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A STUDY OF THE COPPER-CATALYSED DIRECT ARYLATION OF β-DICARBONYL COMPOUNDS WITH 2-BROMOBENZOIC ACIDS[1]

A. BRUGGINK and A. MCKILLOP*
School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, England

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Abstract—The Cu-catalysed condensations of 2-bromobenzoic acids with β-dicarbonyl anions to give α-arylated-β-dicarbonyl compounds have been investigated in detail. Previously recommended experimental conditions for these reactions are shown to be in appropriate and the limited synthetic utility of these processes in the past is explained. Much superior conditions have now been developed by use of which a variety of β-dicarbonyl compounds can readily be arylated in good to excellent yield with a wide range of substituted 2-bromobenzoic acids and with certain other halo-aromatic acids. The scope and limitations of the synthetic method have been established, and a simple, high yield procedure for the preparation of homophthalic acids is described. It is shown that Cu(I) is almost certainly the effective catalyst, and information has been obtained on the probable mechanism of the substitution reaction by examination of steric and electronic effects in the halo-aromatic acids and by consideration of the structure and role of the β-dicarbonyl component.

INTRODUCTION

There has been much interest in recent years in the use of organocuprates and related organocopper(I) reagents for the formation of C–C bonds.[2-4] Efficient procedures for the direct formation of C–C bonds via condensation of aryl and vinyl halides with carbanions in the presence of a *catalytic* amount of copper or copper salt are, on the other hand, relatively uncommon and the mechanisms, scope and limitations of such reactions are in most cases poorly understood. This situation must be regarded as anomalous in as much as the analogous condensations of aryl and vinyl halides with a wide variety of oxygen and nitrogen nucleophiles have been fairly extensively studied and, while most reactions require prolonged reaction times and temperatures up to about 200° to go to completion, satisfactory to excellent yields of products can generally be obtained.[5-10]

As long ago as 1903 Ullmann demonstrated that condensation of 2-halobenzoic acids with aniline and phenol in the presence of potassium carbonate and a copper catalyst proceeded unexpectedly easily to give 2-carboxydiphenylamines and 2-carboxydiphenyl ethers respectively.[11] As these compounds can readily be converted into acridones and xanthones, the Ullmann condensations of 2-halobenzoic acids with anilines and phenols have consequently been investigated in some detail.[12,13] The results of recent kinetic studies on the reactions of halo-substituted benzoic acids with ammonia have confirmed Ullmann's earlier observations and demonstrated conclusively that the carboxylate ion facilitates nucleophilic substitution of halogen atoms in both the ortho and para positions.[14-17] 2-Bromobenzoic acid was shown to react at least 250 times faster than 4-bromobenzoic acid, and, as expected, the bromo-acids were much more reactive than the chloro analogues. Similar results have been obtained for the copper-catalysed hydrolysis of 2- and 4-bromobenzoic acids: conversion of 2-bromobenzoic acid into salicylic acid proceeds smoothly at 80–120°, whereas 4-bromobenzoic acid is unaffected under the same conditions (copper-catalysed conversion of bromobenzene into phenol necessitates temperatures of 210–230°).[18,19]

Attempts to exploit synthetically the high reactivity of the halogen atoms in 2-halobenzoic acids in condensations with carbanions have met with only limited success. In 1929, Hurtley reported that condensation of 2-bromobenzoic acid with resorcinol and various β-dicarbonyl compounds proceeded smoothly in ethanol solution in the presence of sodium ethoxide and either copper powder or Cu(II) acetate as catalyst.[19] Similar reactions have since been employed in a number of natural product syntheses; the reaction conditions employed were uniformly essentially those described by Hurtley, and in virtually every instance low yields of mixtures of products were obtained which were difficult to separate.[18,20-30] Adams utilised 1,3-cyclohexanediones as nucleophiles during his synthetic studies on cannabinoids,[24] and other applications include the preparation of dibenzocoumarins from 2-bromobenzoic acid and 1,3-dihydroxynaphthalene[27] and the synthesis of a number of substituted coumarino[3,4:2',3']isocoumarins from substituted 2-bromobenzoic acids and 4-hydroxycoumarins.[26] Ames and Dodds have shown that Hurtley's method can be extended to halopyridine carboxylic acids.[31]

Cirigottis *et al.* have recently reported the results of an investigation of the reactions of several 2-bromobenzoic acids and other haloaromatic acids with a number of β-dicarbonyl compounds.[32] Variations of Hurtley's experimental procedure were examined, and yields of substitution products varying from zero to moderate were obtained. The authors drew the following tentative conclusions from their results: "(1) Apart from dimethylformamide, which gives a very low yield, the only effective solvents are alcohols or water. (2) The reaction succeeds best with aromatic *o*-bromocarboxylic acids, although *o*-iodo acids can be expected to give low yields. (3) Replacement of the carboxyl group by any other functional group prevents the reaction. (4) A copper species is an essential catalyst".

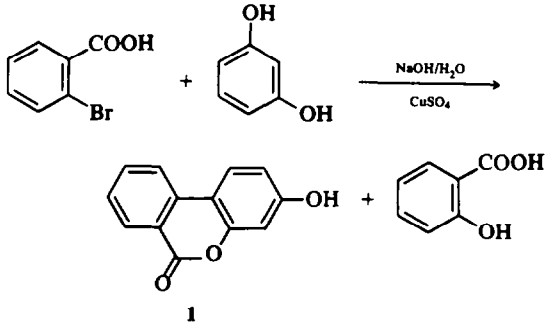
We wish to describe now the results of our systematic investigation of the copper-catalysed reactions of 2-halobenzoic acids and related halo-carboxylic acids with the anions of β-dicarbonyl compounds, which has

resulted in (a) the development of simple procedures for the direct arylation of β-dicarbonyl compounds in good to excellent yield; (b) a simple, high yield synthesis of homophthalic acids; (c) definition of the scope and limitations of the so-called Hurtley reaction; and (d) some insight into the probable mechanism of the displacement reaction.

RESULTS

Condensation of 2-bromobenzoic acids with β-dicarbonyl compounds under the conditions described by Hurtley and others is not a synthetically very useful reaction. Yields of the expected substitution products are at best moderate, the reactions are often difficult to reproduce, mixtures of products are always obtained, and separation and purification of the various products is tedious and time consuming. These experimental disadvantages are, of course, merely a reflection of inappropriate reaction conditions, and hence we began our investigation by re-examining these conditions; this enabled us to readily establish the source of the problems and hence to devise new experimental conditions whereby they can be eliminated.

Substitution of the Br atom in 2-bromobenzoic acid by β-dicarbonyl and related compounds has been effected in either of two ways, namely (i) for β-dicarbonyl compounds, the reaction is carried out in anhydrous ethanol using sodium ethoxide as base and Cu(O) as catalyst, and (ii) for polyhydric phenols such as resorcinol or phloroglucinol, water is used as solvent, sodium hydroxide as base and Cu(II) sulphate as catalyst.[19] In our hands, condensation of resorcinol with 2-bromobenzoic acid under the published reaction conditions gave an approximately 1 : 1 mixture of 3 - hydroxy - 6 - benzopyrone **1** and salicylic acid, together with a small amount (6%) of unchanged 2-bromobenzoic acid. Attempts to suppress the formation of salicyclic acid in this reaction by



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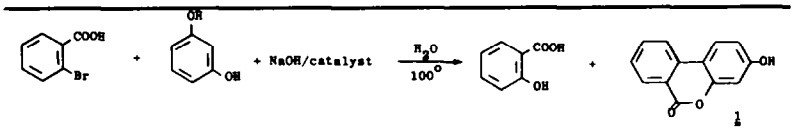
variation of the temperature, reaction time, pH of the medium, and relative stoichiometries of the reactants were unsuccessful. Formation of products was observed only when the pH of the medium was between 6 and 10, and in all cases mixtures of **1** and salicylic acid were obtained. When the pH was below 6, the effective concentration of resorcinolate ions was too low to result in substitution, while at pH values above 10 the copper catalyst was destroyed by conversion into the insoluble and catalytically inactive (q.v.) oxide. Attempts to use catalysts other than Cu(II) sulphate were also largely unsuccessful, as can be seen from the data listed in Table 1.

