Lithiation of 2-Aryl-2-(chloroaryl)-1,3-dioxolanes and Its Application in the Synthesis of New *ortho*-Functionalized Benzophenone Derivatives

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Dedicated to Professor Károly Lempert on the occasion of his 80th birthday

Keywords: Lithiation / Substituent effects / Benzophenones / 1,3-Dioxolanes

2-Aryl-2-(chloroaryl)-1,3-dioxolanes **4** were lithiated *ortho* to the ketal group of the chloroaryl ring by treatment with butyllithium in THF between –78 and 0 °C. The site selectivity of some of the deprotonation reactions was rationalized by the long-range effect of the 4-chloro substituent. The lithio species thus generated were treated with various electrophiles to give *ortho*-functionalized benzophenone derivatives. Intramolecular competition between the aryl rings was observed in the lithiation of 2-(4-chlorophenyl)-2-(4-fluorophenyl)-1,3-dioxolane (**4s**).

Introduction

Several pharmaceutically important drugs have benzannellated heterocycle structures that contain a diphenylmethane moiety, for example, diazepam[1] (and the related anxiolytic 1,4-benzodiazepines), tofisopam[2] (and the related nonsedative anxiolytic 2,3-benzodiazepines), fenoldopam[3] (antihypertensive dopamine agonist), BM 21.1298[4] (HIV-1 reverse transcriptase inhibitor). The key intermediates in the synthesis of condensed heterocyclic compounds that contain the diphenylmethane moiety are the corresponding *ortho*-functionalized benzophenones **1**. The syntheses of polysubstituted benzophenones **1** described in the literature are in most cases tedious and lengthy. The substitution pattern of benzophenones **1** accessible by conventional methods is strongly limited by the regiochemistry of the aromatic electrophilic substitution (S_EAr) reactions used in the construction of the benzophenones and their precursors.

The *ortho*-directing ability of aromatic acetals and ketals in lithiation reactions has previously been demonstrated.[5−7] Recently, we reported the synthesis of *ortho*-functionalized acetophenone derivatives **2** by *ortho*-lithiation of the corresponding ethylene ketals and subsequent treatment with various electrophiles[8] (Scheme 1). These results encouraged us to study the lithiation reactions of readily available chloro-substituted benzophenone ketals **4** with a view to preparing new *ortho*-functionalized benzophenone derivatives (**6** and **7**) suitable for use in the construction of condensed heterocyclic systems.

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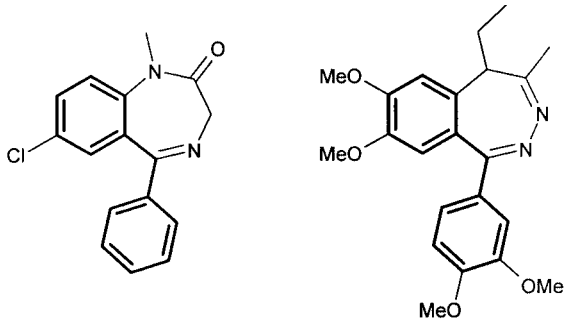
Results and Discussion

Benzophenones **3a**,[9,10] **3c**,[10] **3e**,[11] **3g**,[12] **3h**,[10] **3i**,[13] **3j**,[14] **3k**,[15] **3l**,[16] **3m**,[17] **3n**,[18] **3p**,[19] **3q**[20] and **3s**[13] were synthesized according to procedures described in the literature. The new benzophenones **3b, 3d**, **3f** and **3r** were prepared by Friedel−Crafts acylation reactions. Ethylene ketals **4a**−**s** are new compounds,[21] which were obtained by conventional methods (Scheme 2, Table 1).[22−24]

