Monatshefte für Chemie 127, 701–715 (1996)

Monatshefte für Chemie
Chemical Monthly

Application of Organolithium and Related Reagents in Synthesis XVI [1]: Synthetic Strategies Based on Aromatic Metallation. A Concise Regiospecific Conversion of Chlorobenzoic Acids into their Benzylated Derivatives

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Summary. The reaction of benzyl bromide with *bis*-(N- and C-*ortho*)-lithiated chloroanilides **4**, **5**, and **6** has been examined. It has been found that in the case where the lithiated compound was derived from *meta*-methoxyanilides, pre-addition of LiBr or *TMEDA* was required to achieve C-benzylation. These results were accounted for by the conversion of the usually formed dimer into a mixed dimer with the LiBr or *TMEDA* complex in which the C-lithium bond appears to be more accessible towards electrophiles. The practical synthesis of *o*-benzylchlorobenzoic acids **10**, **11**, and **12** was accomplished *via* ionic reductive cleavage ($Et_3SiH/TiCl_4$) of the corresponding phthalides **18**, **19**, and **20**. The acids **10**, **11b**, and **11c** afforded the corresponding anthrones, upon treatment with trifluoroacetic anhydride which were oxidized by chromium trioxide to the new chloroantraquinones **21**, **22**, and **23**.

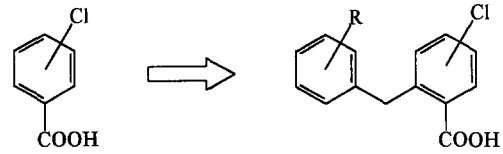
Keywords. Chlorophthalides; Reduction; Benzylation; Benzylbenzoic acids; Chloroantraquinones.

Anwendung von Organolithium und verwandten Reagenzien in organischen Synthesen, 16. Mitt. [1]: Synthesen mittels aromatischer Metallierung. Eine bequeme regiospezifische Umwandlung von Chlorbenzoesäuren in ihre Benzylderivate

Zusammenfassung. Die Reaktion von Benzylbromid mit den *bis*-(N- und C-*ortho*)-lithiierten Chloraniliden **4**, **5** und **6** wurde untersucht. Im Falle lithiierter Verbindungen aus *meta*-Methoxyaniliden ist die Zugabe von LiBr oder *TMEDA* während des Lithiierungsprozesses für die C-Benzylierung erforderlich. Diese Ergebnisse werden durch Umwandlung des gewöhnlich enstehenden Dimers in ein gemischtes Dimer mit dem LiBr- oder *TMEDA*-Komplex erklärt, in welchem die C-Li-Bindung für Elektrophile leichter zugänglich ist. Diese praktische Synthese der *o*-Benzylchlorbenzoesäuren **10**, **11** und **12** wird durch reduktive Spaltung der entsprechenden Phthalide **18**, **19** und **20** mit $Et_3SiH/TiCl_4$ ergänzt. Bei der Reaktion der Säuren **10**, **11b** und **11c** mit Trifluoressigsäureanhydrid entstehen die erwarteten Anthrone, die durch Oxidation mit Chromtrioxid in die neuen Chloranthrachinone **21**, **22** und **23** umgewandelt wurden.

Introduction

In the past few years, great activity has been directed towards the synthesis of *ortho*-benzyl aromatic carboxylic acids as starting materials for the preparation of numerous heterocyclic compounds including important physiologically active products such as anthracyclinones [2] and more recently 3-(2-(phenylmethyl)-benzoyl)-pyrroles as a new class of calcium chancel activators [3]. This has prompted us to examine a methodology for the synthesis of these systems. In particular, our attention has been focussed on the development of a general synthetic route for the preparation of chloro derivatives of *ortho*-benzyl-benzoic acids (**B**) as synthons.



A **B**

Scheme 1

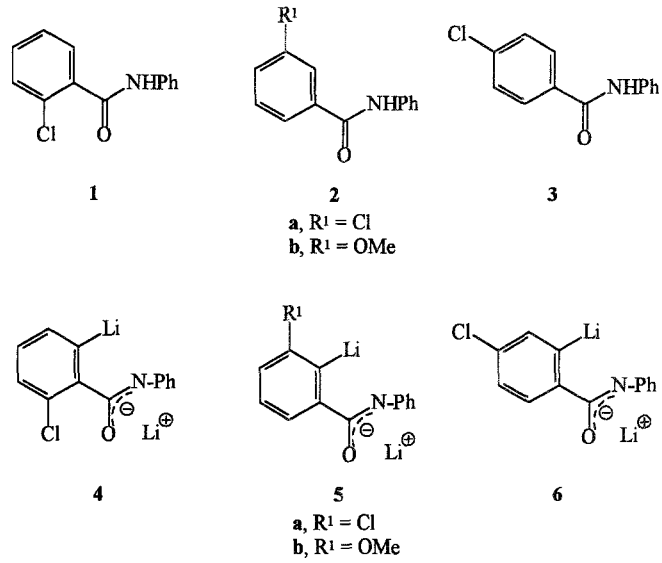
Available methods for the preparation of *ortho*-benzylated aromatic carboxylic acids generally require one of the following techniques. The most common approach involves the reduction of the *ortho*-benzoylated aromatic carboxylic acids (*Friedel-Crafts* products) or the oxidation of hardly available *ortho*-benzylated benzyl alcohols [4]. Alternatively, the desired compounds are accessible by displacing the *o*-methoxy group for benzyl in *o*-methoxyphenyloxazolines upon their reaction with benzylic *Grignard* reagents (*Meyer*'s oxazoline method) [2e, 5] or *via* benzylation of *ortho*-lithiated masked carboxylic acids [6]. However, the latter method is applicable only for some selected cases (see below). The most attractive route so far reported is the reductive cleavage (Pd/C [2a, 7, 8], $CuSO_4$ – activated Zn [2e, 9], Et_3SiH – *Lewis* acid [2f, 10], or HI/H_3PO_2 [11]) of the corresponding 3-arylphthalides which are readily available by aromatic lithiation and subsequent electrophilic substitution (aromatic aldehydes) of the masked carboxylic acids [12]. In this paper, we describe a novel efficient synthetic sequence as a general strategy for the transformation of chlorobenzoic acids (**A**) into their *ortho*-benzylated derivatives (**B**).

