97. *Preparation and Properties of Organic Borates. Part III.* Acylation of Aryl Borates, and Preparation of Aromatic Hydroxyketones.*

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A new method is presented for the preparation of aromatic hydroxyketones by the action of an acid chloride on an aryl borate under Friedel–Crafts conditions. Comparison is made with existing methods, and some new benzophenones are synthesised.

Nuclear-acylated monohydric phenols have been prepared by the following methods: (1) Fries rearrangement:[1,2] the factors influencing the yield and the ratio *o*- : *p*-hydroxyketone are well known.[3–6] (2) After the statement by Friedel and Crafts,[7] numerous text-books report that Friedel–Crafts acylations of phenols as such is impossible; under proper conditions,[5,8–10] however, excellent yields of hydroxy-ketone have been obtained. (3) By condensation of a phenol with aliphatic or aromatic acids in the presence of polyphosphoric acid:[11–14] with aliphatic acids, the combined yields of *ortho*- and *para*-compounds are comparable with those obtained by the Fries method: but aromatic acids give practically no *ortho*-isomers. Methods (2) and (3) give esters in addition to the hydroxy-ketone (in some cases, or under appropriate conditions, the ester is the main product) and it appears that both reactions involve ester formation and Fries rearrangement.

Until recent studies of the Fries rearrangement of nitro-[15,16] and chloro-benzoates,[17] and of the action of substituted benzoic acids on phenol,[18] the number of known substituted benzophenones was limited.[1,19] Our work began before these studies had been reported.

The present method consists of treatment of an aryl borate with an acid chloride under Friedel–Crafts conditions; subsequent decomposition with water hydrolyses the borate to the free hydroxy-compound. Aromatic acid chlorides usually afford an alkali-soluble portion consisting of *o*- and *p*-hydroxy-ketone and an alkali-insoluble portion containing both of these ketones as esters from the acid chloride used. (When *o*-chlorobenzoyl chloride was used, the insoluble portion consisted largely of xanthones; comparison with the conditions described by Kulka [20] make it unlikely that these are derived from the 2-chloro-2′-hydroxybenzophenones by loss of hydrogen chloride during the brief alkali-extraction; they are probably formed during acylation under the agency of the aluminium chloride.) Hydrolysis of the esters gave more hydroxy-ketone and recovered acid, the latter in quantity much more than the equivalent of the hydroxy-ketone content. It appears that esters of

* Previous papers (*J.*, 1946, 820, 823) are regarded as Parts I and II.

[1] "Organic Reactions," John Wiley and Sons, Inc., New York, Vol. I, 1942, p. 342.
[2] Nelson, *Ind. Eng. Chem.*, 1955, **47**, 1926; 1956, **48**, 1670.
[3] Cullinane and Edwards, *J.*, 1958, 2926.
[4] Baltzly, Ide, and Phillips, *J. Amer. Chem. Soc.*, 1955, 2522.
[5] Ralstan, McCorkle, and Bauer, *J. Org. Chem.*, 1940, **5**, 645.
[6] Rosemund and Schnurr, *Annalen*, 1928, **460**, 56.
[7] Friedel and Crafts, *Compt. rend.*, 1877, **84**, 1453.
[8] Rosenmund and Shultz, *Arch. Pharm.*, 1927, **265**, 308.
[9] Sandulesco and Girard, *Bull. Soc. chim. France*, 1930, **47**, 1300.
[10] Cullinane and Edwards, *J. Appl. Chem.*, 1959, **9**, 133.
[11] Nakazawa and Matsuura, *J. Pharm. Soc. Japan*, 1954, **74**, 69.
[12] Snyder and Elston, *J. Amer. Chem. Soc.*, 1955, 364.
[13] Gardner, *J. Amer. Chem. Soc.*, 1954, 4550.
[14] Gardner, *J. Amer. Chem. Soc.*, 1955, 4670.
[15] Saharia and Sharma, *J. Sci. Ind. Res., India*, 1955, **14**, *B*, 263.
[16] Saharia and Sharma, *J. Indian Chem. Soc.*, 1956, **33**, 788.
[17] Saharia and Malik, *J. Sci. Ind. Res., India*, 1956, **15**, *B*, 633.
[18] Nakazawa and Baba, *J. Pharm. Soc. Japan*, 1955, **75**, 378.
[19] C. A. Thomas, "Anhydrous Aluminium Chloride in Organic Chemistry," Reinhold Publ. Corp., New York, 1941, p. 703.
[20] Kulka, *J. Amer. Chem. Soc.*, 1954, **76**, 5469.