The lithiation of compound **4a** with 1.5 equiv. of butyllithium in THF at −78 °C and subsequent quenching of the aryllithium compound **5a** with electrophiles (carbon dioxide and sulfur dioxide, followed by treatment of the isolated aryl sulfinate with sulfuryl chloride in the second case[25]) gave products **6a** and **7a** in 83% and 80% yields, respectively (Table 2). As expected, *ortho*-lithiation of the monosubstituted benzene ring cannot compete with the lithiation of the disubstituted benzene ring at a site adjacent to two *ortho*-directing groups. Although ketal **4b** has two regiochemically distinct sites between a *meta*-chloro and the 1,3-dioxolan-2-yl group, lithiation with 1.5 equiv. of butyllithium in THF at −78 °C followed by carboxylation and chlorosulfonation afforded products **6b** (88%) and **7b** (68%). It is remarkable that the presence of a second chloro substituent in *meta* position with respect to the metalation site determines the regiochemistry of the lithiation. In view of this result, it is not surprising that the directing abilities of the substituents of the *para*-disubstituted benzene moiety in ketals **4c**−**e** cannot overcome the cooperative effect of the directing groups present in the other ring as shown by the high-yielding formation of carboxylic acids **6c**−**e** and sulfonyl chlorides **7c**−**e**. The regioselectivity observed in the lithiation of ketal **4f** is in agreement with the results of

  DOI: 10.1002/ejoc.200400335



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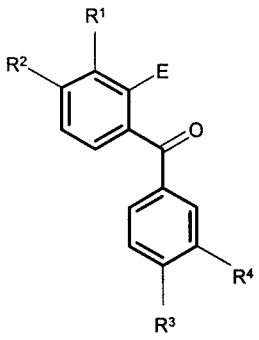

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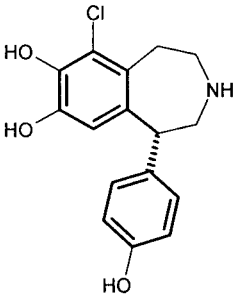

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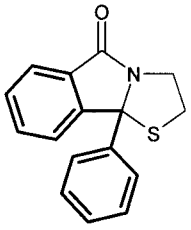

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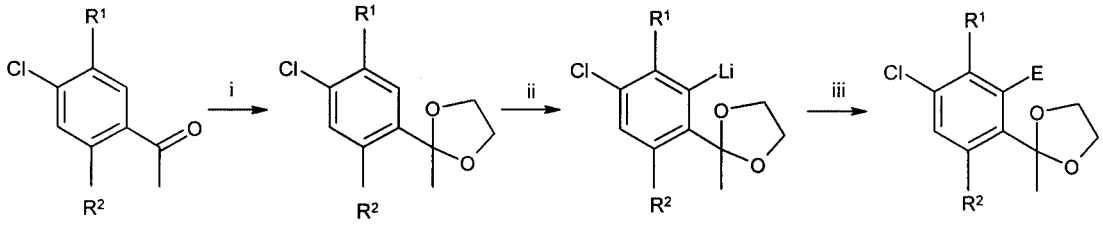


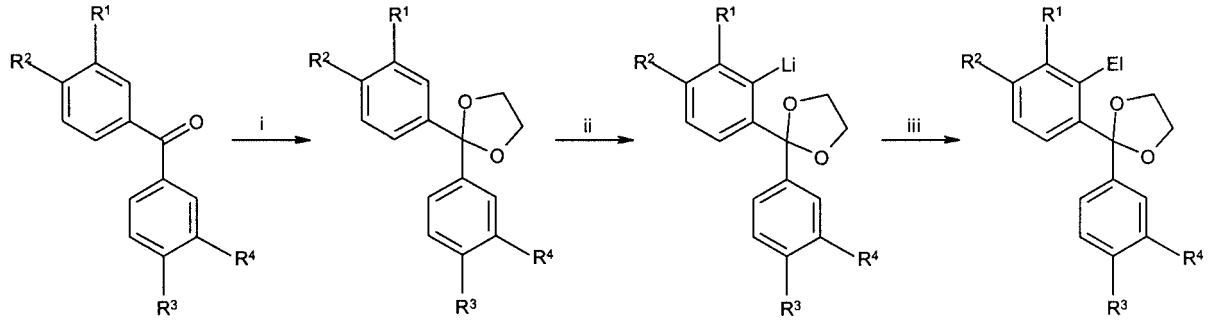
2	a	b	c
R^1	H	Cl	Cl
R^2	H	H	CH_3

(i) ethylene glycol, PTSA/toluene (ii) butyllithium/THF (iii) electrophilic reagent

Scheme 1

Schlosser and co-workers,[26,27] which indicates that the enhancement of acidity provided by the methoxy substituent in its *meta* position is insignificant.