Results and Discussion

For the desired purpose we investigated the following methodologies: (*i*) the straightforward benzylation *via* the reaction of benzyl bromides with *bis*-lithiated anilides; (*ii*) the reductive cleavage of 3-arylchlorophthalides prepared by the reaction of *bis*-lithiated anilides with aromatic aldehydes, followed by the acid catalyzed cyclization of the formed hydroxy products [13, 14]. For both routes, the generation of lithiated species of the masked chloroaromatic carboxylic acids appeared to be necessary.

In recent studies [13, 14] we have reported that the secondary carboxyamide (anilide) moiety provides an excellent possibility for the regiospecific *ortho*-lithiation and the subsequent electrophilic substitution of the benzene ring as a way of transforming chlorobenzoic acids into their C-*ortho*-substituted derivatives.

To achieve this goal, the chloroanilides **1**, **2**, and **3** were reacted with 2.1 equivalents of *n*-BuLi in *THF*, thereby efficiently converting them into the corre-



1 **2** **3**

a, R^1 = Cl
b, R^1 = OMe

4 **5** **6**

a, R^1 = Cl
b, R^1 = OMe

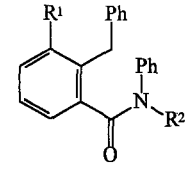
Formulae 1

sponding *bis*-(N- and C-*ortho*)-lithiated anilides **4**, **5**, and **6**. Thus, the *m*-chloroanilide **2** was reacted at low temperature (−78 °C, 0.5 h) to the *bis*-lithiated anilide **5** which appeared to be unstable (conversion to the benzyne) if the reaction solution was allowed to warm above −30 °C [14]. On the other hand, in the case of *o*- and *p*-chloroanilides **1** and **3** the effective generation of the *bis*-lithiated anilides **4** and **6** required an increase of temperature for the lithiation process (−78 °C, 0.5 h → 20 °C, 1 h). The treatment of solutions of the lithiated species with electrophiles yielded the desired *ortho*-substituted products. In the case of the benzylation reaction, 2.2 to 2.4 equivalents of benzyl bromide were used. For the synthesis of phthalides, aromatic aldehydes were applied.

Benzylation of bis-(N- and C-ortho)-lithiated anilides **4**, **5**, *and* **6**

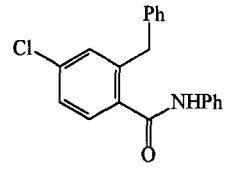
Our first task was to check to what extent the straightforward benzylation of *bis*-(N- and C-*ortho*)-lithiated anilides by benzyl bromides could be applied to the synthesis of the desired compounds. For these tests, the *meta*- and *para*-chloroanilides **2a** and **3** were selected because they are examples for steric hindrance around the formed carbon-lithium bond. Treatment of the solution of the lithiated anilides **5a** and **6** with benzyl bromide afforded the corresponding benzylated anilides **7a** and **8** in good yields (71% and 52%). Replacement of benzyl bromide by *ortho*-bromobenzyl bromide in the case of the reaction with lithiated *p*-chloroanilide **6** gave 2-bromo-4-chlorobenzanilide (**9**, 66.2%) instead of the expected benzylated compound. The formed anilide **9** was accompanied by 2,2′-dibromobibenzyl which is probably formed as a product of metal-halogen exchange and subsequent benzylation. The benzylated anilides **7a** and **8** afforded the benzylated acids **11a** (27.4%) and **12a** (72.9%) upon reaction with boiling 58% sulfuric acid. These were accompanied by the corresponding anthrones **14** (41.1%) and **15** (~15%). Prolonged reaction time

altered the product ratio in favour of anthrone formation. The anthrones were oxidized ($K_2Cr_2O_7 - CH_3COOH/H_2O$) without purification and gave anthraquinones **16** (79.3%) and **17** (83%). The acidic hydrolysis of the anilide **9** (58% H_2SO_4) furnished acid **13** in high yield (90.2%).



7

a, R^1 = Cl; R^2 = H
b, R^1 = OMe; R^2 = H
c, R^1 = OMe; R^2 = CH_2Ph



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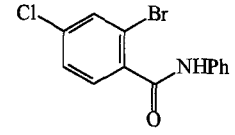

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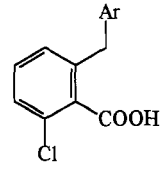
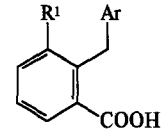


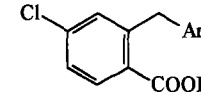
10

Ar = 2-C_6H_4-OMe



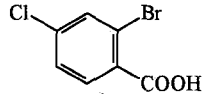
11

a, R^1 = Cl; Ar = C_6H_5
b, R^1 = Cl; Ar = 2-C_6H_4-OMe
c, R^1 = Cl; Ar = 2,3-$C_6H_3(OMe)_2$
d, R^1 = Cl; Ar = 2,4-$C_6H_3(OMe)_2$
e, R^1 = Cl; Ar = 2,5-$C_6H_3(OMe)_2$
f, R^1 = OMe; Ar = C_6H_5

