl aryl ketones[14] which are readily available by Friedel–Crafts reaction of aromatic compounds with industrially very cheap 2-halogenopropionyl halides.

Results and Discussion

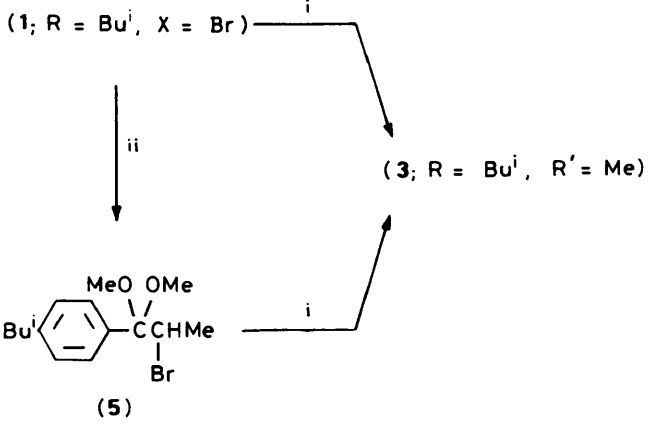
The reaction was generally carried out in a stirred mixture of a 1-halogenoethyl aryl ketone (**1**), TTN (1 mol equiv.), a trialkyl orthoformate (**2**), and perchloric acid at 25—50 °C for 3—30 h. The product was the corresponding 2-arylpropionic acid alkyl ester (**3**) and its alkaline hydrolysis afforded the corresponding acid (**4**) (Scheme 1). Trimethyl or triethyl orthoformate [TMOF (**2**; R′ = Me) or TEOF (**2**; R′ = Et)] was used as the solvent as well as the source of an alkoxy group. Typical results are summarized in Table 1 which shows that the ease of 1,2-aryl migration is strongly affected by the substituent on the phenyl ring and also by the nature of X. Thus, introduction of an electron-releasing substituent such as methyl, methoxy, or phenyl facilitates the rearrangement and the reaction proceeds more rapidly when X = Br than when X = Cl, the results being consistent with those found by Giordano *et al.* in silver salt-mediated rearrangement reactions in methanol.[10]

It has been reported that the products from oxidation of alkyl aryl ketones with TTN depended remarkably on the solvent employed, and the presence of TMOF generally led to a preponderance of oxidative rearrangement.[3,4] Similar or more marked effects for the solvent TMOF were observed in our case. Thus, an almost quantitative yield of ester (**3**; R = Bu^i, R′ = Me) was obtained by reaction of ketone (**1**; R = Bu^i, X = Br) with TTN in acidic TMOF, while in acidic methanol the reaction did not occur and the starting ketone was recovered almost quantitatively (see Table 2). It has been pointed out that TTN catalyses the acetalization of alkyl aryl ketones,[3,4] and that the acetals give the enol ethers which react very rapidly with thallium(II) salts to afford the aryl rearrangement products.[15] Therefore, it is quite plausible that the rearrangement proceeds through the dialkyl acetal forms of the starting ketones in our case as well.

In order to know the nature of the reaction and also the role of TTN it is worthwhile to note the following experimental results from the reaction with ketone (**1**; R = Bu^i, X = Br) or acetal (**5**) under various conditions (Scheme 2, Table 2). (i)



Scheme 1. *Reagents:* i, TTN, H_3O^+; ii, aq. NaOH; iii, aq. HCl



Scheme 2. *Reagents:* i, TTN, TMOF; ii, $MeSO_3H$, TMOF

Table 1. Oxidative rearrangement of 2-halogenoalkyl aryl ketones with TTN

Starting compounds[a] (1) R	X	(2) R′	Reaction conditions (°C, h)	Yield of ester (3) (%)[b]	Unchanged ketone (1) (%)[b]	2-Arylpropionic acid (4) Yield[c] (%)	M.p. (°C) Found	Lit.
H	Cl	Me	25, 25	49	44			
H[d]	Cl	Me	50, 10	62	33	47	14.5—15.5	15—16.5[e]
H	Cl	Et	25, 30	32	64			
Me	Cl	Me	25, 25	79	17			
Me[d]	Cl	Me	50, 3	89	3	71	36—37	34—35[f]
Me	Cl	Et	25, 30	77	18			
MeO[d]	Cl	Me	25, 25	75	3	64	55—56	57[10]
MeO	Cl	Et	25, 30	59	37			
Br	Cl	Me	25, 25	21	74			
Br[d]	Cl	Me	50, 10	58	37	34	71.5—72.5	72—72.5[19]
Br	Cl	Et	25, 30	25	74			
Bu^i[d]	Br	Me	25, 25	97	0	91	75—76	75—76[19]
Bu^i	Br	Et	25, 30	90	9			
Ph[d]	Cl	Me	50, 3	90	2	72	146—146.5	145—147[g]