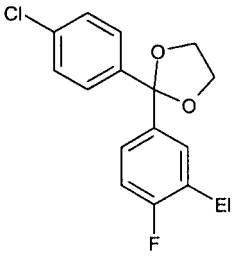
Similarly, the lithiation of ketals **4g−j** occurred at the doubly activated site of the *meta*-chlorophenyl ring as indicated by the formation of the corresponding derivatives **6g−j** and **7g−j**, respectively, in good yields. Ketal **4k** represents a suitable substrate for the study of the relative directing abilities of *meta*-chloro and *meta*-methoxy substituents in cooperation with the 1,3-dioxolan-2-yl group in metalation reactions. Lithiation of ketal **4k** with 1.5 equiv. of butyllithium in THF at −78 °C and subsequent reaction with the corresponding electrophiles afforded products **6k** (64%) and **7k** (54%), which demonstrates that lithiation occurs at the site *ortho* to the chloro moiety. The combined *ortho*-directing aptitude of the chloro and the 1,3-dioxolan-2-yl substituents is obviously more powerful than that of the methoxy and the 1,3-dioxolan-2-yl substituents, presumably due to the stronger acidifying effect of the chloro substituent.[28,29] The lithiation and functionalization sequence of ketals **4l−m** provided products (**6l−m**, **7l−m**) as expected by reason of the preceding results.



(i) ethylene glycol, PTSA/toluene (ii) butyllithium/THF (iii) electrophilic reagent

	R1	R2	R3	R4
a	Cl	Cl	H	H
b	Cl	Cl	H	Cl
c	Cl	Cl	Cl	H
d	Cl	Cl	F	H
e	Cl	Cl	MeO	H
f	Cl	Cl	MeO	Cl
g	Cl	H	H	H
h	Cl	H	Cl	H
i	Cl	H	F	H
j	Cl	H	MeO	H

	R1	R2	R3	R4
k	Cl	H	H	MeO
l	Cl	MeO	H	H
m	Cl	MeO	Cl	H
n	H	Cl	Cl	H
o	H	Cl	H	H
p	H	Cl	MeO	H
q	H	Cl	H	MeO
r	H	Cl	MeO	MeO
s	H	Cl	F	H



8a (El=COOH)
8b (El=SO_2Cl)

Scheme 2

We have also studied the lithiation of benzophenone ketals with a chloro substituent *para* to the 1,3-dioxolan-2-yl substituent. Lithiation of 4,4′-dichlorobenzophenone ketal **4n** (with 1.5 equiv. of butyllithium in THF at −10 °C) and subsequent functionalization gave products **6n** (48%) and **7n** (76%), respectively, which demonstrates that lithiation occurs *ortho* to the ketal substituent. A similar regiochemistry was observed in our studies on the corresponding 4-chloroacetophenone ketal.[8] Metalation *ortho* to the ketal substituent in the 4-chlorophenyl ring was also observed in the lithiation reactions of ketal **4o** (see products **6o** and **7o**). This result clearly indicates that the deprotonation site is determined not only by the *ortho*-directing aptitude of the ketal group (a factor present in both phenyl rings of **4o**), but also by the long-range (*meta*) electron-withdrawing (acidifying) effect of the chloro substituent.[27]

Regioselective lithiation occurred in the reaction of ketals **4p**−**r** with butyllithium at −20 °C in THF for 2 h, however, with low conversion. Partial hydrolysis of the ketal group was observed in the course of the acidic workup of the carboxylated reaction mixture when starting from **4p** and **4r**, and therefore benzophenones **9p** and **9r** were prepared after complete hydrolysis (Scheme 3). Similar lithiation of **4p**−**r** followed by chlorosulfonylation afforded compounds **7p**−**r**. The results obtained from the lithiation reaction of **4p** show that the 4-methoxyphenyl ring cannot compete with the 4-chlorophenyl ring for the lithium reagent under the reaction conditions applied. Clearly, in contrast to the methoxy group, the chloro substituent significantly enhances the acidity at its *meta* position.[26,27] More strikingly, ketals **4q** and **4r**, which have a 3-methoxyphenyl and a 3,4-dimethoxyphenyl group, respectively, were found to react − under identical conditions − also by the lithiation of the 4-chlorophenyl ring. The "*meta*-acidifying" effect of the chloro substituent combined with the ability of the 1,3-dioxolan-2-yl group to coordinate the lithium ion − under the applied conditions − obviously outperforms the cooperative directing effect of the *meta*-methoxy and 1,3-dioxolan-2-yl groups.[26]