the original phenol (used as borate) and acid chloride were always formed, and it may be, as in methods (2) and (3) above, that the reaction proceed through ester which then undergoes Fries rearrangement. The following considerations, however, show that it is more likely that such esters were formed after decomposition, by Schotten–Baumann acylation of the liberated phenols (and hydroxy-ketones) by unconsumed acid chloride: (a) Esters were not encountered in detectable quantity in the reaction products of aryl borate and aliphatic acid chlorides (expts. XV and XVI) in contrast to the results of methods (2) and (3). (b) In preliminary experiments (not here reported) between aryl borates and succinic anhydride, we similarly failed to detect any aryl succinate. (c) Reaction between cresols and benzoyl chloride dissolved in tetrachloroethane and/or carbon disulphide, shaken in contact with aqueous aluminium chloride (thereby simulating as far as possible the conditions of our method), gave high yields of aryl benzoate. (d) In the presence of sufficient alcohol to ensure a homogeneous decomposition product, it has been shown (expt. VIII) that unconsumed aroyl chloride (*m*-toluoyl chloride) reacts preferentially with the alcohol and water, and that no detectable amount or *m*-tolyl *m*-toluate of toluoyl derivative of the hydroxy-ketone is formed.

We thus think it improbable that our method involves a Fries rearrangement. On the other hand, the ratio of *o*- to *p*-hydroxy-ketone formed is quite high and in sharp contrast to the almost complete absence of *ortho*-isomer in the acylation product of

TABLE 1.

Products from 10 g. of aryl borate.

Expt. no.	Borate	Acid chloride	Method	Yield (g.) of *o*-isomer direct	Yield (g.) of *o*-isomer *via* ester	Yield (g.) of *p*-isomer direct	Yield (g.) of *p*-isomer *via* ester	Total yield (%)	Refs.
I	Phenyl	Benzoyl	A	1·2	0	9·4	0	50	3, 4, 6, 14, 18, *a*
II	*o*-Tolyl	,,	,,	0·2	0·2	7·2	2·6	51	3, 6, *b*
III	*m*-Tolyl	,,	,,	3·6	0·1	0·1	0·8	23	4, 6, *b*
IV	*p*-Tolyl	,,	,,	2·9	0	—	—	15	3, 6, 12, *b*
V	Phenyl	*m*-Toluoyl	C	1·7	1·1	0·7	0·4	16	18
VI	*o*-Tolyl	,,	,,	0	1·7	2·2	2·2	29	—
VII	*m*-Tolyl	,,	,,	0·4	7·3	1·0	1·0	44	—
VIII	,,	,,	E	5·4	0	6·2	0	53	—
IX	Phenyl	*m*-Nitrobenzoyl	B	0	0	1·2	1·0	8	16, 18
X	*o*-Tolyl	,,	,,	0	0·7	8·8	0·8	43	16
XI	*m*-Tolyl	,,	,,	0·9	4·9	2·4	1·6	41	16
XII	Phenyl	*p*-Chlorobenzoyl	,,	0	4·4	6·6	1·1	49	17, 18
XIII	*o*-Tolyl	,,	,,	0	0	9·5	1·1	42	17
XIV	*m*-Tolyl	,,	,,	0	5·9	1·2	1·2	33	17
XV	Phenyl	Acetyl	D	3·8	0	5·0	0	54	12, 14, 19, *a*
XVI	*p*-Tolyl	,,	,,	2·0	0	—	—	15	6
XVII	Phenyl	*o*-Chlorobenzoyl	B	0	0·8 *	13·9	0	65 §	18, 20
XVIII	*o*-Tolyl	,,	,,	0	0 †	15·7	0·4	79 §	—
XIX	*m*-Tolyl	,,	,,	0	0 ‡	6·5	0·5	90 §	—

* Also 1·2 g. of xanthone, m. p. 175° (from ethyl alcohol) [Rodd (" Chemistry of Carbon Compounds," Elsevier Publ. Co., Amsterdam, Vol. IV*B*, 1959, p. 968) gives m. p. 173—174°; Kulka [20] gives 175—176°]. † Also 1·6 g. of 4-methylxanthone, m. p. 128° (from methyl alcohol) [Rodd (*op. cit.*) gives 126°]. ‡ Also 11·6 g. of 3-methylxanthone, m. p. 98° (from methyl alcohol) [Rodd (*op. cit.*) gives 98°]. § Calc. on the basis of the borate consumed.