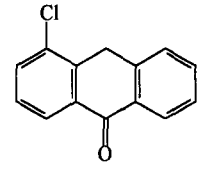


12

a, Ar = C_6H_5
b, Ar = 2-C_6H_4-OMe



13



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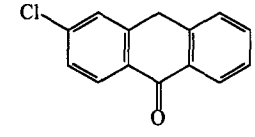

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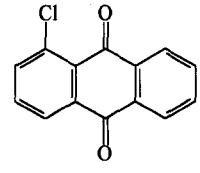
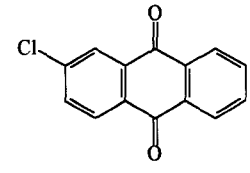


16



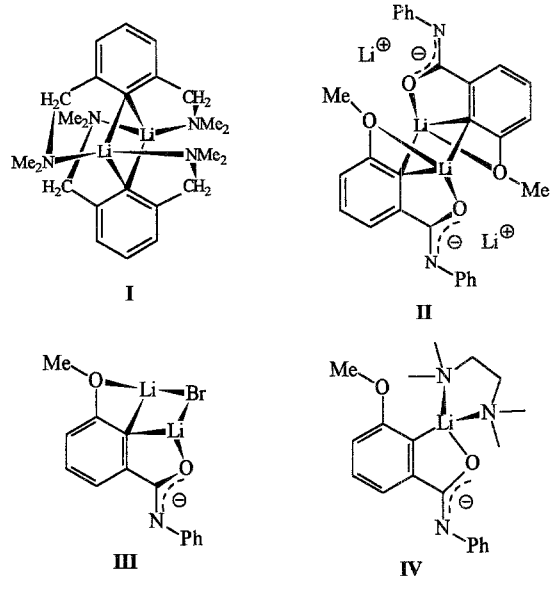
17

Formulae 2

In the course of an attempt to obtain more insight into the benzylation reaction of *bis*-(N- and C-*ortho*)-lithiated anilides, we decided to use lithiated *m*-methoxyanilide (**5b**) as a simple and even at higher temperatures stable model. It was observed that **5b** upon the reaction with benzyl bromide (2.2 equivalents as in all other benzylation reactions) afforded only *bis*-(N- and C-*ortho*)-benzylated anilide **7c** and some amount of recovered starting anilide **2b** (**7c**: 80.1%; **2b**: 17.2%; overall yield: 97.3%). The reaction was changed in favour of the formation of the desired

C-benzylated anilide **7b** when LiBr was pre-added for the generation of the lithiated anilide **5b** (**7b**: 56.1%; **7c**: 15.1%; **2b**: 26.8% overall yield: 98.0%). Pre-adding of tetramethyloethylenediamine (*TMEDA*) gave identical results to that observed in the presence of LiBr (**7b**: 54.6%; **7c**: 14.7%; **2b**: 29.0%; overall yield: 98.3%).

In connection with the observed unexpected *bis*-benzylation of the lithiated anilide **5b** which is in contrast to other examples described herein and previously [6] and a great difference in the course of the benzylation reaction upon pre-adding LiBr or *TMEDA* for the generation of the lithiated species, the following should be considered. It has been shown [15] that the aromatic lithiated compounds derived from the *meta*-disubstituted benzene derivatives exist as dimers. This can be illustrated in the case of 1,3-*bis*-(dialkylamino)-methylbenzene lithiated at position 2 which forms dimers in which the puckering of the five-membered chelated rings (see structure **I**) causes a very high stability of the molecule. It has been proposed that the formed aromatic lithiated compounds, in most cases dimers, frequently exist as dimeric – monomeric equilibria which are shifted towards the monomeric species in the presence of additives such as LiBr, *TMEDA*, or pentamethyldiethylenetriamine (*PMDTA*) [16].



Formulae 3

Although the observed behaviour of the lithiated *m*-methoxyanilide **5b** in the reaction with benzyl bromide cannot be unequivocally explained, two pathways can be proposed on the basis of the difference in the course of the alkylation carried out without of additives or in the presence of LiBr or *TMEDA*. In the first case, the dimeric species **II** is formed in which the carbon-lithium bond appears to be inaccessible for benzyl bromide. The alkylation reaction starts at the anionic amide centre with the formation of the N-benzylated derivative which probably causes the dissociation of the dimer by steric reasons and renders the carbon-lithium bond accessible for benzylation. As a consequence, it then forms the *bis*-benzylated anilide **7c**. In the second case, pre-adding of LiBr causes that mainly the mixed complex **III** is

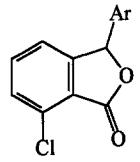
formed or that the initially generated dimer **II** exists in an equilibrium with LiBr as shown below:

$$ArLi_2 + 2LiBr \rightleftharpoons 2ArBrLi_2$$

The carbon-lithium bond of the lithiated anilide **5b** in the mixed complex **III** appears to be sufficiently accessible towards the alkylation reaction and therefore the C-benzylated compound **7b** is formed as the major product. The identical results are obtained after pre-adding *TMEDA* or LiBr suggest that the monomeric complex **IV** is formed; this species probably exists in an equilibrium with dimer **II**.