[a] (1) (10 mmol); TTN (10 mmol); 70% perchloric acid (1 ml); (2) (20 ml). [b] Determined by g.l.c. [c] Yield of the isolated pure product based on (1). [d] (1) (50 mmol); TTN (50 mmol); 70% perchloric acid (100 mmol); (2) (TMOF) (550 ml). [e] A. Fredga and S. Widegvist, *Acta Chem. Scand.*, 1947, **1**, 860; [f] H. Rupe and Fr. Wiederkehr, *Helv. Chim. Acta*, 1924, **7**, 658; [g] F. F. Blicke and N. Grier, *J. Am. Chem. Soc.*, 1943, **65**, 1727.

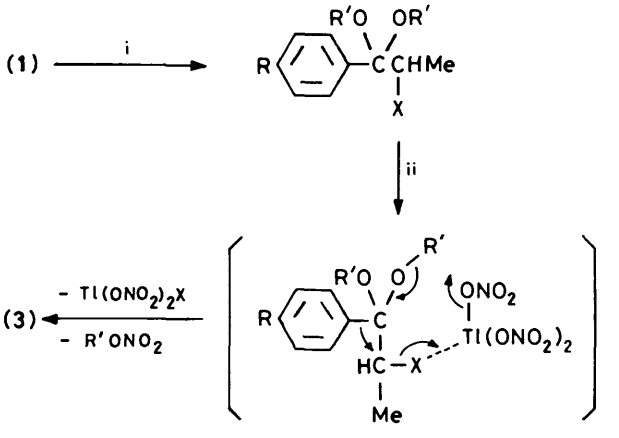
Table 2. Preparation of methyl 2-(4′-isobutylphenyl)propionate (3; R = Bu^i, R′ = Me) under various conditions

Starting compound (mmol)		Reaction conditions: TTN (mmol)	$HClO_4$ (mmol)	TMOF (ml)	Temp. (°C)	Time (h)	Yield[a] of (3; R = Bu^i, R′ = Me) (%)	Yield[a] of (1; R = Bu^i, X = Br) or (5)
(1; R = Bu^i, X = Br)	10	10	0	20	25	25	43	54
(1; R = Bu^i, X = Br)	10	2	10	110	25	25	57	32
(1; R = Bu^i, X = Br)	10	2	10	110	50	8	61	32
(1; R = Bu^i, X = Br)	10	10[b]	10	110	50	8	0	96
(1; R = Bu^i, X = Br)	10	10	10	15[c]	25	24	2	94
(5)	10	10	10	20	25	25	97	0

[a] Determined by g.l.c. Converted amount based on the starting material (1; R = Bu^i, X = Br) or (5). [b] TlOAc was employed instead of TTN. [c] Methanol was used as the solvent instead of TMOF.

The reaction is slow in the absence of perchloric acid and hardly occurs with methanol as solvent; (ii) in the reaction using 2 mmol of TTN, more than 2 mmol of the rearranged products were produced irrespective of the reaction temperature; (iii) thallium(I) acetate was not effective in this rearrangement reaction; and (iv) a dimethyl acetal is much more reactive than the corresponding ketone. Furthermore, we noted that the thallium(I) salt was always produced; and that its amount depended on the reaction conditions, a larger amount of Tl^I salt being formed at 50 °C than at 25 °C. It was confirmed separately (by iodometry) that in the absence of the starting ketone almost all of the Tl^{III} salt was recovered after 48 h at 25 °C, while at 50 °C *ca.* 30% of the Tl^I salt was produced even after 2 h. This may be due to the oxidation of solvent by TTN at 50 °C, although we could not identify the oxidation products.

