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Lithiation of 2-(chloroaryl)-2-aryl-1,3-dioxolanes with butyllithium activated by *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine

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Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract—Intramolecular competition of variously substituted phenyl rings of benzophenone ketals in lithiation reactions proved to be a useful tool to study both *ortho*-directing ability and long-range effects of the substituents. The regioselectivities observed in the reaction of benzophenone ketals having one or two chloro substituents in one of the aryl rings with butyllithium complexed to *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine demonstrate the significance of both *ortho*- and *meta*-acidifying effect of the chloro substituents. The lithio species thus generated were carboxylated resulting in new polysubstituted benzoic acids.

1. Introduction

Relative *ortho*-directing abilities of directed metalation groups (DMGs) in lithiation reactions have been investigated in several studies using intramolecular or intermolecular competitions.[1] Optional site selectivity has been achieved in the lithiation reactions of arene substrates through matching of reagents and neighbouring groups.[2,3] Some results published recently called the attention to the long-range effects of some DMGs resulting in unexpected regioselectivity of the metalation reactions.[4–7]

Intramolecular competition of variously substituted phenyl rings of benzophenone ketals in lithiation reactions proved to be a useful tool to study both *ortho*-directing ability and long-range effects of the substituents.[8] Thus lithiation of ketals **1a**–**e** with butyllithium in THF at 0 to −20 °C occurred in the 4-chlorophenyl ring *ortho* to the ketal substituent (**2a**–**e**) as demonstrated by the formation of products **3a**–**e** and **4a**–**e** after functionalization (Scheme 1). Intramolecular competition between the aryl rings was observed in the lithiation of compound **1f** with butyllithium in THF at −50 °C as indicated by the formation of **3f** and **5** in a 1:2 ratio. The observed regioselectivities were explained by the long-range (*meta*) electron-withdrawing (acidifying) effect of the chloro substituent in addition to the *ortho*-directing aptitude of the ketal group (a factor present in both phenyl rings).[9]

We now report the extension of this work to the metalation of benzophenone ketals with butyllithium complexed to *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA). This reagent is expected to abstract a proton preferentially or exclusively from the most acidic site contrary to butyllithium, which is seeking coordinative assistance by a substituent of the substrate in order to accomplish deprotonation.[3,10] Nevertheless, in most cases it is hardly predictable, which is the most acidic site of benzophenone ketals **1**.

2. Results and discussion

Lithiation of ketals **1a**–**e** with butyllithium complexed with PMDTA in THF at −78 °C followed by carboxylation afforded benzoic acids **8** in good yield (Scheme 2), which demonstrates that lithiation occurred exclusively in the 4-chlorophenyl ring, *ortho* to the chloro substituent. The formation of benzoic acids **8b**–**d** indicates that chloro substituent exhibits superior inductive effect relative to methoxy group at the *ortho* position favouring the formation of lithiated intermediates **7b**–**d** contrary to lithiations at the methoxy adjacent sites.[3,11] With the knowledge of the stronger inductive effect of fluorine relative to chloro substituent it was expected that lithiation of ketal **1f** under similar conditions followed by carboxylation gave compound **6** as the single product in 73% yield.[12–14]

