Copper-Catalysed Direct Arylation of α-Substituted β-Dicarbonyl Compounds with 2-Bromobenzoic Acid

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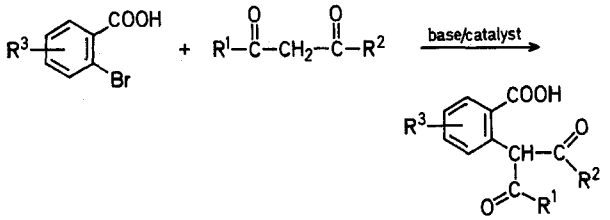
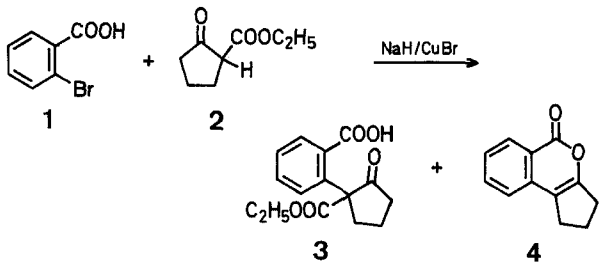
The copper-catalysed direct arylation of β-dicarbonyl compounds with 2-bromobenzoic acids and related halocarboxylic acids

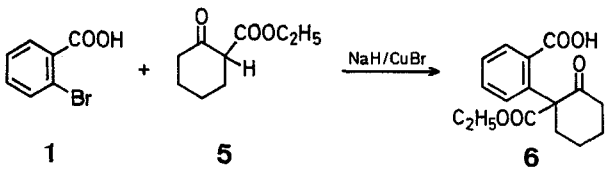


has been studied in some detail during the last few years[1-5], and the scope and limitations of the process have been fairly rigorously defined, particularly with respect to the nature of the catalyst and the halocarboxylic acid[5]. One apparent limitation to this useful substitution process was defined by Ames and Dodds[1], namely that the reaction failed when α-substituted β-dicarbonyl compounds were employed. We now report that Ames and Dodds' conclusion is incorrect, and that the anions of various simple α-substituted β-dicarbonyl compounds undergo arylation in moderate to good yield when treated with 2-bromobenzoic acid in the presence of a catalytic amount of copper(I) bromide.

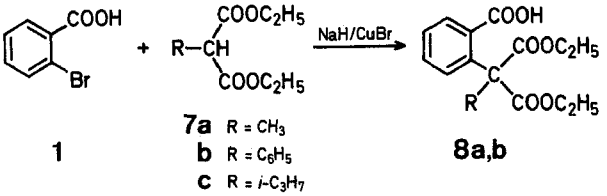
Reaction of 2-bromobenzoic acid (**1**) with 2-ethoxycarbonylcyclopentanone (**2**) and sodium hydride in the presence of copper(I) bromide at 80° for 6 h gave a mixture of the expected substitution product **3** (38%) and the lactone **4** (37%).



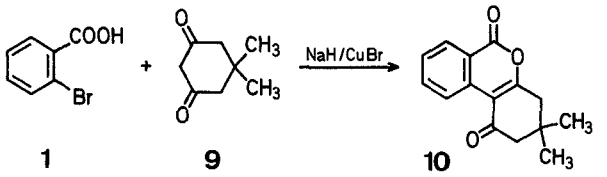
Under these conditions, however, i.e. use of excess **2** as the solvent, the results were poorly reproducible and minor variations in the conditions resulted in significant variations in the relative yields of **3** and **4**. Use of benzene as solvent, on the other hand, led to smooth substitution and pure **3** was isolated in 87% yield; the lactone **4** was not formed under these conditions. By contrast, reaction of **1** with excess 2-ethoxycarbonylcyclohexanone (**5**) proceeded smoothly to give the expected substitution product **6** in 72% yield, uncontaminated by any lactonic product; when benzene was used as solvent the yield of **6** was only 58%.



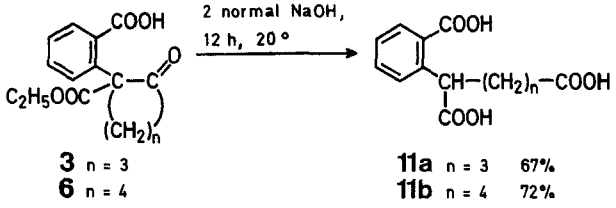
The reactions of **1** with the substituted malonic esters **7a, b, c** were then examined. Substitution was observed with both the methyl (**7a**) and the phenyl (**7b**) derivatives, and the substitution products **8a, b** were isolated in 83 and 45% yield, respectively. There was no reaction, however, with the isopropyl derivative **7c**.



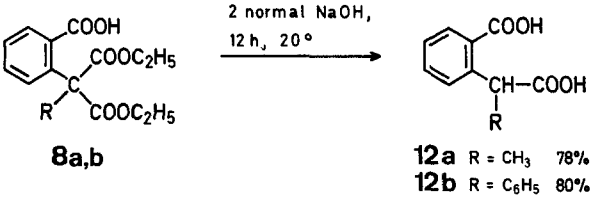
Similarly, while 5,5-dimethylcyclohexane-1,3-dione (**9**) reacted smoothly with **1** to give 3,3-dimethyl-1,6-dioxo-1,2,3,4-tetrahydro-1*H*-dibenzo[*b,d*]pyran (**10**) in 63% yield, there was no reaction when 2-methylcyclohexane-1,3-dione was used.