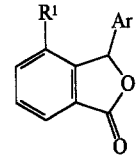
Synthesis of o-benzyl-chlorobenzoic acids via reductive cleavage of the corresponding 3-arylphthalides

The difficulties observed in the straightforward benzylation of anilides **1**, **2** and **3** prompted us to apply reductive cleavage of the 3-arylphthalides for the synthesis of the desired *o*-benzylchlorobenzoic acids. The required 3-arylchlorophthalides were prepared from the lithiated anilides **4**, **5**, and **6** which on reaction with aromatic aldehydes afforded the corresponding hydroxy products; these were cyclyzed without isolation to yield the 3-arylchlorophthalides **18**, **19**, and **20**.



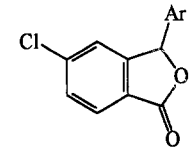
18

Ar = 2-C_6H_4-OMe



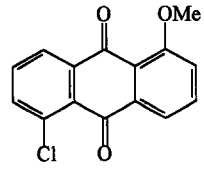
19

a, R^1 = Cl; Ar = 2-C_6H_4-OMe
b, R^1 = Cl; Ar = 2,3-$C_6H_3(OMe)_2$
c, R^1 = Cl; Ar = 2,4-$C_6H_3(OMe)_2$
d, R^1 = Cl; Ar = 2,5-$C_6H_3(OMe)_2$
e, R^1 = OMe; Ar = 2-C_6H_4-Cl
f, R^1 = OMe; Ar = 2-C_6H_4-Br

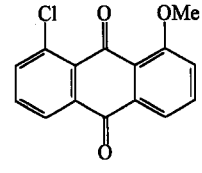


20

Ar = 2-C_6H_4-OMe



21



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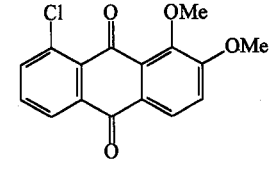

23

Formulae 4

However, we encountered difficulties in this reductive cleavage: in the case of the tested phthalides **18**, **19a**, and **19b**, hydrogenation by HI/H_3PO_2 [11] gave intractable mixtures. The application of $CuSO_4$-activated Zn in the basic medium [2a, 2c, 9] caused – in addition to the cleavage of the phthalide ring – a removal of the chlorine atom, resulting in a mixture of acids.

The ionic hydrogenation of the hydroxy group in alcohols by a triethylsilane – acid mixture is known to proceed in good yields [10]. It was therefore presumed

that the ionic hydrogenation of the chlorophthalides would also proceed smoothly. Indeed, upon ionic hydrogenation and reductive cleavage of the chlorophthalides **18**, **19**, and **20** by a triethylsilane – $TiCl_4$ mixture the *o*-benzyl-chlorobenzoic acids **10**, **11**, and **12** were obtained in good yields.

The described methodology for introducing an alkyl substituent in the *ortho* position to the anilide function of chlorobenzoic acids shows considerable versatility for the regiospecific synthesis of trisubstituted benzenes. Thus, in connection with the effective removal of the anilide moiety by acid hydrolysis or reductive cleavage of phthalides to the corresponding, acids, this strategy should allow the access to a wide variety of benzenes.

In order to provide more details for the presented methods the 3-arylphthalides **19e** and **19f** were tested in which the halogen atom is displaced from the acid ring to the benzylic one. In this cases, the reductive cleavage of the phthalide ring was accompanied by the total removal of halogen, and as a consequence, acid **11f** was formed.

The fact that the *o*-benzylbenzoic acids are convenient starting materials for the regiospecific synthesis of anthraquinones is demonstrated by the cyclization of acids **10**, **11b**, and **11c** to the corresponding anthrones *via* treatment with trifluoroacetic anhydride and subsequent oxidation by chromium trioxide in acetic acid to the new chloroanthraquinones **21**, **22**, and **23**, respectively.

Experimental

M.p.s. were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Zeiss-Jena Specord 71-IR (KBr pellets). ^1H NMR spectra were determined on Tesla BS-467 (60 MHz) or a Varian-Gemini-200 (200 MHz) NMR spectrometers using *TMS* as internal standard. Compounds were purified until observed as single spots on TLC (Kieselgel GF-254 type 60). The anilides **1**, **2**, and **3** were obtained by known methods [14]. 2-Bromobenzyl bromide, 2-methoxybenzaldehyde, 2,3-dimethoxybenzaldehyde, 2,4-dimethoxybenzaldehyde, and 2,5-dimethoxybenzaldehyde (Aldrich) were used without purification. *n*-Butyllithium (*n*-BuLi, Aldrich) was titrated before use.

General procedure for the metallation and electrophilic substitution of **1**, **2**, *and* **3**

To the anilide (0.01 mol) in anhydrous *THF* (25 cm^3) *n*-BuLi (0.021 mol) was added dropwise at −78 °C (in the case of reaction of anilide **2b**, 0.03 mol of etheral solution of LiBr or 0.03 mol of *TMEDA* were added). The solution was held at −78 °C for 0.5 h. In the cases of the anilides **1**, **2b**, and **3** the mixtures were warmed up to room temperature and kept at this temperature for 1 h and then cooled to −78 °C again. To the solution of the lithiated species, benzyl bromide (0.022 mole), 2-bromobenzyl bromide (0.022 mole), or an appropriate aromatic aldehyde (0.011 mole) were added at −78 °C. After 1 h at −78 °C the mixture was allowed to reach room temperature and was stirred at this condition for 1 h; then, water (10 cm^3) was added. In the cases in which the reaction was carried on with an aromatic aldehyde, the mixture was acidified with hydrochloric acid (15%). Next, the reaction mixture, after evaporation of part of *THF*, was extracted with $CHCl_3$ (3 × 50 cm^3), the layers were separated, and the organic phase was dried ($MgSO_4$). The solvent was removed and the residue purified by column chromatography (silica gel; benzene, chloroform, and chloroform:ether = 8:2). Yields, physical properties, IR and NMR spectroscopic data, and elemental analyses are given in Tables 1 and 3.