Table 1. Investigation of metal salts as catalysts for the nucleophilic displacement of bromine from 2-bromobenzoic acid by resorcinol/sodium hydroxide[a]



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Metal Salt	Time, min	Salicylic Acid Yield, %[b]	1, Yield, %[b]	Recovered 2-Bromobenzoic Acid Yield, %[b]
$CuSO_4$	5	34	42	6
$Hg(OCOCH_3)_2$	60	46	45	-
$CoSO_4$	60	36	30	19
$HgSO_4$	60	10	19	60
$MnSO_4$	60	8	8	74
$CdSO_4$	60	6	6	80
$Fe_2(SO_4)_3$	60	2	4	88
$NiSO_4$	60	-	4	88
$FeSO_4$	60	-	-	92
Ag_2SO_4	60	-	-	92
$AgOCOCH_3$	60	-	-	96
$CeSO_4$	60	-	-	80
$Cr_2(SO_4)_3$	60	-	-	92
$C_6H_5HgOCOCH_3$[c]	120	-	-	88

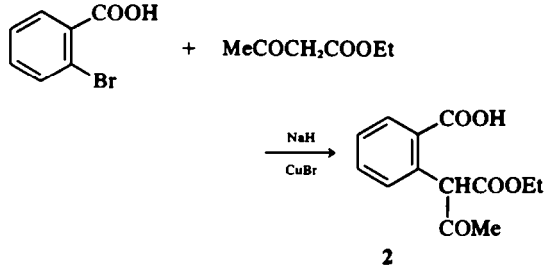
[a] All reactions were carried out using 1 eq of 2-bromobenzoic acid, 1.8 eq of resorcinol, 2 eq of sodium hydroxide and 0.02 eq of metal salt. [b] Refers to isolated material. [c] Reaction carried out in ethanol.

Effective but slow catalysis of the condensation was observed only with Co(II) sulphate and, somewhat surprisingly, Hg(II) acetate, but again in each case an approximately 1:1 mixture of 1 and salicylic acid was obtained. The results summarised in Table 1 therefore complement those of Cirigottis, Ritchie and Taylor, who found that silver nitrate, magnesium turnings, Fe(III) chloride, Hg(II) chloride, zinc dust, Zn(II) chloride, Ni(II) chloride, Pd(II) chloride, Cd(II) chloride and Tl(I) ethoxide were all completely ineffective catalysts for the condensation of 2-bromobenzoic acid with benzoylacetone in ethanolic sodium ethoxide.[32] That is, catalysis of these reactions by some copper species is essential.

Formation of salicylic acid in the above reactions obviously derives from competition between resorcinol and hydroxide ion for the 2-bromobenzoic acid, and is a not unexpected reaction. The same situation pertains with respect to reactions carried out with β-dicarbonyl compounds using the sodium ethoxide/ethanol system. Reaction of 2-bromobenzoic acid with a number of β-dicarbonyl compounds under conditions identical to those used by Hurtley resulted in formation of the expected products (Table 2); in two of the cases for which comparative data are available, however, the yields of products differed substantially from those claimed by Hurtley. Somewhat cleaner and more easily handled reaction mixtures were obtained when Cu(I) acetate, chloride or, preferably, bromide was employed as catalyst, and the yields of substitution products were slightly higher in some cases. Using Cu(I) bromide as catalyst, for example, reaction between 2-bromobenzoic acid and diethyl malonate proceeded smoothly, and careful column chromatography of the crude products gave 2-bromobenzoic acid (15%), 2-ethoxybenzoic acid (25%) and diethyl 2-carboxyphenylmalonate (55%). Similar results were obtained with ethyl acetoacetate and benzoylacetone; in each case 15–25% of 2-ethoxybenzoic acid was formed.

As mentioned above, participation of the conjugate base of the solvent in these reactions is predictable, and hence attempts were made to devise alternative solvent/base systems in which this undesired side-reaction would be prohibited. The reaction of 2-bromobenzoic acid with diethyl malonate in the presence of Cu(I) bromide was studied in various solvents (tetrahydrofuran, t.-butanol, 1,2-dimethoxyethane) and using various bases (n-butyllithium, sodium and lithium t.-butoxide, lithium hydride); in each case 2-bromobenzoic acid was recovered in virtually quantitative yield. Acetal, acetonitrile, pyridine, dimethylformamide and dimethyl sulphoxide have also been shown to be ineffective as solvents.[32]

In contrast to the above results, direct arylation of β-dicarbonyl compounds with 2-halobenzoic acids in the presence of Cu(I) bromide as catalyst and sodium hydride as base occurs smoothly and in excellent yield in most cases in the absence of added solvent. Thus, condensation of 2-bromobenzoic acid (12·5 mmole) with ethyl acetoacetate (20 ml) in the presence of sodium hydride (30 mmole) and Cu(I) bromide (0·7 mmole) is complete within 20 min at 60–80°, and ethyl β - (2 - carboxyphenyl)acetoacetate **2** can readily be isolated in virtually quantitative yield. These conditions are ideal for small scale reactions (10–20 mmole of acid); for larger scale operations, however, addition of either anhydrous benzene or toluene as a diluent is advantageous from a manipulative point of view, although slightly longer reaction times are then necessary.



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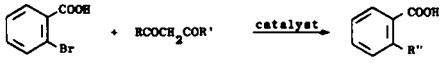
These are the only reaction conditions we have been able to find whereby competition between the β-dicarbonyl anion and the conjugate base of an added protic solvent for the 2-bromobenzoic acid is completely eliminated. The reactions are, moreover, extremely simple to perform, pure products can readily be isolated, and, as can be seen from the data in Table 3, the process is of wide applicability with respect to both the halo-benzoic acid and the β-dicarbonyl compound.

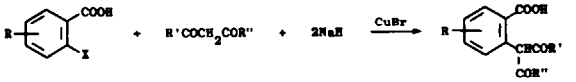
Table 2. Reactions of 2-bromobenzoic acid with β-dicarbonyl compounds using the sodium ethoxide/ethanol/copper catalyst procedure



R	R'	Catalyst (Conc.)	R''	Yield, % A[a,b]	Yield, % B[c]
CH_3	OC_2H_5	Cu (0.06eq)	$CH_2COOC_2H_5$[d]	56	95
CH_3	CH_3	Cu (0.06eq)	$CH(COCH_3)_2$	34	75
C_6H_5	CH_3	Cu (0.06eq)	$CH_2COC_6H_5$[d]	78	[e]
OC_2H_5	OC_2H_5	Cu $(OCOCH_3)_2$ (0.04eq)	$CH(COOC_2H_5)_2$	34	[e]

[a]This work. [b]Refers to pure, isolated material. [c]Ref. 19. [d]The acetyl group is lost during reaction by retro-Claisen cleavage of the arylated β-dicarbonyl product; see text for discussion. [e]No yield quoted in ref. 19.