Finally, lithiation of 2-(4-chlorophenyl)-2-(4-fluorophenyl)-1,3-dioxolane (**4s**) with butyllithium in THF at −50 °C followed by carboxylation afforded carboxylic acid **8a** in low yield (15%), which indicates that lithiation occurs at the position adjacent to the fluorine atom. ^{1}H NMR analysis of the product mixture obtained after a similar lithiation of **4s** and chlorosulfonation demonstrated the formation of compounds **7s** and **8b** in a 1:2 ratio. This result indicates that lithiation of **4s** occurred at the site *ortho* to the ketal substituent (*meta* to the chloro substituent!) in the 4-chlorophenyl ring and at the site adjacent to the fluorine atom in a 1:2 ratio. Note that metalation *meta* to the fluoro substituent was not observed. This result demonstrates that the chloro substituent exerts a stronger acidifying effect on its *meta* site than does the fluoro substituent.[30,31]

Table 1. Experimental data for 1,3-dioxolanes **4**

	R^1	R^2	R^3	R^4	Yield [%]	B.p./m.p. [°C]	Empirical formula	Elemental analysis Calcd.	Found	^{1}H NMR: δ [ppm]
4a	Cl	Cl	H	H	94	m.p. 65−66 (ethanol)[a]	$C_{15}H_{12}Cl_2O_2$ (295.17)	C 61.04, H 4.10, Cl 24.02	C 61.00, H 4.20, Cl 23.83	7.65−7.63 (m, 1 H), 7.51−7.25 (m, 7 H), 4.06 (s, 4 H)
4b	Cl	Cl	H	Cl	71	b.p. 172−174 (0.3 Torr)[b]	$C_{15}H_{11}Cl_3O_2$ (329.61)	C 54.66, H 3.36, Cl 32.27	C 54.29, H 3.43, Cl 31.97	7.62 (d, J = 1.8 Hz, 1 H), 7.51−7.49 (m, 1 H), 7.39 (d, J = 8.4 Hz, 1 H), 7.36−7.25 (m, 3 H), 7.29 (dd, J = 8.4, 1.8 Hz, 1 H), 4.05 (s, 4 H)
4c	Cl	Cl	Cl	H	92	m.p. 60−61 (ethanol)[a]	$C_{15}H_{11}Cl_3O_2$ (329.61)	C 54.66, H 3.36, Cl 32.27	C 54.55, H 3.39, Cl 32.01	7.60 (d, J = 2.0 Hz, 1 H), 7.41 (d, J = 8.8 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 1 H), 7.30 (d, J = 8.8 Hz, 2 H), 7.60 (dd, J = 8.4, 2.0 Hz, 1 H), 4.04 (s, 4 H)