Table 1. Reaction of lithiated anilides **4**, **5**, and **6** with benzyl bromides

Starting materials	Product	Yield[a] (%)	M.p. (°C) (solvent)	Analysis (%) Found (required) C	H	N	Cl	IR (cm^{-1})	^1H NMR (relative to internal *TMS*)
2a/benzyl bromide	**7a** ($C_{20}H_{16}ClNO$)	66	153–155 (benzene-heptane 1:1)	74.60 (74.65)	5.34 (5.01)	4.23 (4.35)	11.10 (11.02)	3230 (NH) 1640 (C=O)	δ_H(60 MHz, *DMSO*-d_6) = 10.5(s, 1 H, NH), 7.9–6.8 (m, 13 H, Ar-H), 4.20 (s, 2 H, CH_2) ppm
3/benzyl bromide	**8** ($C_{20}H_{16}ClNO$)	47	151–153 (benzene-heptane 1:1)	74.49 (74.65)	4.80 (5.01)	4.31 (4.35)	11.18 (11.02)	3180 (NH) 1650 (C=O)	δ_H(60 MHz, $CDCl_3$) = 7.6–6.8 (m, 14 H, Ar-H, NH), 4.10 (s, 2 H, CH_2) ppm
3/2-bromobenzyl bromide	**9** ($C_{13}H_9BrClNO$)	61.2	156–158.5 (benzene)	50.47 (50.27)	3.06 (2.92)	4.22 (4.51)	11.27 (11.41)	3250 (NH) 1670 (C=O)	δ_H(60 MHz, $CDCl_3$ + *DMSO*-d_6) = 9.8 (s, 1 H, NH), 7.8–6.6 (m, 8 H, Ar-H) ppm
2b/benzyl bromide	**7b** ($C_{21}H_{19}NO_2$)	52 [b]	132–134 (benzene-heptane 2:8)	79.54 (79.47)	6.13 (6.03)	4.28 (4.41)		3300 (NH) 1640 (C=O)	δ_H(200 MHz, *DMSO*-d_6) = 10.17 (s, 1 H, NH, exchangeable with D_2O), 7.70 (d, 2 H, J = 8.1 Hz, Ar-H), 7.40–7.00 (m, 11 H, Ar-H), 4.09 (s, 2 H, CH_2), 3.78 (s, 3 H, OCH_3) ppm
	7c ($C_{28}H_{25}NO_2$)	75 [b]	108–110 (benzene-heptane 9:1, then ethanol)	82.55 (82.53)	6.25 (6.18)	3.47 (3.44)		1640 (C=O)	δ_H(200 MHz, $CDCl_3$) = 7.30–6.30 (m, 18 H, Ar-H), 5.06 (s, 2 H, N–CH_2), 4.19 (s, 2 H, CH_2), 3.71 (s, 3 H, OCH_3) ppm

[a] All yields represent isolated pure material; [b] data given in the following represent yields of anilides **7b** and **7c** which were determined by ^1H NMR spectroscopy ($CDCl_3$, internal *TMS*) from the peak areas of the C–CH_2– and N–CH_2– protons: *i*) without additives: **7c**: 80%, **2b**: 17%; *ii*) with LiBr: **7b**: 56%, **7c**: 15%, **2b**: 27%; *iii*) with *TMEDA*: **7b**: 54%, **7c**: 15%, **2b**: 29%

Table 2. Hydrolysis of anilides **7a**, **8** and **9**

Starting anilide	Product	Time of hydrolysis (h)	Yield[a] (%)	M.p. (°C) (solvent)	Analysis (%) Found (required) C	H	Cl	IR (cm^{-1})	^1H NMR (relative to internal *TMS*)
7a	**11a** ($C_{14}H_{11}ClO_2$)	50	27.4[b]	128–130[c] (ethanol)	67.95 (68.16)	4.40 (4.49)	14.31 (14.37)	3300 (OH) 1710 (C=O)	δ_H(60 MHz, $CDCl_3$) = 8.3–7.0 (m, 9 H, Ar-H, COOH), 4.0 (s, 2 H, CH_2) CH_2) ppm
	16 ($C_{14}H_7ClO_2$)		74.3[d]	162–164[e] (heptane-benzene 30:6)	69.25 (69.30)	2.85 (2.91)	14.55 (14.61)	1680 (C=O)	δ_H(200 MHz, $CDCl_3$) = 8.37–8.23 (m, 3 H, Ar-H), 7.89–7.74 (m, 3 H, Ar-H), 7.68 (t, 1 H, J = 8.0 Hz, Ar-H) ppm
8	**12a** ($C_{14}H_{11}ClO_2$)	24	72.9[b]	150–151[f]	68.34 (68.16)	4.25 (4.49)	14.28 (14.37)	3300 (OH) 1700 (C=O)	δ_H(200 MHz, $CDCl_3$) = 8.02 (d, 1 H, J = 8.3 Hz, *o*-Ar-H), 7.38–7.06 (m, 8 H, Ar-H, COOH), 4.43 (s, 2 H, CH_2) ppm
	17 ($C_{14}H_7ClO_2$)		78[d]	211–213[g] (ethanol)	69.40 (69.30)	2.97 (2.91)	14.65 (14.61)	1680 (C=O)	δ_H(200 MHz, $CDCl_3$) = 8.50–7.00 (m) ppm
9	**13** ($C_7H_4BrClO_2$)	3	85.2	156–158[h] (methanol-water 1:2)	35.51 (35.71)	1.80 (1.71)		3100 (OH) 1705 (C=O)	δ_H(200 MHz, *DMSO*-d_6) = 13.5 (br s, 1 H, COOH), 7.88 (d, 1 H, J = 2.1 Hz, 3-Ar-H), 7.78 (d, 1 H, J = 8.4 Hz, 5-Ar-H), 7.57 (dd, 1 H, J_1 = 2.1 Hz, J_2 = 8.3 Hz, 6-Ar-H) ppm