From these results we propose Scheme 3 for the reaction pathway where TTN works as a Lewis acid to catalyse the first step (acetalization), and also to facilitate the aryl migration by co-ordinating to halogen. The pathway *via* hemiacetalization is also conceivable. It is known that thallium(III) salts such as acetate, bromide, and chloride behave as Lewis acid catalysts for reactions such as bromination, alkylation, and acylation.[16–18] However, it is not as strong a Lewis acid as TTN, and a large amount of the salt is generally required, consistent with our observation that the rearrangement is easier in the case of a 1:1 ratio of TTN:substrate than for a 0.2:1 ratio. Our finding that thallium(I) acetate is not effective at all in this reaction is consistent with the known fact that thallium(I) salts hardly show any Lewis acid activity.[17]



Scheme 3. *Reagents:* i, TTN, (2), H^+; ii, TTN

Experimental

^{1}H N.m.r. spectra were recorded with JEOL FX-90Q (90 MHz) instrument for solutions in $CDCl_3$ with Me_4Si as internal standard. G.l.c. analyses were carried out on a Shimadzu

GC-7AS apparatus with EGA-Chromosorb-G(HP) (3 mm × 1 m) and Silicone GE SE-30-Chromosorb-W (3 mm × 2 m) columns.

All organic and inorganic materials were commercial products of the purest grade and were used without further purification. All substrates and products are known compounds. The compounds (**1**; X = Cl or Br) were prepared by Friedel–Crafts reaction of aromatic compounds with 2-halogenopropionyl chlorides in CCl_4 or CCl_4–nitrobenzene. Their purification was carried out by fractional distillation with a Heli-Pack packing column (20 cm) under reduced pressure, or by recrystallization. Thus were prepared compounds (**1**; R = H, X = Cl) b.p. 102 °C/4 Torr; 79% isolated yield; δ_H 1.70 (d, 3 H), 5.30 (q, 1 H), and 7.4—7.7 (m, 5 H); (**1**; R = Me, X = Cl) b.p. 92 °C/2 Torr; 73%; δ_H 1.68 (d, 3 H), 2.19 (s, 3 H), 5.21 (q, 1 H), 7.27 (d, 2 H), and 7.92 (d, 2 H); (**1**; R = MeO, X = Cl) b.p. 105—108 °C/2 Torr; 36% δ_H 1.63 (d, 3 H), 3.82 (s, 3 H), 5.21 (q, 1 H), 6.98 (d, 2 H), and 8.00 (d, 2 H); (**1**; R = Br, X = Cl) b.p. 100—103 °C/2 Torr; 74%; δ_H 1.62 (d, 3 H), 5.15 (q, 1 H), 7.56 (d, 2 H), and 7.84 (d, 2 H); (**1**; R = Ph, X = Cl) b.p. 179—183 °C/2 Torr; 75% δ_H 1.80 (d, 3 H), 5.31 (q, 1 H), and 7.4—8.2 (m, 9 H); and (**1**; R = Bu^i, X = Br) m.p. 65 °C (from hexane) (lit.,[20] 65 °C); δ_H (90 MHz)[20] 0.91 (d, 6 H), 1.76 (d, 2 H), 1.84 (m, 1 H), 2.52 (d, 2 H), 5.25 (q, 1 H), 7.22 (d, 2 H), and 7.92 (d, 2 H).

The oily compound (**5**) was prepared in 90% yield by acetalization of ketone (**1**; R = Bu^i, X = Br) with TMOF in the presence of methanesulphonic acid under reflux for 12 h; δ_H 0.90 (d, 6 H), 1.32 (d, 3 H), 1.72 (m, 1 H), 2.44 (d, 2 H), 3.20 (s, 3 H), 3.36 (s, 3 H), 4.38 (q, 1 H), and 7.1—7.5 (m, 4 H).