Refs.: (*a*) Bruce, Sorri, and Thomson, *J.*, 1953, 2403. (*b*) Cox, *J. Amer. Chem. Soc.*, 1927, **49**, 1029.

hydrocarbons, halogenobenzenes, and alkyl aryl ethers.[21] Thus, whereas the *para*-isomer probably arises by direct, normal Friedel–Crafts acylation of the borate, the *ortho*-isomer may involve some intramolecular migration other than a Fries migration from oxygen.

The yields by our method (Table 1) are for non-recrystallised materials (but with m. p.

[21] " Organic Reactions," John Wiley and Sons, Inc., New York, Vol. V, 1957, p. 238.

within 3° of the accepted value). Eight new compounds are tabulated in Table 2. For the nine cases where comparison can be made, our yields are only about half of those obtained by the Fries method. However, in four of these cases, the latter yields refer

TABLE 2.

Substituted benzophenones.

Expt. no.	Substituents	M. p. or b. p./mm.*	Found (%) C	H	Cl	Formula	Required (%) C	H	Cl
VI	2-HO-3,3′-Me_2	42°	79·6	6·4	—	$C_{15}H_{14}O_2$	79·6	6·2	—
,,	4-HO-3,3′-Me_2	158°	79·8	6·3	—	,,	,,	,,	—
VII	2-HO-4,3′-Me_2	194—195°/8	79·9	6·2	—	,,	,,	,,	—
,,	4-HO-2,3′-Me_2	110°	79·6	6·3	—	,,	,,	,,	—
XVII	2-Cl-4′-HO	128° †	67·4	4·2	15·1	$C_{13}H_9ClO_2$	67·1	3·9	15·3
XVIII	2′-Cl-4-HO-3-Me	167°	68·4	4·6	14·7	$C_{14}H_{11}ClO_2$	68·2	4·4	14·4
XIX	2′-Cl-4-HO-2-Me	153°	68·3	4·6	14·2	,,	,,	,,	,,
		2,4-Dinitrophenylhydrazones							
			C	H	N		C	H	N
II	2-HO-3-Me	251°	62·0	4·6	13·7	$C_{20}H_{16}N_4O_5$	61·2	4·1	14·3
V	2-HO-3′-Me	230°	61·6	4·2	14·1	,,	,,	,,	,,

* Corr. Solids were recrystallised from aqueous ethanol. † Lit.,[18] 118°.

to the best of various conditions; our yields are, except in one case (expts. VI and VII), for single experimental runs. The two experiments quoted make it probable that better yields would be obtained by increasing the reaction time.

The yields by the " polyphosphoric acid method " are inferior to ours.

EXPERIMENTAL

Borates.—*p*-Tolyl borate was prepared by Thomas's method.[22] Phenyl and *o*-tolyl borate were similarly prepared, in 75% yield, but with xylene as diluent. m-*Tolyl borate* (Found: B, 3·2. $C_{21}H_{21}O_3B$ requires B, 3·3%), m. p. 56°, was prepared in the same way, in 70% yield, from boron oxide, xylene, and *m*-cresol.

Hydroxy-ketones.—(A) A stirred mixture of aryl borate (10 g., 1 mol.), aluminium chloride (3·3 mol.), and carbon disulphide (25 c.c.) was treated with the acid chloride (3 mol.) in carbon disulphide (25 c.c.) during ¼ hr. The mixture was refluxed for 2 hr., and dry air was aspirated through it for a further 1—3 hr. until only traces of hydrogen chloride were evolved. The mixture was decomposed with dilute hydrochloric acid (50 c.c.), and the carbon disulphide distilled off. The insoluble residue was separated and refluxed for ½ hr. with dilute hydrochloric acid (50 c.c.) to remove any remaining aluminium salts (omission of this step may lead to contamination of the product), cooled, and extracted with 10% sodium hydroxide solution (several portions may be necessary to remove all the *ortho*-isomer). The extract was acidified with the minimum quantity of concentrated hydrochloric acid, the precipitate filtered off (remaining traces of aluminium may be present in the solution), and stirred with 5% sodium hydrogen carbonate solution to remove any free acid. The residue was steam-distilled until the distillate was clear and/or gave no colour with ferric chloride. The distillate was extracted with ether, and the extract was dried and evaporated, leaving the *o*-hydroxy-ketone as a pale yellow oil which slowly crystallised in a desiccator over paraffin wax.