[a] All yields represent isolated pure material; [b] acids **11a** and **12a** were accompanied by the corresponding anthrons **14** (41%) and **15** (15%), respectively; the anthrons were identified after oxidation to anthraquinones **16** and **17**; [c] Ref. [17]: m.p. 126–127 °C; [d] total yields of the cyclization of acids **11a** and **12a** (concentrated H_2SO_4) and subsequent oxidation of the corresponding anthrons to the anthraquinones **16** and **17**; [e] Ref. [18]: m.p. 162 °C; [f] Ref. [19]: m.p. 149–151 °C; [g] Ref. [20]: m.p. 211 °C; [h] Ref. [21]: m.p. 154–155 °C

Table 3. Synthesis of phthalides

Starting materials	Product	Yield[a] (%)	M.p. (°C) (solvent)	Analysis (%) Found (required) C	H	Cl	IR (cm^{-1})	^1H NMR (relative to internal *TMS*)
1a/2-methoxy-benzaldehyde	**18** ($C_{15}H_{11}ClO_3$)	69	150–152[b] (ethanol)				1780 (C=O)	δ_H(60 MHz, $CDCl_3$) = 7.7–6.7 (m, 8 H, Ar-H and C–H), 3.80 (s, 3 H, OCH_3) ppm
2a/2-methoxy-benzaldehyde	**19a** ($C_{15}H_{11}ClO_3$)	71	161–162[c] (acetone)				1780 (C=O)	δ_H(60 MHz, $CDCl_3$) = 8.0–6.7 (m, 8 H, Ar-H and C–H), 3.71 (s, 3 H, OCH_3) ppm
2a/2,3-dimethoxy-benzaldehyde	**19b** ($C_{16}H_{13}ClO_4$)	68	117–119 (ethanol)	63.24 (63.06)	4.28 (4.30)	11.50 (11.63)	1770 (C=O)	δ_H(200 MHz, $CDCl_3$) = 7.88 (d, 1 H, J = 7.0 Hz, Ar-H), 7.66–7.43 (m, 2H, Ar-H), 7.09–6.89 (m, 2H, Ar-H), 6.72 (s, 1H, C–H), 6.64–6.48 (m, 1H, Ar-H), 3.86 (s, 3 H, OCH_3), 3.79 (s, 3H, OCH_3) ppm
2a/2,4-dimethoxy-benzaldehyde	**19c** ($C_{16}H_{13}ClO_4$)	61	143–144 (ethanol)	62.99 (63.06)	4.48 (4.30)	11.37 (11.63)	1770 (C=O)	δ_H(200 MHz, $CDCl_3$) = 7.87 (d, 1H, J = 7.2 Hz, Ar-H), 7.66–7.45 (m, 2H, Ar-H), 6.84 (d, 1H, J = 8.6 Hz, Ar-H), 6.71 (s, 1H, C–H), 6.50–6.36 (m, 2H, Ar-H), 3.81 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3) ppm
2a/2,5-dimethoxy-benzaldehyde	**19d** ($C_{16}H_{13}ClO_4$)	41	153–155 (benzene-hexane 1:1)	62.95 (63.06)	4.37 (4.30)	11.50 (11.63)	1780 (C=O)	δ_H(60 MHz, $CDCl_3$) = 8.0–7.8 (m, 1H, Ar-H), 7.7–7.3 (m, 2 H, Ar-H), 7.0–6.85 (m, 2 H, Ar-H), 6.7 (s, 1 H, C–H), 6.6–6.4 (m, 1 H, Ar-H), 3.66 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3) ppm
3/2-methoxy-benzaldehyde	**20** ($C_{15}H_{11}ClO_3$)	62	111–113[d] (ethanol)				1780 (C=O)	δ_H(60 MHz, $CDCl_3$) = 8.0–6.6 (m, 8 H, Ar-H and C–H), 3.80 (s, 3H, OCH_3) ppm
1b/2-chloro-benzaldehyde	**19e** ($C_{15}H_{11}ClO_3$)	54	142–144 (ethanol)	65.47 (65.59)	3.94 (4.04)	12.89 (12.91)	1780 (C=O)	δ_H(200 MHz, $CDCl_3$) = 7.75–7.68 (m, 1H, Ar-H), 7.63–7.54 (m, 2H, Ar-H), 7.28–7.21 (m, 2H, Ar-H), 7.15–7.05 (m, 1H, Ar-H), 6.84 (s, 1H, C–H), 6.81–6.75 (m, 1H, Ar-H), 3.70 (s, 3 H, OCH_3) ppm
1b/2-bromo-benzaldehyde	**19f** ($C_{15}H_{11}BrO_3$)	55	168–170 (ethanol)	56.45 24.88(Br) (56.45)	3.49 (3.47)	(25.04)	1770 (C=O)	δ_H(200 MHz, $CDCl_3$) = 7.66–7.60 (m, 1 H, Ar-H),7.57–7.52 (m, 2 H, Ar-H), 7.23–7.16 (m, 2 H, Ar-H), 7.14–7.06 (m, 1 H, Ar-H), 6.87 (s, 1 H, C–H), 6.85–6.77 (m, 1 H, Ar-H), 3.74 (s, 3 H, OCH_3) ppm