Keywords: Lithiation; Substituent effects; Benzophenones; 1,3-Dioxolanes.
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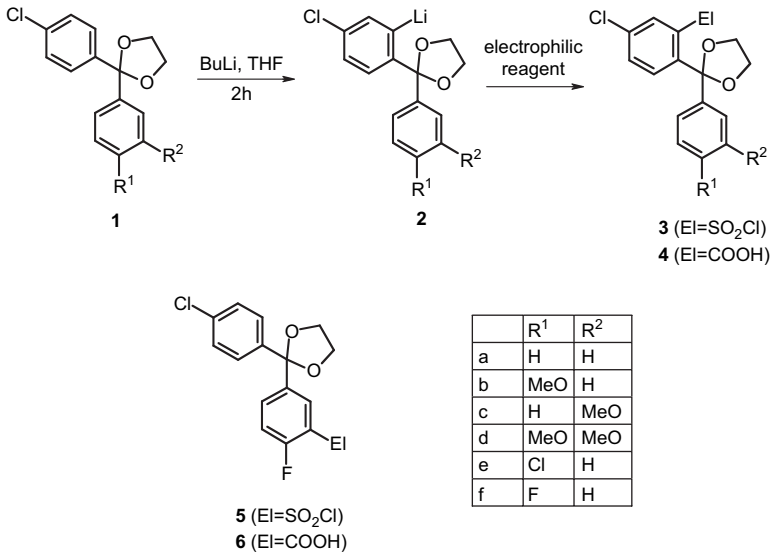
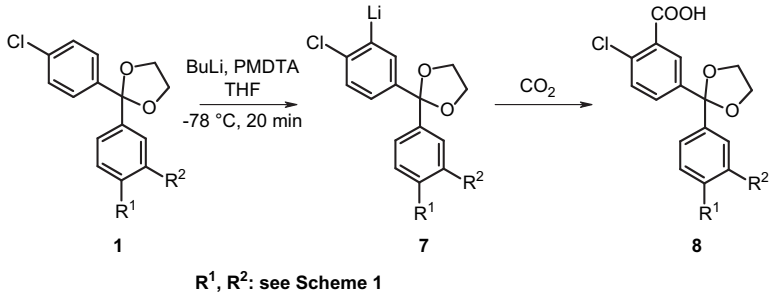


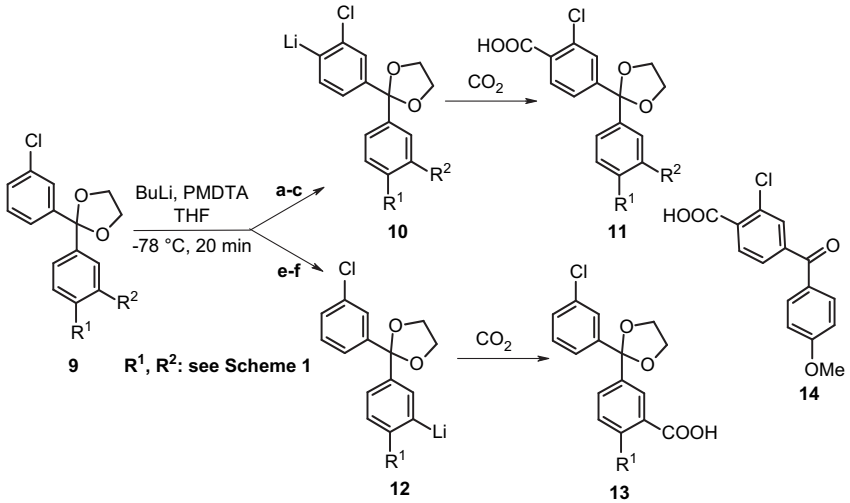
	R^1	R^2
a	H	H
b	MeO	H
c	H	MeO
d	MeO	MeO
e	Cl	H
f	F	H

Scheme 1.

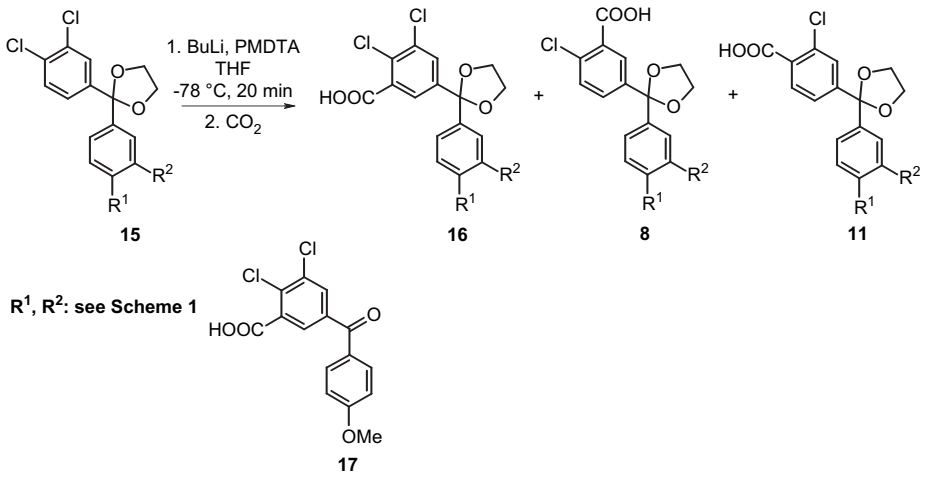


Scheme 2.