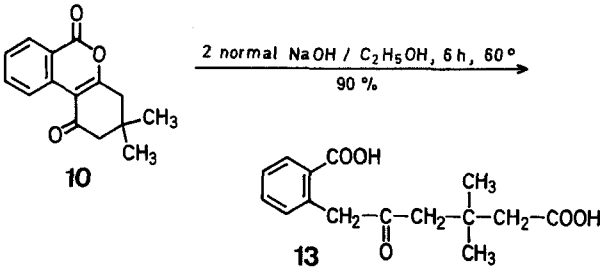
These results show that direct arylation of α-substituted β-dicarbonyl compounds with 2-bromobenzoic acid is almost certainly limited to those dicarbonyl compounds in which the α-substituent is either an R—CH_2— group or a non-*o*-substituted aryl group. Even so, these reactions are useful for the preparation of certain types of specifically substituted benzoic acids; moreover, as expected[5], the substitution products are readily hydrolysed under mild conditions. Thus, with compounds **3** and **6**, "base cleavage" of the cycloalkanone ring occurs with formation of 2-(2-carboxyphenyl)-alkanedioic acids (**11**).



The *o*-carboxyphenylmalonic esters **8** are hydrolysed and decarboxylated to give the homophthalic acids **12**,



and the tricyclic lactone **10** is cleaved to 6-(2-carboxyphenyl)-3,3-dimethyl-5-oxohexanoic acid (**13**).



Reaction of 2-Bromobenzoic Acid (1) with β-Dicarbonyl Compounds (2, 5, 7, 9); General Procedure:

Sodium hydride (30 mmol, 80% suspension in paraffin) is added during 10 min to a stirred mixture of 2-bromobenzoic acid (2.52 g, 12.5 mmol) and copper(I) bromide (0.1 g, 0.7 mmol) in either the β-dicarbonyl compound (20–25 ml) or a solution of the β-dicarbonyl compound (12.5 mmol) in benzene (30 ml). The mixture is stirred and heated under nitrogen at 60–80° for 4–6 h, then cooled, diluted with water (100 ml), and any unreacted organic material removed by extraction with ether. The aqueous phase is acidified with conc. hydrochloric acid, and the solid which precipitates is collected by filtration, washed with cold water, dried, and recrystallised.

Table 1. Products obtained from the Reaction of 2-Bromobenzoic Acid (**1**) with β-Dicarbonyl Compounds (**2**, **5**, **7**, and **9**)

Compound	Yield [%]	m.p. (recryst. solvent)	Molecular formula[a]
3	38	131–132° (methanol/water)	$C_{15}H_{16}O_5$ (276.3)
4	37	150–151° (ethanol)	$C_{12}H_{10}O_2$ (186.2)
6	72	124–125° (methanol/water)	$C_{16}H_{18}O_5$ (290.3)
8a	83	98–100° (ethyl acetate)	$C_{15}H_{18}O_6$ (294.3)
8b	45	120° (ethyl acetate)	$C_{20}H_{20}O_6$ (356.4)
10	63	143–145°[b] (ethanol)	

[a] The microanalyses showed the following maximum deviation from the calculated values: C, ±0.32 (except for **8b**: −0.41); H, ±0.31.

[b] Ref. [6], m.p. 145–146°.

Hydrolytic Cleavage of Compounds 3, 6, 8, and 10; General Procedure:

Compounds **3**, **6**, **8**, or **10** (0.01 mol) are dissolved in 2 normal sodium hydroxide solution, or in 2 normal sodium hydroxide solution containing a little ethanol, and the mixture is either stirred at room temperature for 12–16 h or heated at 60° for 6–8 h. It is then acidified with conc. hydrochloric acid and chilled; the crystalline solid which precipitates is collected by filtration, washed with cold water, and recrystallised.

Spectrometric data (I.R., ^{1}H-N.M.R.) consistent with the proposed structures were obtained for all new compounds.

Table 2. Products obtained by Hydrolytic Cleavage of Carbonyl Compounds **3**, **6**, **8a**, **b**, and **10**

Compound	Yield [%]	m.p. (recryst. solvent)	Molecular formula[a]
11a	67	149–150° (ethyl acetate)	$C_{13}H_{14}O_6$ (266.2)
11b	72	143–144° (ethyl acetate)	$C_{14}H_{16}O_6$ (280.3)
12a	78	148–150° (water)	$C_{10}H_{10}O_4$ (194.2)
12b	80	153–156° (water)	$C_{15}H_{12}O_4$ (256.3)
13	90	146–148° (ethyl acetate)	$C_{15}H_{18}O_5$ (278.3)

[a] The microanalyses showed the following maximum deviation from the calculated values: C, ±0.35; H, ±0.20.

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