4d	Cl	Cl	F	H	81	m.p. 51−53 (ethanol)[a]	$C_{15}H_{11}Cl_2FO_2$ (313.16)	C 57.53, H 3.54, Cl 22.64	C 57.52, H 3.54, Cl 22.44	7.61 (d, J = 2.2 Hz, 1 H), 7.44 (ddm, J = 8.8 Hz, $^4J_{H,F}$ = 5.5 Hz, 2 H), 7.40 (d, J = 8.4 Hz, 1 H), 7.30 (dd, J = 8.4, 2.2 Hz, 1 H), 7.61 (tm, J = 8.8 Hz, 2 H), 4.05 (s, 4 H)
4e	Cl	Cl	CH_3O	H	77	m.p. 74−75 (ethanol)[a]	$C_{16}H_{14}Cl_2O_3$ (325.19)	C 59.10, H 4.34, Cl 21.80	C 58.82, H 4.36, Cl 21.64	7.61 (d, J = 1.8 Hz, 1 H), 7.39 (d, J = 8.4 Hz, 1 H), 7.37 (d, J = 9.2 Hz, 2 H), 7.31 (dd, J = 8.4, 1.8 Hz, 1 H), 6.85 (d, J = 9.2 Hz, 2 H), 4.05 (m, 4 H), 3.79 (s, 3 H)
4f[c]	Cl	Cl	CH_3O	Cl	85	m.p. 59−61 (hexane)[a]	$C_{16}H_{13}Cl_3O_3$ (359.64)	C 53.44, H 3.64, Cl 29.57	C 53.67, H 3.72, Cl 29.32	7.64 (d, J = 2.0 Hz, 1 H), 7.62 (d, J = 8.4 Hz, 1 H), 7.46 (d, J = 2.2 Hz, 1 H), 7.39 (dd, J = 8.4, 2.0 Hz, 1 H), 7.34 (dd, J = 8.6, 2.2 Hz, 1 H), 7.13 (d, J = 8.6 Hz, 1 H), 4.01 (m, 4 H), 3.85 (s, 3 H)
4g	Cl	H	H	H	82	m.p. 40−41 (hexane)[a]	$C_{15}H_{13}ClO_2$ (260.72)	C 69.10, H 5.03, Cl 13.60	C 69.28, H 5.24, Cl 13.48	7.57−7.45 (m, 3 H), 7.42−7.21 (m, 6 H), 4.06 (s, 4 H)
4h	Cl	H	Cl	H	99	m.p. 41−43 (hexane)[a]	$C_{15}H_{12}Cl_2O_2$ (295.17)	C 61.04, H 4.10, Cl 24.02	C 61.00, H 4.09, Cl 23.91	7.53−7.49 (m, 1 H), 7.43 (d, J = 8.9 Hz, 2 H), 7.37−7.23 (m, 3 H), 7.30 (d, J = 8.9 Hz, 2 H), 4.05 (s, 4 H)
4i	Cl	H	F	H	99	b.p. 136−138 (0.3 Torr)[b]	$C_{15}H_{12}ClFO_2$ (278.71)	C 64.64, H 4.34, Cl 12.72	C 64.65, H 4.45, Cl 12.47	7.56−7.21 (m, 6 H), 7.00 (tm, J = 8.8 Hz, 2 H), 4.02 (s, 4 H)
4j	Cl	H	CH_3O	H	85	b.p. 174−176 (0.4 Torr)[b]	$C_{16}H_{15}ClO_3$ (290.75)	C 66.10, H 5.20, Cl 12.19	C 65.73, H 5.01, Cl 12.57	7.56−7.49 (m, 1 H), 7.43−7.31 (m, 1 H), 7.39 (d, J = 8.9 Hz, 2 H), 7.25−7.22 (m, 2 H), 6.85 (d, J = 8.9 Hz, 2 H), 4.03 (m, 4 H), 3.77 (s, 3 H)
4k	Cl	H	H	CH_3O	92	b.p. 157−158 (0.4 Torr)[b]	$C_{16}H_{15}ClO_3$ (290.75)	C 66.10, H 5.20, Cl 12.19	C 65.87, H 5.33, Cl 11.95	7.54 (m, 1 H), 7.39−7.36 (m, 1 H), 7.26−7.20 (m, 3 H), 7.09−7.04 (m, 2 H), 6.81 (ddd, J = 8.3, 2.6, 0.7 Hz, 1 H), 4.03 (s, 4 H), 3.77 (s, 3 H)