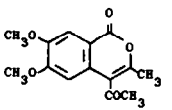
Table 3. Cu(I) bromide-catalysed arylation of β-dicarbonyl compounds with 2-halobenzoic acids



				Product		
X	R	R'	R''	Compound No.	Time, h[a]	Yield, %[b]
Cl	H	CH_3	OC_2H_5	2	0.8	91
Cl	H	OC_2H_5	OC_2H_5	3	20	80
Br	H	CH_3	CH_3	4	1	91
Br	H	CH_3	OC_2H_5	2	0.3	96
Br	H	OC_2H_5	OC_2H_5	3	1.7	92
Br	H	C_6H_5	OC_2H_5	5	1	98
Br	H	CH_2COOCH_3	OCH_3	6	0.5	60[c]
Br	5-OCH_3	CH_3	OC_2H_5	7	2	98
Br	4,5-$(OCH_3)_2$	CH_3	CH_3	8	3	59[d]
Br	4,5-$(OCH_3)_2$	CH_3	OC_2H_5	11	2.5	90
Br	4,5-$(OCH_3)_2$	OC_2H_5	OC_2H_5	12	4	92
Br	3,4,5-$(OCH_3)_3$	CH_3	CH_3	13	7	84
Br	3,4,5-$(OCH_3)_3$	CH_3	OC_2H_5	14	7	99
Br	3,4,5-$(OCH_3)_3$	OC_2H_5	OC_2H_5	15	3	84
Br	4-CH_3	CH_3	CH_3	16	0.8	82
Br	4-CH_3	CH_3	OC_2H_5	17	1	99
Br	4-CH_3	OC_2H_5	OC_2H_5	18	2	90
Br	4,6-Br_2	OC_2H_5	OC_2H_5	19	4.5	83[e]
Br	4-NO_2	CH_3	CH_3	20	0.5	91
Br	4-NO_2	CH_3	OC_2H_5	21	0.7	98
Br	4-NO_2	OC_2H_5	OC_2H_5	22	0.8	88
Br	3-NO_2	CH_3	CH_3	23	5	0

Br	3-NO_2	CH_3	OC_2H_5	24	2.5	51[f]
Br	3-NO_2	OC_2H_5	OC_2H_5	25	2	[g]
Br	5-OH	CH_3	CH_3	26	6.5	77[h,i]
Br	5-OH	OC_2H_5	OC_2H_5	27	12	27[h,j]
Br	5-NH_2	CH_3	CH_3	28	6	73[k]
Br	5-NH_2	OC_2H_5	OC_2H_5	29	6	[l]
Br	3-COOH	CH_3	CH_3	30	38	[h,m]
Br	3-COOH	OC_2H_5	OC_2H_5	31	25	[h,n]

[a]Time taken for the reaction mixture to become neutral; for details see Experimental. [b]Except where otherwise noted these values refer to pure, isolated material. [c]The yield of crude material was 90%; this product decomposes readily during both isolation and purification. [d]The lactone 9 (21%) and the ketone 10 (15%) were also isolated. [e]The product isolated was the 2,6-disubstituted benzoic acid 19. [f]The yield of crude material was 90%; the isolated product exists completely in



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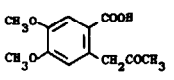

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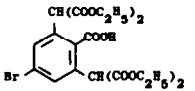

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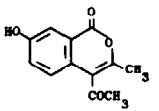
the enolic form and is difficult to purify. [g]The yield of crude product was 70%; attempted purification resulted in decomposition. [h]Three equivalents of sodium hydride were used. [i]The product isolated was the lactone 26. [j]Decomposition occurred both during reaction and purification of the of the product. [k]The isolated product has structure 28. [l]The yield of crude product was 70%;



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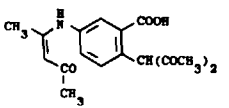

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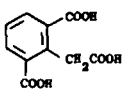

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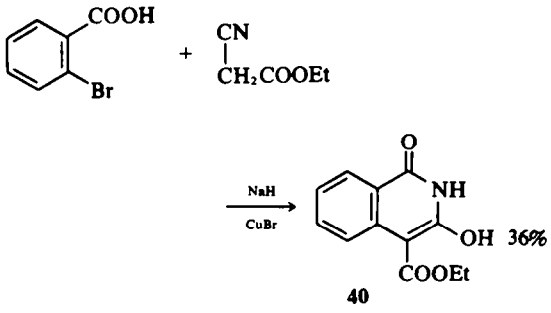
attempted purification resulted in decomposition. [m]Completion of reaction could not be achieved; after 38 hours the product was a mixture of starting material (60%) and substitution product (40%). [n]The product isolated (85% yield) was a mixture of the acid 31 (75%) and unchanged starting material (25%).

Having thus established suitable experimental conditions for 2-bromobenzoic acids, a number of reactions were carried out in order to derive additional information to that available from Table 3 on steric and electronic effects operative in these substitution processes. The results of the reactions of 2-bromonicotinic acid and 8 - bromo - 1 - naphthoic acid with various β-dicarbonyl compounds under the same reaction conditions as described above are summarised in Table 4 together with comparative yield data for the same reactions carried out using the sodium ethoxide/ethanol/copper catalyst system. The reactions of 8 - bromo - 1 - naphthoic acid are of particular interest in as much that if substitution of 2-bromobenzoic acid proceeds via an S_NAr type of mechanism, then the analogous reactions with 8 - bromo - 1 - naphthoic acid should proceed either very much more slowly or not at all, as there is no mesomeric effect in the latter compound similar to that in 2-bromobenzoic acid. In fact, 8 - bromo - 1 - naphthoic acid proved to be one of the most reactive substrates studied, which suggests that the proximity of the carboxyl and bromo groups is one of the key controlling factors in these reactions. Further data pertinent to both proximity and electronic effects, which are discussed in detail later, can be obtained by inspection of the results listed in Table 5 for the reactions of acids of the types 2-BrArXCOOH (X = CH_2, CH_2CH_2, $CH_2CHCOOH$, CH=CH, O) with various β-dicarbonyl compounds under conditions similar to those used for the reactions summarised in Tables 3 and 4.

Two further aspects of these reactions which are relevant to the overall mechanism of substitution were then examined briefly, namely the roles of the β-dicarbonyl compound and of the carboxylate group. The anions of both of these functional groups are excellent bidentate ligands for copper ions but, as is discussed later, a reasonable substitution mechanism can be postulated in which each of these components participates effectively as a monodentate ligand for copper. Consequently, it was of interest to discover whether reactants other than β-dicarbonyl compounds and 2-bromobenzoic acids could be employed successfully.

Attempts to condense 2-bromobenzoic acid with the anions of cyclopentadiene, nitromethane and dimethyl sulphoxide were unsuccessful, and in each case the starting acid was recovered in almost quantitative yield. Reaction with ethyl cyanoacetate, on the other hand, did lead to formation of the isoquinolone derivative **40** in



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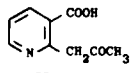
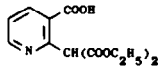
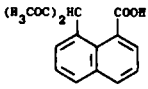
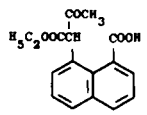
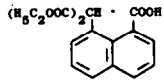
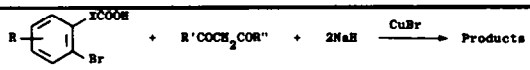
modest yield. Consequently, it appears that facile substitution occurs only with β-dicarbonyl anions or with closely related compounds such as ethyl cyanoacetate.