Butyllithium in THF at −78 °C abstracts a proton from compounds **9a–c** at the common *ortho* position of the chlorine and ketal groups.[9] Lithiation of benzophenone ketals **9a–c** with butyllithium complexed with PMDTA in THF at −78 °C followed by carboxylation afforded products **11a–c** (Scheme 3) indicating that metalation occurs solely at the sterically uncongested 4-position of the *meta*-chlorophenyl ring (**10a–c**). The oily product **11b** was hydrolyzed to crystalline benzophenone derivative **14**. It is worth mentioning that ^{1}H NMR analysis of



Scheme 3.



Scheme 4.

the crude acid fractions did not indicate the presence of regioisomers.

Simultaneous proton abstraction from the 4-position of the *meta*-chlorophenyl and 3-position of the *para*-chlorophenyl ring was observed in similar lithiation of compound **9e**. ^{1}H NMR analysis of the product mixture isolated after carboxylation demonstrated the formation of acids **11e** and **13e** in a 1:3.5 ratio, demonstrating that in the course of the lithiation reaction the developing negative charge is more destabilized by the electron-donating ketal group in the *para* than *meta* position. Benzoic acid **13e** was isolated in pure form and the structure **11e** could be unambiguously assigned to the minor product on the basis of the doublet at δ 7.94 ppm in the ^{1}H NMR spectrum of the product mixture, characteristic to the proton adjacent to a carboxylic function (see also compounds **11a–c**). As expected, fluoro derivative **9f** was lithiated exclusively at the 3-position of the *para*-fluorophenyl ring (**12f**), resulting in benzoic acid **13f** as the single product.

Ketals **15a**, **15b**, **15e** and **15f** were lithiated with butyllithium in THF at −78 °C at the site between the 1,3-interrelated chlorine and ketal group.[9] Lithiation of ketals **15a** with butyllithium complexed to PMDTA followed by carboxylation afforded a mixture of acids in 79% combined yield, the major product **16a** being isolated in 27% yield (Scheme 4). The metalation at the uncongested site next to the chlorine was accompanied with minor chlorine–lithium exchange reactions resulting acids **16a**, **8a** and **11a** in a 9:1.3:1 ratio, as indicated by the ^{1}H NMR analysis of the product mixture (see Table 1).

As expected, ketal **15b** produced similar result: acids **16b**, **8b** and **11b** were obtained in a 7.5:1.5:1 ratio and in a 83% combined yield. Since the major product **16b** could not be isolated in crystalline form, the mixture was hydrolyzed and benzophenone **17** was prepared in 31% yield.

Surprisingly, 3,4,4′-trichlorobenzophenone ketal **15e** was deprotonated exclusively at the 5-position of the dichlorophenyl ring as shown by the formation of **16e** as the main product in addition to minor products **8e** and **11e** originating from chlorine–lithium exchange reactions. The cooperating

Table 1. Products formed in the lithiation reaction of compounds **15** followed by carboxylation

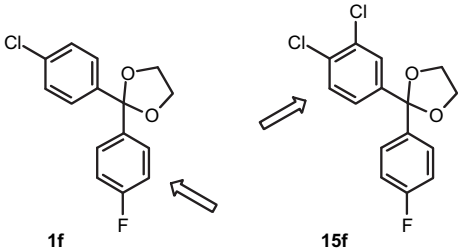
Starting compound	Product mixture		Recov. **15** (%)	Yield of isolated **16** (%)
	Yield (%)	**16**:**8**:**11**[a]		
15a	79	9:1.3:1	4	27
15b	83	7.5:1.5:1	15	31[b]
15e	54	9:1.5:1	42	22
15f	75	8:1.5:1	20	26

[a] The ratios were assessed by ^{1}H NMR spectroscopy. In the case of **8a**,**b**,**e** and **11a**,**b** the structure assignment based on ^{1}H NMR spectra of the product mixtures is supported also with a comparison of the ^{1}H NMR data of authentic samples.

[b] Isolated as the benzophenone **17**, see Section 3.

ortho- and *meta*-acidifying effect of the adjacent chlorine substituents on the less crowded *ortho* position determined the regioselectivity of the deprotonation. The preferred formation of by-products **8** versus **11** can be explained by a similar electrical effect of the ketal group as discussed in the case of the deprotonation reaction of compound **9e**.