4l	Cl	CH_3O	H	H	93	b.p. 177−179 (0.3 Torr)[b]	$C_{16}H_{15}ClO_3$ (290.75)	C 66.10, H 5.20, Cl 12.19	C 65.98, H 5.13, Cl 12.14	7.54 (d, J = 2.2 Hz, 1 H), 7.52−7.42 (m, 2 H), 7.36−7.22 (m, 4 H), 6.81 (d, J = 8.6 Hz, 1 H), 3.99 (s, 4 H), 3.80 (s, 3 H)
4m	Cl	CH_3O	Cl	H	89	m.p. 89−90 (ethanol)[a]	$C_{16}H_{14}Cl_2O_3$ (325.19)	C 59.10, H 4.34, Cl 21.80	C 59.36, H 4.38, Cl 21.83	7.51 (d, J = 2.2 Hz, 1 H), 7.43 (d, J = 8.8 Hz, 2 H), 7.33−7.25 (m, 3 H), 6.86 (d, J = 8.8 Hz, 1 H), 4.04 (m, 4 H), 3.81 (s, 3 H)
4n	H	Cl	Cl	H	87	m.p. 78−79 (2-propanol)[a]	$C_{15}H_{12}Cl_2O_2$ (295.17)	C 61.04, H 4.10, Cl 24.02	C 60.67, H 4.30, Cl 23.81	7.42 (d, J = 8.9 Hz, 4 H), 7.29 (d, J = 8.9 Hz, 4 H), 4.04 (s, 4 H)
4o	H	Cl	H	H	99	m.p. 35−37 (hexane)[a]	$C_{15}H_{13}ClO_2$ (260.72)	C 69.10, H 5.03, Cl 13.60	C 69.41, H 5.04, Cl 13.58	7.44 (d, J = 8.9 Hz, 2 H), 7.54−7.39 (m, 2 H), 7.32−7.22 (m, 3 H), 7.26 (d, J = 8.9 Hz, 2 H), 3.97 (s, 4 H)
4p	H	Cl	CH_3O	H	95	m.p. 37−38 (methanol)[a]	$C_{16}H_{15}ClO_3$ (290.75)	C 66.10, H 5.20, Cl 12.19	C 65.78, H 5.18, Cl 12.15	7.43 (d, J = 8.9 Hz, 2 H), 7.38 (d, J = 8.9 Hz, 2 H), 7.28 (d, J = 8.9 Hz, 2 H), 6.84 (d, J = 8.9 Hz, 2 H), 4.03 (m, 4 H), 3.77 (s, 3 H)
4q	H	Cl	H	CH_3O	93	m.p. 65−67 (hexane)[a]	$C_{16}H_{15}ClO_3$ (290.75)	C 66.10, H 5.20, Cl 12.19	C 66.42, H 5.01, Cl 12.35	7.45 (d, J = 8.8 Hz, 2 H), 7.28 (d, J = 8.8 Hz, 2 H), 7.24 (t, J = 8.1 Hz, 1 H), 7.10−7.02 (m, 86−6.80 (ddd, J = 8.1, 2.6, 1.1 Hz, 1 H), 4.05 (s, 4 H), 3.79 (s, 3 H)
4r	H	Cl	CH_3O	CH_3O	82	m.p. 74−76 (ethanol)[a]	$C_{17}H_{17}ClO_4$ (320.78)	C 63.65, H 5.34, Cl 11.05	C 63.39, H 5.31, Cl 11.06	7.44 (d, J = 8.8 Hz, 2 H), 7.30 (d, J = 8.8 Hz, 2 H), 7.03 (t, J = 1.8 Hz, 1 H), 7.00 (dd, J = 8.1, 1.8 Hz, 1 H), 6.81 (d, J = 8.1 Hz, 1 H), 4.22−3.98 (m, 4 H), 3.85 (s, 6H)
4s	H	Cl	F	H	96	m.p. 53−54 (ethanol)[a]	$C_{15}H_{12}ClFO_2$ (278.71)	C 64.64, H 4.34, Cl 12.72	C 64.08, H 4.43, Cl 12.64	7.45 (ddm, J = 9.0, $^4J_{H,F}$ = 5.5 Hz, 2 H), 7.43 (d, J = 8.8 Hz, 2 H), 7.29 (d, J = 8.8 Hz, 2 H), 7.00 (tm, J = 9.0 Hz, 2 H), 4.04 (s, 4 H)