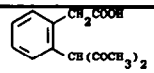
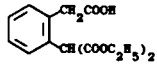
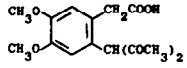
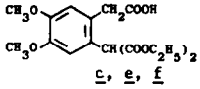
Table 4. Cu(I) bromide-catalysed arylation of β-dicarbonyl compounds with 2-bromonicotinic acid (*A*) and 8-bromo-1-naphthoic acid (*B*)

Acid	β-Dicarbonyl Compound	Time, min[a]	Product	Yield, %[b]	Lit. Yield, %
A	$CH_2(COCH_3)_2$	5	 **32**	66	52[c]
A	$CH_2(COOC_2H_5)_2$	30	 **33**	77	25[c]
B	$CH_2(COCH_3)_2$	10	 **34**	78[d]	70[e]
B	$CH_3COCH_2COOC_2H_5$	5	 **35**	81[d]	32[e]
B	$CH_2(COOC_2H_5)_2$	50	 **36**	84	0[e]

[a]See footnote a, Table III. [b]Refers to pure, isolated material. [c]Ref. 31; see text for discussion of the retro-Claisen reaction. [d]This compound exists entirely in the enolic form, both in solution ($CDCl_3$) and in the solid state. [e]Ref. 32.

Table 5. Cu(I) bromide-catalysed arylation of β-dicarbonyl compounds with 2-BrArXCOOH

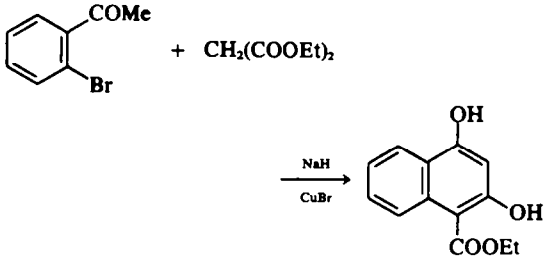


X	R	R'	R''	Time, h	% Reaction[a]	Product	Yield, %[b]	Recovered 2-BrArXCOOH Yield, %[b]
CH_2	H	CH_3	CH_3	18	100	 **37**	72	-
CH_2	H	CH_3	OC_2H_5	16	100	c		-
CH_2	H	OC_2H_5	OC_2H_5	24	100	 **38**	41	-
CH_2	4,5-$(OCH_3)_2$	CH_3	CH_3	24	40	 **39**	25	45
CH_2	4,5-$(OCH_3)_2$	OC_2H_5	OC_2H_5	7	100		95[d]	-
CH_2	4,6-Br_2	CH_3	CH_3	32	50	c, e, f	-	10
CH_2	4,6-Br_2	OC_2H_5	OC_2H_5	32	60	c, e, f	-	-
CH_2CH_2	H	CH_3	CH_3	24	0	-	-	72
CH_2CH_2	H	OC_2H_5	OC_2H_5	30	20	c, e	-	65
CH_2CH_2	4,5-$(OCH_3)_2$	CH_3	CH_3	24	0	-	-	94
CH_2CH_2	4,6-Br_2	CH_3	CH_3	30	0	e	-	90
CH_2CH_2	4,6-Br_2	OC_2H_5	OC_2H_5	30	40	e, f	-	-
$CH_2CH(COOH)$	H	CH_3	CH_3	32	0	e	-	87
$CH_2CH(COOH)$	H	OC_2H_5	OC_2H_5	32	0	e	-	87
$CH_2CH(COOH)$	4,6-Br_2	CH_3	CH_3	30	0	g	-	90
$CH_2CH(COOH)$	4,6-Br_2	OC_2H_5	OC_2H_5	30	0	g	-	93
CH=CH	H	CH_3	CH_3	16	0	-	-	97
CH=CH	H	OC_2H_5	OC_2H_5	30	10	c	-	71
O	H	CH_3	CH_3	16	0	c	-	97
O	H	OC_2H_5	OC_2H_5	16	5	-	-	90

[a]Estimated by nmr. [b]Refers to pure isolated material, except where otherwise stated. [c]No pure product could be isolated. [d]Refers to crude product; this compound could not be satisfactorily purified. [e]Three equivalents of sodium hydride were used. [f]Spectroscopic analysis of the crude product showed that both mono- and disubstitution products were present. [g]Four equivalents of sodium hydride were used.

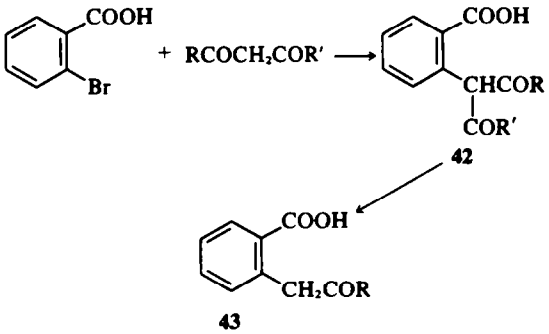
It has also long been tacitly assumed that only 2-bromobenzoic acids will react with β-dicarbonyl anions, and it has been reported that the following compounds are unaffected by the β-dicarbonyl anion/sodium ethoxide/ethanol/copper catalyst(s) systems: 2-BrC_6H_4X (X = COOEt, $CONH_2$, CH_2OH, NO_2, COMe, CHO, CN, CH_2COOH, SO_3H, CONHOH).[19,32] Ethyl 2-bromobenzoate, 2-bromophenol and 2-bromobenzaldoxime are also recovered unchanged under our reaction conditions, but as can be seen from the data in Table 5, low to moderate yields of substitution products can be obtained with 2-bromophenylacetic acids, although relatively long reaction times are generally necessary. A particularly interesting result was obtained with 2-

bromoacetophenone, which condensed smoothly with diethyl malonate under our standard reaction conditions to give ethyl 1,3 - dihydroxy - 4 - naphthoate **41** in 80% yield. With this one exception therefore, facile substitution is observed only with 2-bromobenzoic acids.



41

One feature of the Hurtley reaction that has occasionally been noted before is that the substitution product from reaction of 2-bromobenzoic acid with a β-dicarbonyl compound is not that expected but is in fact the compound **43** derived by retro-Claisen reaction of the initially formed arylated β-dicarbonyl compound **42**. We have found that such cleavage reactions occur quite readily using the sodium ethoxide/ethanol system when

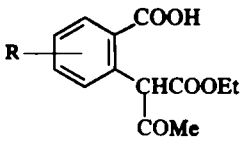


42

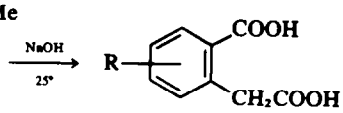
43

excess base is present, but seldom when the reactions are carried out in the absence of solvent and using sodium hydride as base. The transformation **42**→**43** thus represents an added complication with the sodium ethoxide/ethanol system and increases the separation/purification problems inherent in that method. Under our conditions, condensation of 2-bromobenzoic acids with β-dicarbonyl compounds generally led directly to the expected substitution products (Table 3), and deliberate retro-Claisen condensation of these could subsequently be carried out under controlled conditions. Here again the carboxylate group performs a unique role and, because of the possibility of intramolecular anchimeric assistance, renders many of the arylated β-dicarbonyl compounds remarkably sensitive to base.

Thus, when **2** is dissolved in aqueous 2N NaOH solution at room temperature both retro-Claisen condensation of the acetyl group and hydrolysis of the ester function are complete within a few minutes; homophthalic acid **44a** is obtained in almost quantitative yield on acidification of the reaction mixture. The overall yield of homophthalic acid prepared thus is 92% based on 2-bromobenzoic acid. 4-Methyl-, 4-nitro- and 5-methoxyhomophthalic acids **44b–d** were prepared in the same way from the appropriately substituted 2-bromobenzoic acids in overall yields of pure, isolated materials of 88, 90 and 91% respectively.