The residues from the steam-distillations consisted in most cases of light buff-coloured crystals, and clarification by boiling in dilute alcoholic solution with charcoal was rarely necessary.

The material insoluble in alkali was refluxed with 10% aqueous sodium hydroxide (100 c.c.) for 1—3 hr. until dissolved, and then worked up as above, to give a further quantity of hydroxy-ketones.

[22] Thomas, *J.*, 1946, 820.

2-Hydroxy-3-methylbenzophenone was characterised by conversion into its 2,4-dinitrophenylhydrazone by Siggia's quantitative method [23] in yield such that the ketone must have been of 99—100% purity.

(B) With acid chlorides other than benzoyl chloride, reaction in carbon disulphide was slow. Instead, the reaction was carried out in tetrachloroethane (100 c.c.) at 100°. After decomposition, the solvent layer was separated, refluxed for ½ hr. with dilute hydrochloric acid (50 c.c.), cooled, and then extracted with alkali, etc., as above, to give a mixed product. The residual solvent layer was steam-distilled and the esters filtered off and hydrolysed as in procedure (A), to give a second lot of mixed hydroxy-ketones. (In expts. XVII—XIX, the xanthone remained as a pale material unattacked by the alkali.) The mixed products were boiled with 10% sodium carbonate solution (30 c.c.), cooled, and filtered. Acidification of the filtrate gave the *p*-hydroxy-ketone. The procedure was repeated until no more *para*-isomer was thus extracted. The *para*-isomers thus formed pale crystals containing only traces of *ortho*-isomer. The residual *ortho*-isomers were completely free from *para*-isomers but were sometimes contaminated with a little dark impurity (readily removed by boiling with charcoal in alcohol).

(C) This method was identical with procedure (B) as far as the isolation of the mixed ketone. Thereafter, separation into *o*- and *p*-hydroxy-ketones was accomplished as under procedure (A), *i.e.*, by steam-distillation. The *ortho*-isomer from expt. V was analysed as its 2,4-dinitrophenylhydrazone (cf. expt. 11 above). It was of at least 96% purity. The *ortho*-isomer from expt. VII was an oil and was distilled *in vacuo*.

(D) This was identical with procedure (A) as far as the removal of the carbon disulphide by distillation. Thereafter, the product was steam-distilled, the distillate extracted with ether, the extract dried, and the ether distilled, to leave a mixture of *ortho*-isomer and unchanged phenol (it was entirely soluble in dilute sodium hydroxide, thereby demonstrating the absence of phenyl acetate) which could be separated by fractionation. The residue from the steam distillation (expt. XV only) was pure *para*-isomer.

(E) *m*-Tolyl borate (10 g.) was treated with *m*-toluoyl chloride in tetrachloroethane as above, and the product decomposed by pouring it, with stirring, into concentrated hydrochloric acid (6 c.c.), alcohol (200 c.c.), and ice (33 g.). After 24 hr. the alcohol was removed by distillation and the residue refluxed for ½ hr. with dilute hydrochloric acid (50 c.c.). It was then extracted with several lots of warm 10% sodium hydroxide solution, and the extract was treated successively with hydrochloric acid and sodium hydrogen carbonate solution in the usual way, affording mixed hydroxy-ketones. Light petroleum (b. p. 40—60°; 150 c.c.) removed all the *ortho*-isomer, leaving pure *para*-isomer (5·6 g.). The petroleum extract was dried (K_2CO_3) and evaporated, and the residue was distilled *in vacuo*, to give the *ortho*-isomer (5·4 g.), b. p. 194—195°/8 mm., and a residue of *para*-isomer (0·6 g.). The tetrachloroethane layer, after alkali-extraction, was steam-distilled, and the residue (~2 c.c.) hydrolysed with 10% aqueous sodium hydroxide. Subsequent treatment with hydrochloric acid and then sodium hydrogen carbonate solution gave no precipitate. Re-acidification, however, gave *m*-toluic acid (1·0 g.), showing that the ester was essentially ethyl *m*-toluate.

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Glamorgan College of Technology, Treforest. [*Received, May 24th*, 1962.]

[23] Siggia, "Quantitative Organic Analysis via Functional Groups," Chapman and Hall Ltd., 2nd edn., London, p. 31.