Rearrangement Procedure.—A typical experimental procedure is as follows (reaction conditions and product yields are shown in Table 1). A mixture of 2-bromo-4′-isobutylpropiophenone (1; R = Bu^i, X = Br) (13.0 g, 50 mmol), TTN (22.2 g, 50 mmol), 70% perchloric acid (9.3 ml, 100 mmol), and TMOF (550 ml) was stirred at 25 °C for 25 h. About three-quarters of the TMOF was then distilled off under reduced pressure and the residue was treated with $CHCl_3$ (200 ml). The precipitated thallium(I) salt (4.35 g) was filtered off and the filtrate was washed with water (200 ml), dried over Na_2SO_4, and evaporated under reduced pressure. The resulting oily residue was distilled with a Heli-Pack packing coloumn (20 cm) under reduced pressure to give methyl 2-(4′-isobutylphenyl)propionate (9.4 g, 85%) (**3**; R = Bu^i, R′ = Me), b.p. 106—108 °C/1.1 Torr (lit.,[19] 104—106 °C/1.0 Torr). The i.r. spectrum of the above thallium(I) salt was nearly the same as that of authentic $TlClO_4$ ($\nu_{max.}$ 1 060—1 140 cm^{-1}). The thallium(I) salt was dissolved in water, and addition of aqueous KI afforded a yellow precipitate of TlI (4.2 g, 12.7 mmol). Thallium(I) salt (as the iodide) was also detected in the water washings by addition of aq. KI (6.95 g, 21.0 mmol), while thallium(III) ion (*ca.* 16—17 mmol) was detected in the same washings by iodometry.

Alkaline Hydrolysis of Alkyl Esters of 2-Arylpropionic Acids.—A mixture of an ester (**3**) (30 mmol) and aqueous 2M-NaOH (20 ml) was heated under reflux for 2—10 h until the reaction mixture became clear. After the mixture had been cooled, $CHCl_3$ (10 ml × 2) was added. The water layer was separated, and acidified with conc. hydrochloric acid to give precipitates of crude products (**4**), which were collected by filtration. The acids (**4**; R = Bu^i, Br, or Ph) were recrystallized from 40—80% aqueous AcOH, while the low-m.p. products (**4**; R = H or Me) were purified by distillation.

References

1 See, for example, T.Y. Shen, *Angew. Chem., Int. Ed. Engl.*, 1972, 11, 460.
2 For a recent review, see C. Giordano, G. Castaldi, and F. Uggeri, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 413.
3 A. McKillop, B. P. Swann, and E. C. Taylor, *J. Am. Chem. Soc.*, 1973, **95**, 3340.
4 E. C. Taylor, R. L. Robey, K.-T. Liu, B. Favre, H. T. Bozimo, R. A. Conley, C.-S. Chiang, A. McKillop, and M. E. Ford, *J. Am. Chem. Soc.*, 1976, **98**, 3037.
5 E. C. Taylor, C.-S. Chiang, A. McKillop, and J. F. White, *J. Am. Chem. Soc.*, 1976, **98**, 6750.
6 S. D. Higgins and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1982, 235.
7 Y. Tamura, Y. Shirouchi, and J. Haruta, *Synthesis*, 1984, 231.
8 T. Shioiri and N. Kawai, *J. Org. Chem.*, 1978, **43**, 2936.
9 C. Giordano, G. Castaldi, F. Casagrande, and L. Abis, *Tetrahedron Lett.*, 1982, **23**, 1385.
10 C. Giordano, G. Castaldi, F. Casagrande, and A. Belli, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2575.
11 G. Castaldi, A. Belli, F. Uggeri, and C. Giordano, *J. Org. Chem.*, 1983, **48**, 4658.
12 G. Tsuchihashi, K. Kitajima, and S. Mitamura, *Tetrahedron Lett.*, 1981, **22**, 4305.
13 G. Tsuchihashi, S. Mitamura, K. Kitajima, and K. Kobayashi, *Tetrahedron Lett.*, 1982, **23**, 5427.
14 Preliminary communication: K. Fujii, K. Nakao, and T. Yamauchi, *Synthesis*, 1983, 444; Jpn. Kokai Tokkyo Koho 58-192848 [83, 192848] (*Chem. Abstr.*, 1984, **100**, 120696 m).
15 J. A. Walker and M. D. Pillai, *Tetrahedron Lett.*, 1977, 3707.
16 A. McKillop, D. Bromley, and E. C. Taylor, *Tetrahedron Lett.*, 1969, 1623; *J. Org. Chem.*, 1972, **37**, 88.
17 S. Uemura, K. Sohma, M. Okano, and K. Ichikawa, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 2490.
18 S. Uemura, K. Sohma, and M. Okano, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 860.
19 K. Fujii, K. Nakao, and T. Yamauchi, *Synthesis*, 1982, 456.
20 S. Uemura, S. Fukuzawa, T. Yamauchi, K. Hattori, S. Mizutaki, and K. Tamaki, *J. Chem. Soc., Chem. Commun.*, 1984, 426; *J. Chem. Soc., Perkin Trans. 1*, 1986, 1983.

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