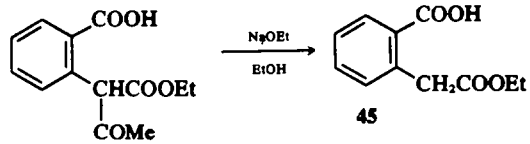


2: R = H
17: R = 4-Me
21: R = 4-NO_2
7: R = 5-OMe



44a: R = H
b: R = 4-Me
c: R = 4-NO_2
d: R = 5-OMe

Ethanolysis of **2** is considerably slower than hydrolysis, simply because of the insolubility of the sodium salt in ethanol, but may nevertheless be a useful reaction. Thus, treatment of **2** with one equivalent of sodium ethoxide in ethanol at room temperature for 3 hr gave a mixture of ethyl 2-carboxyphenylacetate **45** (62%) together with 28% of unchanged **2**, while at reflux temperature the yield of **45** increased to 88%, and only 5% of **2** remained after 3 hr.



2

45

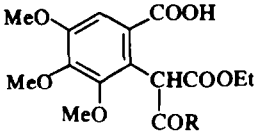
When two equivalents of sodium ethoxide were used, a mixture of **45** (33%) and homophthalic acid **44a** (62%) was obtained.

The sensitivity of α - (2 - carboxyaryl) - β - dicarbonyl compounds to base depends on both steric and electronic effects. Thus, cleavage of one of the acetyl groups from 3 - (2 - carboxy - 4,5 - dimethoxyphenyl)pentane - 2,4 - dione **8** proceeds smoothly on treatment with sodium bicarbonate solution to give 1 - (2 - carboxy - 4,5 - dimethoxyphenyl)propane - 2 - one. In the reaction of 2 - bromopyridine - 3 - carboxylic acid with acetylacetone, on the other hand, the expected substitution product 3 - (3 - carboxy - 2 - pyridyl) - pentane - 2,4 - dione could not be isolated, even under conditions of neutral work-up; instead, 2 - acetonylpyridine - 3 - carboxylic acid **32** was obtained in 66% yield. Finally, spectroscopic examination of the crude product obtained from the reaction of 2-bromoisophthalic acid with diethyl malonate clearly established that substitution of the Br atom by the diethyl malonate had occurred; on treatment of the crude product with water, however, hydrolysis and decarboxylation took place very rapidly to give 2,6-dicarboxyphenylacetic acid (75%).

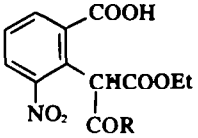
The simple, high yield synthesis of homophthalic acids outlined above compares very favourably with other procedures available for the preparation of these compounds. Most of the methods which have been used are classical, multi-stage syntheses, or necessitate the use of difficulty accessible starting materials or reaction conditions which are not compatible with many nuclear substituents.[33,34] More recent porcedures include the Diels-Alder reaction of 1 - methoxycyclohexa - 1,3 - diene with dimethyl 1,3 - allenedicarboxylate to give, eventu-

ally, dimethyl 3-methoxyhomophthalate in 42% yield,[35] and the reaction of diethyl malonate with benzynes.[36] Treatment of bromobenzene with sodium amide in the presence of diethyl malonate, for example, gives a mixture of diethyl phenylmalonate (20%), ethyl 2-carboxyphenylacetate (10%) and homophthalimide (50%).[36]

While we have not carried out an extensive investigation of the above procedure, the method appears from the results obtained to be applicable to a wide range of homophthalic acids carrying a variety of nuclear substituents. The only severe limitation we encountered was in reaction with 3 - substituted - 2 - bromobenzoic acids, where controlled hydrolysis of the intermediate substitution products with diethyl malonate or ethyl acetoacetate proved to be impossible. Thus, treatment of **14**, **15**, **24** or **25** with 2N NaOH at room temperature failed to effect



14: R = Me
15: R = OEt



24: R = Me
25: R = OEt

either retro-Claisen condensation or hydrolysis, and the compounds were recovered in quantitative yield. Prolonged treatment with more concentrated alkali or heating of the reaction mixtures resulted in formation of tars from which none of the expected homophthalic acids could be isolated.

DISCUSSION

It is not yet possible to give a detailed mechanism for the above substitution reactions nor, indeed, to assign unambiguously the exact roles of the catalyst, the carboxylate anion or the β-dicarbonyl compound. It has been reported that, using the sodium ethoxide/ethanol system, when reactions are carried out in the presence of atmospheric oxygen, there is no significant variation in yield between reactions carried out with copper powder, Cu(I) oxide or Cu(I) chloride as catalyst, but that there is a substantial decrease in yield when Cu(II) acetate is employed.[32] Moreover, it has been shown that while condensation of 2-bromobenzoic acid with benzoylacetone in ethanolic sodium ethoxide gives deoxybenzoin - 2' - carboxylic acid in 40% yield, the yield falls to only 8% when oxygen is bubbled through the reaction mixture.[32] That is, under conditions where reduction of Cu(II) to Cu(I) (or, less likely, Cu(O)) is highly unlikely, there is negligible effective catalysis.

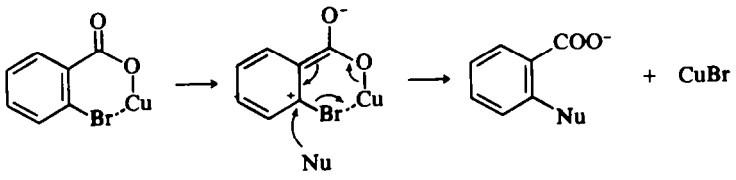
Further evidence that neither Cu(II) nor Cu(O) is the active catalyst comes from the present study. All of the reactions listed in Tables 3–5 were carried out under an atmosphere of dry nitrogen, thus eliminating ariel oxidation of the Cu(I) catalyst. Even so, in a number of the reactions a small amount of the substituted benzoic acid product was isolated as the Cu(II) salt, while in all of the reactions carried out with acetylacetone formation of small amounts of $Cu(acac)_2$ and copper metal was always noted. These observations clearly indicate redox processes within the reacting system, but the exact details remain obscure.

The reactions of 2-bromobenzoic acid with acetylacetone in the presence of freshly prepared copper powder and under an atmosphere of dry nitrogen were then studied. Under the standard conditions used for the reactions listed in Table 3, condensation proceeded slowly and **4** was obtained in only 30% yield after one hour, compared with 91% yield using Cu(I) bromide. The results obtained with the sodium ethoxide/ethanol/copper powder system were even more conclusive: 2-bromobenzoic acid was recovered in quantitative yield after 3 hr reflux. That is, in the absence of oxygen, copper powder does not catalyse the Hurtley reaction under these conditions.