More strikingly, ketal **15f** was also found to react with butyllithium complexed to PMDTA exclusively in the 3,4-dichlorophenyl ring affording after carboxylation **16f** as the main product. ^{1}H NMR spectrum of the product mixture indicated that the compounds formed contain ‘intact’ 4-fluorophenyl moiety. Deprotonation occurred at the 5-position of the 3,4-dichlorophenyl ring rather than at the fluorine adjacent site of the 4-fluorophenyl moiety and chlorine-lithium exchange products **8f** and **11f** were formed in minor



Scheme 5.

Table 2. Experimental data for compounds **6**, **8**, **11**, **13** and **16** synthesized according to the general procedure

	R^1	R^2	Yield (%)	Recov. starting material (%)	Mp (°C)	Molecular formula	Elemental analysis		IR (KBr): ν (cm^{-1})	^1H NMR ($CDCl_3$, 200 MHz, 25 °C)
							Calcd	Found		
6	F	H	73	19	159–160 (EtOAc/hexane 1:3)	$C_{16}H_{12}ClFO_4$ (322.72)	C 59.55, H 3.75, Cl 10.99	C 59.00, H 3.81, Cl 10.68	1686 (C═O)	8.17 (dd, $^4J_{HF}$=7.0 Hz, J=2.4 Hz, 1H), 7.67 (ddd, J=8.6 Hz, $^4J_{HF}$=4.5 Hz, J=2.4 Hz, 1H), 7.44 (d, J=8.7 Hz, 2H), 7.32 (d, J=8.7 Hz, 2H), 7.13 (dd, $^3J_{HF}$=10.4 Hz, J=8.6 Hz, 1H), 4.11–3.96 (m, 4H)
8a	H	H	73	21	144–146 (EtOAc/hexane 1:1)	$C_{16}H_{13}ClO_4$ (304.73)	C 63.06, H 4.30, Cl 11.63	C 62.97, H 4.36, Cl 11.57	1684 (C═O)	8.19 (d, J=2.2 Hz, 1H), 7.59 (dd, J=8.4, 2.2 Hz, 1H), 7.54–7.47 (m, 2H), 7.43 (d, J=8.4 Hz, 1H), 7.40–7.24 (m, 3H), 4.07 (s, 4H)
8b	MeO	H	60	19	139–144 (EtOAc/hexane 3:7)	$C_{17}H_{15}ClO_5$ (334.76)	C 61.00, H 4.52, Cl 10.59	C 62.97, H 4.36, Cl 11.57	1691 (C═O)	8.17 (d, J=2.2 Hz, 1H), 7.58 (dd, J=8.0, 2.2 Hz, 1H), 7.43 (d, J=8.0 Hz, 1H), 7.41 (d, J=9.1 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 4.06 (br s, 4H), 3.79 (s, 3H)
8c	H	MeO	59	40	107–109 (EtOAc/hexane 3:7)	$C_{17}H_{15}ClO_5$ (334.76)	C 61.00, H 4.52, Cl 10.59	C 60.63, H 4.72, Cl 10.67	1689 (C═O)	8.18 (d, J=2.2 Hz, 1H), 7.58 (dd, J=8.4, 2.2 Hz, 1H), 7.44 (d, J=8.1 Hz, 1H), 7.26 (t, J=8.1 Hz, 1H), 7.10–7.04 (m, 2H), 6.84 (dq, J=8.1, 1.1 Hz, 1H), 4.08 (s, 4H), 3.80 (s, 3H)
8d	MeO	MeO	63	35	171–173 (EtOAc/hexane 1:3)	$C_{18}H_{17}ClO_6$ (364.78)	C 59.27, H 4.70, Cl 9.72	C 59.64, H 4.64, Cl 9.60	1698 (C═O)	8.18 (d, J=2.2 Hz, 1H), 7.58 (dd, J=8.4, 2.2 Hz, 1H), 7.44 (d, J=8.4 Hz, 1H), 7.00 (s, 1H), 6.99 (d, J=2.2 Hz, 1H), 6.82 (d, J=8.8 Hz, 1H), 4.08 (s, 4H), 3.87 (s, 3H), 3.86 (s, 3H)
8e	Cl	H	73	25	152–153 (EtOAc/hexane 1:3)	$C_{16}H_{12}Cl_2O_4$ (339.18)	C 56.66, H 3.57, Cl 20.91	C 56.32, H 3.61, Cl 20.31	1693 (C═O)	9.30 (br s, 1H), 7.50–7.44 (m, 3H), 7.34–7.26 (m, 3H), 4.15–4.05 (m, 2H), 4.05–3.95 (m, 2H)