Table 4. Synthesis of acids **10**, **11b–f**, and **12a** by reductive cleavage of phthalides

Starting phthalide	*o*-Benzyl-benzoic acid	Time of reaction (h)	Yield[a] (%)	M.p. (°C) (solvent)	Analysis (%) Found (required) C	H	Cl	IR (cm^{-1})	^1H NMR (relative to internal *TMS*)
18	**10** ($C_{15}H_{13}ClO_3$)	7 h at 0 °C and 12 h at r.t.	57.8	134–136 (benzene-toluene 2:5)	65.32 (65.11)	4.51 (4.74)	12.64 (12.81)	3230 (OH) 1710 (C=O)	δ_H(60 MHz, $CDCl_3$ + *DMSO*-d_6) = 9.5 (1H, COOH), 7.3–6.7 (m, 7H, Ar-H), 4.1 (s, 2H, CH_2), 3.6 (s, 3H, OCH_3) ppm
19a	**11b** ($C_{15}H_{13}ClO_3$)	7 h at 0 °C and 12 h at r.t.	78	193–195 (toluene)	65.40 (65.11)	4.66 (4.74)	12.70 (12.81)	3220 (OH) 1695 (C=O)	δ_H(200 MHz, $CDCl_3$ + *DMSO*-d_6) = 11.0 (br s, 1H, COOH), 7.78 (dd, 1H, J_1 = 7.8 Hz J_2 = 1.5 Hz, Ar-H), 7.53 (dd, 1H, J = 7.9 Hz, J_2 = 1.3 Hz, Ar-H), 7.30 (t, 1H, J = 7.8 Hz, Ar-H), 7.19–7.07 (m, 1H, Ar-H), 6.86 (d, 1H, J = 8.1 Hz, Ar-H), 6.80–6.68 (m, 1H, Ar-H), 6.57 (d, 1H, J = 7.5 Hz, Ar-H), 4.46 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3) ppm
19b	**11c** ($C_{16}H_{15}ClO_4$)	7 h at 0 °C and 12 h at r.t.	62.5	188–190 (ethanol-water)	62.50 (62.65)	4.73 (4.93)	11.48 (11.56)	3000 (OH) 1710 (C=O)	δ_H(200 MHz, $CDCl_3$) = 7.88 (dd, 1H, J_1 = 1.4 Hz, J_2 = 7.8 Hz, *o*-Ar-H), 7.58 (dd, 1H, J_1 = 1.4 Hz, J_2 = 8.0 Hz, Ar-H), 7.35–7.23 (m, 1H, Ar-H), 6.93–6.72 (m, 2H, Ar-H), 6.29 (dd, 1H, J_1 = 1.7 Hz, J_2 = 7.5 Hz, Ar-H), 4.56 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3) ppm
19c	**11d** ($C_{16}H_{15}ClO_4$)	7 h at 0 °C and 12 h at r.t.	52	142.5–144.5 (ethyl acetate-heptane 1:1)	62.28 (62.65)	5.12 (4.93)	11.23 (11.56)	3500 (OH) 1690 (C=O)	δ_H(200 MHz, $CDCl_3$) = 10.5 (1H, COOH), 7.88 (d, 1H, J = 7.7 Hz, *o*-Ar-H), 7.58 (d, 1H, J = 7.7 Hz, Ar-H), 7.28 (t, 1H, J = 7.8 Hz, Ar-H), 6.62 (d, 1H, J = 8.5 Hz, Ar-H), 6.43 (d, 1H, J = 2 Hz, Ar-H), 6.32 (dd, 1H, J_1 = 8.5 Hz, J_2 = 2.0 Hz, Ar-H), 4.46 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3) ppm

(Continued)

Table 4. *(Continued)*

19d	**11e** ($C_{16}H_{15}ClO_4$)	1 h at 0 °C and 1 h at r.t.	59.6	181–183 (ethanol-water)	62.50 (62.65)	4.99 (4.93)	11.70 (11.56)	3450 (OH) 1700 (C=O)	δ_H(200 MHz, $CDCl_3$ + *DMSO*-d_6) = 12.7 (br s, 1 H, COOH), 7.79 (dd, 1 H, J_1 = 7.7 Hz, J_2 = 1.4 Hz, Ar-H), 7.55 (dd, 1H, J_1 = 9.4 Hz, J_2 = 1.4 Hz, Ar-H), 7.32 (t, 1H, J = 7.8 Hz, Ar-H), 6.79 (d, 1H, J = 8.9 Hz, Ar-H), 6.63 (dd, 1H, J_1 = 8.9 Hz, J_2 = 3.0 Hz, Ar-H), 6.10 (d, 1H, J = 3.0 Hz, Ar-H), 4.42 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.59 (s, 3 H, OCH_3) ppm
20	**12b** ($C_{15}H_{13}ClO_3$)	2 h at 0 °C and 12 h at r.t.	48.5	172–174 (benzene)	65.32 (65.11)	4.98 (4.74)	12.72 (12.81)	3450 (OH) 1690 (C=O)	δ_H(200 MHz, $CDCl_3$) = 7.96 (d, 1H, J = 8.4 Hz, *o*-Ar-H), 7.30–6.83 (m, 7H, Ar-H, COOH), 4.40 (s, 2H, CH_2), 3.78 (s, 3H, OCH_3) ppm
19e or **19f**	**11f** ($C_{15}H_{14}O_3$)	0.1 h at 0 °C	46 55	205–207 (benzene)	74.25 (74.36)	5.80 (5.82)		3300 (OH) 1685 (C=O)	δ_H(60 MHz, $CDCl_3$ + *DMSO*-d_6) = 10.1 (1 H, COOH), 7.7–6.3 (m, 8H, Ar-H), 4.40 (s, 2 H, CH_2), 3.62 (s, 3H, OCH_3) ppm