The above results thus strongly indicate that Cu(I) is the effective catalyst and that the Hurtley reaction, at least in this respect, is analogous to a number of other copper-catalysed reactions. Bacon *et al.* have shown, for example, that the reactions of aryl and vinyl halides with oxygen and nitrogen nucleophiles in dimethylformamide solution are catalysed by Cu(I) bromide and iodide,[5–8] while Cairncross *et al.*[37] and Cohen and Schambach[38] have demonstrated that Cu(I) is the active catalyst in copper salt/quinoline decarboxylations of aromatic carboxylic acids. The results of the latter study in fact provide an interesting parallel to the above results on the Hurtley reaction. Thus, decarboxylation can be effected using either the free acid and copper powder, or the Cu(I) or Cu(II) carboxylate. Reactions of the latter salts have been shown to be the faster processes, and rapid reduction of Cu(II) to Cu(I) carboxylates in the basic medium prior to loss of carbon dioxide has been demonstrated. Consequently, decarboxylation proceeds best when the reactions are carried out under nitrogen, as the presence of oxygen results in a decrease in Cu(I) ions and a concomitant increase in Cu(II) ions; this in turn leads to a different type of reaction, namely oxidative decarboxylation. The widespread use of copper powder in this and related types of reactions is apparently largely of historical origin and it is highly probable that, in many such high temperature reactions where copper is used in the presence of atmospheric oxygen, the effective catalyst is Cu(I) (or less probably, Cu(II)) which is formed by oxidation of the copper metal.

Similar observations have been made with respect to the solvent assisted Ullmann ether synthesis,[39] while Goldberg has found that the copper-catalysed hydrolysis of 2-bromobenzoic acid proceeds best when Cu(I) iodide/potassium iodide is used, i.e. environmental conditions under which Cu(II) ions cannot exist.[13] Finally, the kinetic data obtained by Russian workers for copper-catalysed nucleophilic substitutions of 2-halobenzoic acids are compatible only with participation of Cu(I) ions as catalyst,[14–17,40] and both Cu(II) and Ag(I) ions have been shown to be inactive in one particular case.[14]

Goldberg,[13] and Mayer and Fikentscher[18] have postulated that the mechanism of the Hurtley reaction involves formation of a copper chelate of the 2-bromobenzoic acid (Scheme 1), and activition of the bromine towards nucleophilic displacement can then be readily understood in terms of polarisation of the C–Br bond by the copper, reinforced by electron withdrawal by the carboxylate anion. The results of the present study clearly demonstrate, however, that this mechanism is an oversimplification. Thus, the most reactive bromoacid is 8 - bromo - 1 - naphthoic acid, in which mesomersim similar to that outlined in Scheme 1 is impossible, but in which the bromine-carboxyl distance is shorter than in 2-bromobenzoic acid. Hence in this substrate the proximity of the two groups, and consequently the ease of chelate formation, is the more important factor.



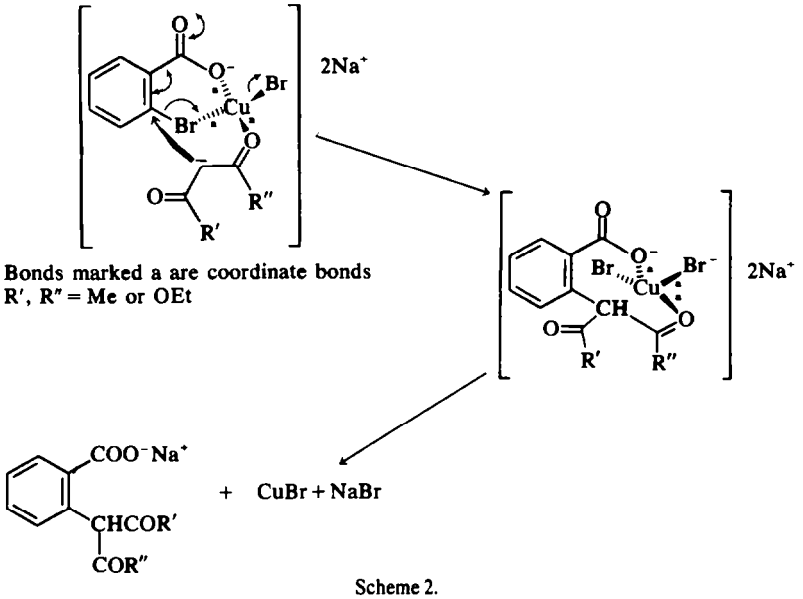
Scheme 1.

The results obtained with 2-bromophenylacetic acids also give an indication of the relative importance of C–Br bond polarisation and of chelate formation. The electronic situation in these substrates is the reverse of that found in 2-bromobenzoic acids, i.e. the CH_2COOH substituent should deactivate the bromine atom with respect to nucleophilic substitution. Substitution nevertheless occurs under much milder conditions than would be anticipated, presumably via formation of a 7-membered chelate system in which there is copper-induced C–Br bond polarisation. The reactions are predictably slower than those of 2-bromobenzoic acids, due to a combination of the electronic effects of the acetic acid group and the necessity for formation of a sterically less favourable seven membered chelate system. When the bromine-carboxyl distance is increased even further, as in 3 - (2 - bromophenyl) - propionic acids, reaction is almost completely inhibited. 2 - Bromocinnamic acid is a vinylogue of 2-bromobenzoic acid and, on purely mesomeric grounds, would be expected to react readily. Formation of an eight membered chelate, on the other hand, would necessitate initial isomerism of the C=C bond and is highly unlikely; it is therefore not surprising that this substrate does not undergo nucleophilic substitution under the standard reaction conditions.

The electronic effects of substituent groups in the 2-bromobenzoic acids are generally predictable: electron releasing substituents exert a rate retarding effect and electron withdrawing substituents a rate accelerating effect. 2 - Bromo - 5 - hydroxybenzoic acid, for example, reacts approx. 15 times slower than 2 - bromo - 4 - nitrobenzoic acid. The expected electronic effects can, however, be complicated by steric effects. Thus, on electronic grounds the bromine atom in 2 - bromo - 3 - nitrobenzoic acid should be highly reactive, much more so, certainly, than that in 2 - bromo - 4 - nitrobenzoic acid. The latter compound, however, reacts very much more rapidly with β-dicarbonyl compounds while the former acid does not react at all with acetylacetone although the expected substitution products are obtained from diethyl malonate and ethyl acetoacetate. From these and other results in Table 3 it is clear that the ease of reaction of β-dicarbonyl compounds with 3-substituted 2-bromobenzoic acids is in the order diethyl malonate > ethyl acetoacetate > acetylacetone. This order is effectively reversed in sterically unhindered 2-bromobenzoic acids; that is, acetylacetone > ethyl acetoacetate > diethyl malonate.

These results can be explained in terms of the relative nucleophilicities of the β-dicarbonyl anions and their structural rigidity. Thus, diethyl malonate anion is the most nucleophilic but the anion of acetylacetone is the structurally most rigid, and the above relative orders of reactivity can readily be understood from examination of molecular models. It is simple to construct a model of the reacting system as shown in Scheme 2, in which the Cu(I) ion is coordinated in a tetrahedral manner to the 2-bromobenzoic acid and one of the oxygen atoms in the β-dicarbonyl anion.

The incoming carbon nucleophile is then within easy bonding distance of the C atom bearing the Br substitutent, and reaction can proceed as shown. There is little or no steric hindrance to bond formation in 2-bromobenzoic acids which have no substituent group at the 3-position with respect to the rigidly planar, coordinated acetylacetone anion. A closely similar situation pertains for the anion of ethyl acetoacetate, although rotation of the O–Et group can lead to distortion of the tetrahedral



Scheme 2.

intermediate and some steric hindrance to approach of the carbanionic centre. This effect is more pronounced in the non-rigid diethyl malonate anion and, while it does not inhibit reaction, it does account for the higher reactivity of acetylacetone and ethyl acetoacetate to 3-unsubstituted 2-bromobenzoic acids. Where there is a 3-substituent group, however, the situation is obviously reversed. The planar, bulky acetylacetone anion can no longer assume the necessary steric position for displacement of the Br atom, and reaction is therefore inhibited. The steric situation is also unfavourable for the diethyl malonate anion, but not so severe that reaction is completely impossible; the carbethoxy groups can rotate away from the aromatic nucleus, the 3-substituent, and the copper, and hence reaction, albeit slow, can still occur. The case of ethyl acetoacetate is intermediate; provided that complexation with the copper ion involves the ketone rather than the ester carbonyl group, the steric situation approximates to that for diethyl malonate, and reaction can occur.