11a	H	H	81	16	79–80 (EtOAc/hexane 1:3)	$C_{16}H_{13}ClO_4$ (304.73)	C 63.06, H 4.30, Cl 11.63	C 62.68, H 4.60, Cl 12.06	1704 (C═O)	7.95 (d, J=8.0 Hz, 1H), 7.69 (d, J=1.5 Hz, 1H), 7.54–7.45 (m, 3H), 7.36–7.28 (m, 3H), 4.01 (s, 4H)
11b	MeO	H	40	43	Isolated in crystalline form as benzophenone **14**					7.94 (d, J=8.4 Hz, 1H), 7.66 (d, J=1.5 Hz, 1H), 7.48 (dd, J=8.1, 1.5 Hz, 1H), 7.40 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 4.14–4.01 (m, 4H), 3.78 (s, 3H)
11c	H	MeO	60	40	99–101 (EtOAc/hexane 3:7)	$C_{17}H_{15}ClO_5$ (334.76)	C 61.00, H 4.52, Cl 10.59	C 60.79, H 4.52, Cl 10.44	1705 (C═O)	7.95 (d, J=8.1 Hz, 1H), 7.68 (d, J=1.5 Hz, 1H), 7.48 (dd, J=8.1, 1.5 Hz, 1H), 7.27 (t, J=8.1 Hz, 1H), 7.11–7.03 (m, 2H), 6.85 (dd, J=8.1, 2.2 Hz, 1H), 4.08 (br s, 4H), 3.80 (s, 3H)
13e	Cl	H	31	33	128–130 (EtOAc/hexane 1:2)	$C_{16}H_{12}Cl_2O_4$ (339.18)	C 56.66, H 3.57, Cl 20.91	C, 56.85, H, 3.71, Cl, 20.81	1719 (C═O)	8.16 (d, J=2.2 Hz, 1H), 7.58 (dd, J=8.4, 2.2 Hz, 1H), 7.54–7.51 (m, 1H), 7.45 (d, J=8.4 Hz, 1H), 7.40–7.27 (m, 3H), 4.08 (s, 4H)
13f	F	H	86	14	130–132 (EtOAc/hexane 1:3)	$C_{16}H_{12}ClFO_4$ (322.72)	C 59.55, H 3.75, Cl 10.99	C 59.36, H 3.82, Cl 10.84	1709, 1688 (C═O)	8.20 (dd, $^4J_{HF}$=7.0 Hz, J=2.2 Hz, 1H), 7.68 (ddd, J=8.6 Hz, $^4J_{HF}$=4.4 Hz, J=2.2 Hz, 1H), 7.53 (br s, 1H), 7.41–7.25 (m, 3H), 7.13 (dd, $^3J_{HF}$=10.2 Hz, J=8.8 Hz, 1H), 4.08 (s, 4H)
16a	H	H	27	4	142–144 (EtOAc/hexane 1:3)	$C_{16}H_{12}Cl_2O_4$ (339.18)	C 56.66, H 3.57, Cl 20.91	C 56.28, H 3.72, Cl 19.89	1711, 1688 (C═O)	8.00 (d, J=2.2 Hz, 1H), 7.81 (d, J=2.2 Hz, 1H), 7.53–7.45 (m, 2H), 7.42–7.30 (m, 3H), 4.08 (s, 4H)
16b	MeO	H		15	Isolated in crystalline form as benzophenone **17**					7.99 (d, J=2.2 Hz, 1H), 7.79 (d, J=2.2 Hz, 1H), 7.39 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H), 4.10–4.08 (m, 2H), 4 08–4.07 (m, 1H), 3.80 (s, 3H)
16e	Cl	H	22	42	175–177 (EtOAc/hexane 1:2)	$C_{16}H_{11}CI_3O_4$ (373.62)	C 51.44, H 2.97, Cl 28.47	C 51.93, H 3.09, Cl 27.43	1710, 1681 (C═O)	7.97 (d, J=2.2 Hz, 1H), 7.78 (d, J=2.2 Hz, 1H), 7.44 (d, J=8.8 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 4.07 (s, 4H)
16f	F	H	26	20	129–130 (EtOAc/hexane 1:3)	$C_{16}H_{11}Cl_2FO_4$ (357.17)	C 53.81, H 3.10, Cl 19.85	C 53.97, H 2.94, Cl 19.21	1698 (C═O)	7.96 (d, J=2.2 Hz, 1H), 7.78 (d, J=2.2 Hz, 1H), 7.47 (ddd, J=8.8 Hz, J_{HF}=5.5 Hz, J=2.2 Hz, 2H), 7.04 (tm, J=8.8 Hz, 2H), 4.07 (s, 4H)