[a] All yields represent isolated pure material

Table 5. Synthesis of anthraquinones **21–23**

Starting material	Anthraquinone	Yield[a] (%)	M.p. (°C) (solvent)	Analysis (%) Found (Required) C	H	Cl	IR (cm^{-1})	^1H NMR (relative to internal *TMS*)
10	**21** ($C_{15}H_9ClO_3$)	53.1	216–218 (ethyl acetate)	65.70 (66.05)	3.38 (3.30)	12.99 (13.03)	1680-doublet (C=O)	δ_H(60 MHz, $CDCl_3$) = 8.2(dd, 1 H, J_1 = 6 Hz, J_2 = 3 Hz, Ar-H), 8.0–7.2 (m, 5 H, Ar-H), 3.9 (s, 3 H, OCH_3) ppm
11b	**22** ($C_{15}H_9ClO_3$)	58.7	171.5–172.5 (ethyl acetate)	66.16 (66.05)	3.48 (3.30)	13.21 (13.03)	1680-doublet (C=O)	δ_H(60 MHz, $CDCl_3$) = 8.2 (dd, 1 H, J_1 = 7 Hz, J_2 = 2 Hz, Ar-H), 8.0–7.2 (m, 5 H, Ar-H), 3.9 (s, 3 H, OCH_3) ppm
11c	**26** ($C_{16}H_{11}ClO_4$)	45	183.5–185 (ethyl acetate)	63.57 (63.48)	3.69 (3.66)	11.74 (11.71)	1680 (C=O)	δ_H(200 MHz, $CDCl_3$) = 8.20 (dd, 1 H, J_1 = 1.4 Hz, J_2 = 7.6 Hz, 7-Ar-H), 8.07 (d, 1 H, J = 8.6 Hz, 3 or 4-Ar-H), 7.75 (dd, 1 H, J_1 = 1.4 Hz, J_2 = 8.0 Hz, 5-Ar-H), 7.60 (t, 1 H, J = 7.8 Hz, 6-Ar-H), 7.24 (d, 1 H, J = 8.7 Hz, 4 or 3-Ar-H), 4.04 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3) ppm

[a] All yields represent isolated pure material

Hydrolysis of the benzylated anilides **7a**, **8**, *and* **9**

Amides **7a**, **8**, or **9** (0.005 mol) were refluxed in a mixture of 15 cm^3 of acetic acid, 3.0 cm^3 of water, and 4.0 cm^3 of concentrated sulfuric acid for the period given in Table 2. Next, the solution was poured into 60 cm^3 of water and ice. The solid was filtered and dissolved in 50 cm^3 of 5% Na_2CO_3. The remaining insoluble solid consisted in each case of a mixture of anthrone and substrate. The filtrate was acidified with HCl (10%). The precipitated white solid was separated and purified (if necessary) by crystallization (see Table 2). The crude acids (**11a** or **12a**; 1.0 g) were dissolved in concentrated H_2SO_4 (10 cm^3), stirred for 5 h, and poured into 50 cm^3 of ice water. The products were separated and washed with 5% Na_2CO_3 solution. The crude anthrones were dissolved in 30 cm^3 of acetic acid. A saturated aqueous solution of 2.00 g $K_2Cr_2O_7$ was added, and the mixture was warmed to 90 °C for 1 h. After cooling, the mixture was poured into 200 cm^3 of water. The separated solids were filtered, chromatographed on a silica column (benzene, then chloroform), and then purified by crystallization (for details see Table 2).

Reductive cleavage of the 3-arylphthalides **18**, **19**, *and* **20**

To a stirred solution of phthalide (0.01 mol) and Et_3SiH (0.03 mol) in 10 cm^3 of CH_2Cl_2, a solution of $TiCl_4$ (2.0 cm^3) in CH_2Cl_2 (10 cm^3) was added dropwise at 0 °C. The mixture was stirred for the time given in Table 4. The excess of Et_3SiH was removed under vacuum, and 75 cm^3 of water were added. The mixture was extracted with chloroform (3 × 25 cm^3). The combined extracts, after removal of the solvent, gave a solid residue. This solid was dissolved in 100 cm^3 of 5% Na_2CO_3 solution. After filtering, the aqueous layer was acidified with 5% HCl. The precipitated benzylated chlorobenzoic acids were filtered and purified by crystallization (see Table 4).

Cyclization of benzylbenzoic acids to anthraquinones **21**, **22**, *and* **23**

To a stirred solution of 0.01 mol of benzylbenzoic acid in 40 cm^3 dichloromethane, trifluoroacetic anhydride (5.0 cm^3) was added at 0 °C. The solution was stirred at room temperature for 2 h; then solvent was distilled off. To the residue, 70 cm^3 of water were added. The product was extracted with chloroform (3 × 20 cm^3). The combined extracts, after removal of the solvent, gave a solid residue. This residue was dissolved in 40 cm^3 of acetic acid, and a saturated solution 0.3 g of chromium trioxide in water was added. The mixture was heated on a steam bath for 30 min. After cooling, the solution was poured into 150 cm^3 of water, and the precipitated product was filtered. The formed anthraquinons were isolated by column chromatography (silica gel; chloroform) and purified by crystallization (for details, see Table 5).

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (No. 3 TO9A 041 09) from the *Polish Committee for Scientific Research* (KBN).

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Received November 30, 1995. Accepted December 8, 1995