CONCLUSIONS

From the above results it is evident that the experimental conditions originally formulated by Hurtley for the condensation of 2-bromobenzoic acids with the anions of β-dicarbonyl compounds and subsequently adopted by all other workers in this area are totally inappropriate for the reactions involved. The claim by Cirigottis *et al.* that the only effective solvents are alcohols and water has been shown to be incorrect. Using the new experimental conditions described above, the Hurtley reaction is a valuable synthetic process for the preparation of both α - arylated - β - dicarbonyl compounds and homophthalic acids, and the scope and limitations of the former synthesis have been investigated in detail. There is little doubt that Cu(I) is the effective catalyst, and the steric and electronic effects observed in the various reactions can reasonably be accounted for in terms of a tetrahedrally coordinated Cu(I) complex.

EXPERIMENTAL

M.ps were determined on a Kofler hot-stage microscope apparatus and are uncorrected. Microanalyses were performed by Mr. A. R. Saunders and Mr. J. Robinson of the University of East Anglia. IR spectra were recorded on a Perkin-Elmer Model 257 Grating Infrared Spectrophotometer using the standard nujol mull technique. NMR spectra were recorded on a Perkin-Elmer R12, 60 MHz Spectrometer using TMS as internal standard.

Starting materials. All of the β-dicarbonyl compounds used were commercial samples; they were stored over anhyd K_2CO_3 to remove water and acidic impurities and distilled prior to use. Commercially available suspensions (60 or 80%) of sodium hyrdide in mineral oil were used as supplied. Cu(I) Br was prepared freshly every three months and stored in a tightly stoppered bottle. 2-Chloro- and 2-bromobenzoic acid were commercial samples and were recrystallised prior to use. The following acids were prepared by known methods (any relevant deviations from published procedures are indicated): 2 - bromo - 5 - methoxybenzoic acid;[41] 2 - bromo - 4,5 - dimethoxybenzoic acid (from veratric acid and bromine in 1:1-aqueous AcOH; yield 60–80%);[42–45] 2 - bromo - 3,4,5 - trimethoxybenzoic acid;[46] 2 - bromo - 4 - methylbenzoic acid;[47] 2,4,6 - tribromobenzoic acid;[48] 2 - bromo - 4 - nitrobenzoic acid;[49] 2 - bromo - 3 - nitrobenzoic acid;[50] 2 - bromo - 5 - hydroxybenzoic acid;[45] 2 - bromo - 5 - aminobenzoic acid;[51] 2 - bromo - isophthalic acid[52,53] (bromination was carried out as described for 2 - bromo - 3 - nitrobenzoic acid[54,55]); 2 - bromopyridine - 3 - carboxylic acid;[31] 8 - bromo - 1 - naphthoic acid;[54,55] 2-bromophenylacetic acid;[56,57] 2 - bromo - 4,5 - dimethoxyphenylacetic acid;[58] 3 - (2 - bromophenyl)propionic acid;[59] 3 - (2 - bromo - 4,5 - dimethoxy - phenyl)propionic acid;[60] 2-bromobenzylmalonic acid;[59] 2 - bromocinnamic acid;[61] and 2-bromophenoxyacetic acid.[62] 2 - Bromoacetophenone was prepared by the method of Klein and Bergmann.[63]

2,4,6-*Tribromophenylacetic acid.* A mixture of 2,4,6-tribromotoluene[64] (66 g; 0·20 mole), N-bromosuccinimide (37 g; 0·21 mole) and dibenzoyl peroxide (1 g) in 200 ml of CCl_4 was heated under reflux for 5 hr, then cooled to room temp and the succinimide removed by filtration and washed with CCl_4 (2 × 50 ml). The combined filtrate and washings were washed with 15% $NaHSO_3$ aq, water, 15% $FeCl_2$ aq, water and dried over anhyd $NaSO_4$. Evaporation of the solvent gave 72 g of crude product; recrystallisation from MeOH/CCl_4 (10:1) using charcoal gave 60 g (75%) of pure product as pale orange needles, m.p. 70–71° (lit.[65] m.p. 75°).

The corresponding cyanide was prepared using a standard procedure for the benzyl halide to benzyl cyanide conversion,[66] and a sample of the crude product (22 g; 0·062 mole) was hydrolysed by heating under reflux in a mixture of conc H_2SO_4 (55 ml), water (60 ml) and glacial AcOH (80 ml) until an aliquot dissolved completely in NaOH aq (*ca.* 14 hr). The mixture was cooled to room temp, poured on to ice-water and the supernatant layer decanted from the crystalline residue. The crude product was dissolved in dil NaOH aq and the alkaline soln was washed with ether, filtered to remove a small amount of solid impurities, and acidified with conc HCl. The product which precipitated was collected by filtration, dried, and recrystallised from MeOH/$CHCl_3$; this gave 17·9 g (78%) of pure 2,4,6-tribromophenylacetic acid, m.p. 234–235°. (Found: C, 25·52; H, 1·45; Br, 64·32. Calc. for $C_8H_5Br_3O_2$: C, 25·77; H, 1·35; Br, 64·29%).

Diethyl 2,4,6-*tribromobenzylmalonate.* A warm (50°) soln of 2,4,6-tribromobenzyl bromide (14 g, 0·034 mole) in 50 ml anhyd toluene was added dropwise during 30 min to a rapidly stirred suspension of sodium diethyl malonate (from 1·2 g (0·05 mole) of NaH and 8 g (0·05 mole) of diethyl malonate) in 50 ml anhyd toluene. The mixture was stirred and heated at 80° for 5 hr then cooled and poured into 200 ml water, and the aqueous mixture extracted with ether. The ether extracts were dried over Na_2SO_4 and the solvent removed by distillation under reduced pressure. This gave 15·3 g crude product; recrystallisation from MeOH gave 14 g (85%) pure diethyl 2,4,6-tribromobenzylmalonate, m.p. 83·5–84°. (Found: C, 34·80; H, 3·39; Br, 49·09. Calc. for $C_{14}H_{15}Br_3O_4$: C, 34·52; H, 3·10; Br, 49·23%).

2,4,6-*Tribromobenzylmalonic acid.* Diethyl 2,4,6-tribromobenzylmalonate (10 g, 0·021 mole) was added to a soln of KOH (7 g) in 40 ml water and 5 ml EtOH and the mixture heated under reflux for 1 hr. The cooled mixture was then washed with ether, acidified with 2N HCl, and the resulting colourless ppt collected by filtration, washed with water and recrystallised from 80% MeOH aq to give 8·7 g (96%) of pure 2,4,6-tribromobenzylmalonic acid, m.p. 179–180° (with loss of CO_2). (Found: C, 28·05; H, 1·43; Br, 56·05. Calc. for $C_{10}H_7Br_3O_4$: C, 27·85; H, 1·64; Br, 55·64%).

3 - (2,4,6 - *Tribromophenyl)propionic acid.* 2,4,6 - Tribromobenzylmalonic acid (8·3 g) was heated at 200° for 10 min, during which time CO_2 was evolved. The pyrolysate was cooled to room temp and recrystallised from MeOH to give 7·1 g (95%) pure 3 - (2,4,6 - tribromophenyl)propionic acid as pale yellow needles, m.p. 155–157°. (Found: C, 28·20; H, 1·70; Br, 61·88. Calc. for $C_9H_7Br_3O_2$: C, 27·94; H, 1·82; Br, 61·96%).