amounts. In the ^{1}H NMR spectrum of the mixture no signals characteristic for 2-fluoro-substituted benzoic acid could be detected. The contrasting reactivity of 4-chlorophenyl-4-fluorophenyl ketal and 3,4-dichlorophenyl-4-fluorophenyl ketal (**1f** and **15f**) in deprotonation reaction with butyllithium complexed to PMDTA (Scheme 5) provides further evidence for the strong *meta*-acidifying effect of the chloro substituent.

3. Experimental section

3.1. General procedure

N,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) (11.5 mmol) was added at −78 °C under argon to buthyllithium (4.6 ml of a 2.5 M solution in hexane, 11.5 mmol) followed by addition dropwise of the ketal (10 mmol) in THF (10 ml). The reaction mixture was stirred at −78 °C for an additional 20 min, then it was poured onto a large excess of dry ice (200 g). After 3 h, water (30 ml) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (30 ml). An aqueous solution of hydrochloric acid (10%, 20 ml) was added to the aqueous layer and it was extracted with diethyl ether (2×30 ml). The solvent was evaporated and the oil thus obtained was crystallized from suitable solvent affording the corresponding carboxylated derivative. For yields, melting points, solvents of recrystallization, elemental analyses and ^{1}H NMR data see Table 2.

3.2. 2-Chloro-4-(4-methoxybenzoyl)-benzoic acid hemihydrate (14)

2-Chloro-4-[2-(4-methoxyphenyl)-1,3-dioxolane-2-yl]-benzoic acid (**11b**) (3.34 g, 0.01 mol) (prepared according the general procedure) in an aqueous solution of hydrochloric acid (10%, 25 ml) was refluxed for 4 h. The crystalline product was filtered to give **14** (2.61 g, 90% based on **11b** and 36% based on **8b**) as colourless crystals, mp 203–204 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ=8.07 (d, J=8.1 Hz, 1H), 7.83 (d, J=1.5 Hz, 1H), 7.81 (d, J=8.8 Hz, 2H), 7.67 (dd, J=8.1, 1.5 Hz, 1H), 7.00 (d, J=8.8 Hz, 2H), 3.91 (s, 3H). IR (KBr): ν=1702, 1642 cm^{-1}. Anal. Calcd $C_{15}H_{11}ClO_4$ (299.71) C 60.11, H 4.04, Cl 11.83; found C 60.52, H 3.92, Cl 11.73.

3.3. 2,3-Dichloro-5-(4-methoxybenzoyl)-benzoic acid (17)

The product mixture obtained after lithiation and carboxylation of **15b** in an aqueous solution of hydrochloric acid (10%, 25 ml) was refluxed for 4 h. The crystalline product was filtered and recrystallized from ethyl acetate to give **17** (1.35 g, 31%, based on **15b**) as colourless crystals, mp 195–197 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ=8.19 (d, J=2.2 Hz, 1H), 8.05 (d, J=2.2 Hz, 1H), 7.81 (d, J=8.8 Hz, 2H), 7.00 (d, J=8.8 Hz, 2H), 3.91 (s, 3H). IR (KBr): ν=1735, 1707 cm^{-1}. Anal. Calcd $C_{15}H_{10}C_{12}O_4$ (325.15) C 55.41, H 3.10, Cl 21.81; found C 55.76, H 3.25, Cl 21.59.

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