General procedure for the arylation of β-dicarbonyl compounds with halo-aromatic acids. A suspension of sodium hydride (30 mmole) in mineral oil was added during 5 min to a rapidly stirred suspension of the halo-aromatic acid (12·5 mmole) and CuBr (0·7 mmole) in 15–20 ml of the β-dicarbonyl compound, while a slow stream of dry N_2 was passed over the mixture. When addition of the sodium hydride had been completed, the mixture was stirred at 80° (external hot water bath) until an aliquot diluted with water was neutral to litmus (Tables 3–5 for reaction times). The mixture was then poured into water and extracted with ether (4 × 30 ml) to remove excess β-dicarbonyl compound. The aqueous layer was filtered and acidified with conc HCl; products which precipitated at this stage were collected by filtration, while water-soluble products were extracted with dichloromethane. The

majority of the products were purified by recrystallisation from either benzene/petroleum ether (b.p. 60–80°) or EtOH aq; in some cases purification was accompanied by extensive decompsoition (for details see footnotes to Tables 3–5). For reactions on a larger scale a 5-fold excess of the β-dicarbonyl compound was used and anhyd benzene or toluene added during the reaction to facilitate rapid stirring.

In some cases a small amount (5–10%) of the product was present as the copper chelate in the ether extract from the neutral mixture, and was isolated as follows. The combined ethereal extracts were dried over Na_2SO_4, the solvent and excess β-dicarbonyl compound removed by distillation under reduced pressure, and mineral oil removed from the residue by washing with petroleum ether (b.p. 40–60°). The resulting crude product was stirred for 4 hr with a 1:1 mixture of MeOH and 4N HCl to hydrolyse the copper chelate, and the organic material isolated by extraction with dichloromethane or ether.

All of the products obtained from the reactions of haloaromatic acids with acetylacetone exist completely in the enolic form, and in each case the enolic proton appears as a well defined singlet in the NMR spectrum ($CDCl_3$) at δ16–17. The products from ethyl acetoacetate, ethyl benzoylacetate and dimethyl acetonedicarboxylate exist as mixtures of keto and enol tautomers, the compositions of which are dependent on solvent, temperature and concentration. These compounds were isolated as glasses or low melting solids which were very difficult to purify without extensive decomposition, and they were therefore characterised spectroscopically (IR, NMR). The products from diethyl malonate were almost all well defined solids and were purified and characterised using normal techniques.

The spectral (IR, NMR) properties of all of the products listed in Tables 3–5 were fully consistent with the assigned structures. M.p. and analytical data for the crystalline compounds are given in Table 6.

Table 6. M.p. and analytical data for the crystalline products listed in Tables 3–5

			Anal.							
			Calcd.				Found			
Compound	m.p., °C	Mol. Formula	C	H	N	Br	C	H	N	Br
3	102.5-103	$C_{14}H_{16}O_6$								
4	143-144	$C_{12}H_{12}O_4$								
8	200-202	$C_{14}H_{16}O_6$	60.00	5.75			60.07	5.87		
9	147-148	$C_{14}H_{14}O_5$	64.12	5.38			64.34	5.58		
11	196-198	$C_{12}H_{14}O_5$	60.50	5.92			59.68	6.02		
12	139-140	$C_{16}H_{20}O_8$	56.47	5.92			57.04	5.78		
13	140-142	$C_{15}H_{18}O_7$	58.06	5.85			58.19	5.89		
15	105-106	$C_{17}H_{22}O_9$	54.89	5.99			55.24	6.01		
16	177-178	$C_{13}H_{14}O_4$	66.65	6.02			66.57	5.85		
18	81-82	$C_{15}H_{18}O_6$	61.22	6.16			61.26	6.10		
19	90.5-91.5	$C_{21}H_{25}BrO_{10}$	48.75	4.87		15.45	48.72	4.87		15.51
20	185-187	$C_{12}H_{11}NO_6$	54.34	4.18	5.28		53.97	4.31	5.23	
22	102-103	$C_{14}H_{15}NO_8$	51.69	4.65	4.30		51.44	4.52	4.21	
24	123-124	$C_{13}H_{13}NO_7$	52.89	4.44	4.74		53.01	4.63	4.81	
26	202-204	$C_{12}H_{10}O_4$	66.05	4.62			65.72	4.91		
27	124-125	$C_{14}H_{16}O_7$	56.75	5.44			56.33	5.49		
28	180 (dec.)	$C_{17}H_{19}NO_5$	64.34	6.04	4.45		63.42	6.03	4.43	
32	140-141	$C_9H_9NO_3$								
33	120-122	$C_{13}H_{15}NO_6$	55.51	5.38	4.98		55.30	5.38	4.99	
34	177-179	$C_{16}H_{14}O_4$	71.10	5.22			70.90	5.29		
35	147-148	$C_{17}H_{16}O_5$	67.99	5.37			68.05	5.47		
36	135-136	$C_{18}H_{18}O_6$	65.45	5.49			65.46	5.41		
37	126-127	$C_{13}H_{14}O_4$	66.65	6.02			66.70	6.07		
38	80.5-81.5	$C_{15}H_{18}O_6$	61.22	6.16			61.21	6.09		
39	183-186	$C_{15}H_{18}O_6$	61.22	6.16			61.28	6.34		
40	193-195	$C_{12}H_{11}NO_4$	61.80	4.75	6.01		60.98	4.69	5.95	
41	133-134	$C_{13}H_{12}O_4$	67.23	5.21			66.97	5.34		
44b	195-197	$C_{10}H_{10}O_4$	61.85	5.19			62.02	5.34		
44c	186.5-187	$C_9H_7NO_6$	48.01	3.13	6.22		47.92	3.46	6.18	
44d	184-186	$C_{10}H_{10}O_5$	57.14	4.80			57.28	5.03		

Condensation of 2-bromoacetophenone with diethyl malonate

Preparation of ethyl 2,4 - dihydroxy - 1 - naphthoate, **41**. A total of 0·9 g sodium hydride dispersion (80% in mineral oil, 30 mmol) was added portionwise to a mixture of 2·5 g (12·5 mmol) 2-bromoacetophenone, 15 ml diethyl malonate and 0·1 g CuBr. The resulting green–yellow suspension (pH > 12) was stirred and heated at 80°; after 30 min the colour had changed to organge–yellow and the pH had dropped to 9–10. After 2 hr the mixture was red–brown in colour, and the pH was *ca.* 8. The mixture was cooled, poured into 150 ml water and the resulting mixture extracted with CH_2Cl_2 (4 × 40 ml). The aqueous layer was filtered to remove inorganic solids and acidified with conc HCl. This resulted in precipitation of a yellow oil which rapidly solidified; it was collected by filtration, washed with water and dried. This gave 2·3 g crude product; recrystallisation from CH_2Cl_2/petroleum ether (b.p. 60–80°) gave the pure material as long, colourless needles, m.p. 133–134°.

General procedure for the preparation of homophthalic acids. The crude product obtained from reaction of the appropriate 2-bromobenzoic acid with ethyl acetoacetate was dissolved in 25 ml 2N NaOH; the mixture was stirred at room temp for 30 min, and then acidified with conc HCl. The crystalline product which precipitated (70–80%) was collected by filtration, and the remaining 20–30% obtained by concentration of the aqueous soln. This gave 95–100% of the crude homophthalic acid, which was recrystallised from water.

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