[a] Colourless crystals. [b] Colourless oil. [c] ^{1}H NMR spectrum was measured in [D_6]DMSO.

Table 2. Experimental data for compounds **6** and **7** synthesized according to Scheme 2

	R^1	R^2	R^3	R^4	E	T [°C]	Yield [%]	M.p. [°C]	Empirical formula	Elemental analysis Calcd.	Found	IR (KBr): $\tilde{\nu}$ [cm^{-1}]	^{1}H NMR: δ [ppm]
6a	Cl	Cl	H	H	COOH	–78	83	152–153 (EtOAc/ hexane, 1:1)	$C_{16}H_{12}Cl_2O_4$ (339.18)	C 56.66, H 3.57, Cl 20.91	C 56.70, H 3.70, Cl 20.61	1718 (C=O)	7.57–7.53 (m, 2 H), 7.45 (d, J = 8.6 Hz, 1 H), 7.35–7.28 (m, 3 H), 7.33 (d, J = 8.6 Hz, 1 H), 4.10–4.06 (m, 2 H), 4.04–4.00 (m, 2 H)
7a	Cl	Cl	H	H	SO_2Cl	–78	80	165–167 (ethanol)	$C_{15}H_{11}Cl_3O_4S$ (393.68)	C 45.77, H 2.82, Cl 27.02, S 8.14	C 45.65, H 2.90, Cl 26.69, S 7.95	1384 (S=O) 1188 (S=O)	8.06 (d, J = 8.8 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 7.37–7.28 (m, 5 H), 4.36–4.19 (m, 2 H), 3.93–3.76 (m, 2 H)
6b	Cl	Cl	H	Cl	COOH	–78	88	153–154 (EtOAc/ hexane, 1:10)	$C_{16}H_{11}Cl_3O_4$ (373.62)	C 51.44, H 2.97, Cl 28.47	C 51.78, H 3.03, Cl 28.05	1714 (C=O)	7.60–7.55 (m, 1 H), 7.49 (d, J = 8.6 Hz, 1 H), 7.44–7.36 (m, 1 H), 7.32 (d, J = 8.6 Hz, 1 H), 7.32–7.23 (m, 2 H), 4.16–4.06 (m, 2 H), 4.06–3.96 (m, 2 H)
7b	Cl	Cl	H	Cl	SO_2Cl	–78	68	180–182 (2-propanol)	$C_{15}H_{10}Cl_4O_4S$ (428.12)	C 42.08, H 2.35, Cl 33.12, S 7.49	C 41.83, H 2.39, Cl 32.91, S 7.40	1381 (S=O) 1189 (S=O)	8.04 (d, J = 8.6 Hz, 1 H), 7.86 (d, J = 8.6 Hz, 1 H), 7.36–7.12 (m, 4 H), 4.32–4.18 (m, 2 H), 3.94–3.80 (m, 2 H)
6c	Cl	Cl	Cl	H	COOH	–78	75	162–164 (EtOAc/ hexane)	$C_{16}H_{11}Cl_3O_4$ (373.62)	C 51.44, H 2.97, Cl 28.47	C 51.65, H 3.13, Cl 27.83	1707 (C=O)	9.30 (br. s, 1 H), 7.50–7.44 (m, 3 H), 7.34–7.26 (m, 3 H), 4.15–4.05 (m, 2 H), 4.05–3.95 (m, 2 H)
7c	Cl	Cl	Cl	H	SO_2Cl	–78	72	190–191 (acetone)	$C_{15}H_{10}Cl_4O_4S$ (428.12)	C 42.08, H 2.35, Cl 33.12, S 7.49	C 42.05, H 2.34, Cl 33.33, S 7.32	1386 (S=O) 1192 (S=O)	8.04 (d, J = 8.6 Hz, 1 H), 7.85 (d, J = 8.6 Hz, 1 H), 7.31 (d, J = 8.9 Hz, 2 H), 7.24 (d, J = 8.9 Hz, 2 H), 4.30–4.22 (m, 2 H), 3.87–3.79 (m, 2 H)
6d	Cl	Cl	F	H	COOH	–78	86	142–143 (EtOAc/ hexane, 1:10)	$C_{16}H_{11}Cl_2FO_4$ (357.17)	C 53.81, H 3.10, Cl 19.85	C 53.71, H 3.11, Cl 19.96	1711 (C=O)	8.90 (br. s, 1 H), 7.51 (ddm, J = 8.8, $^4J_{H,F}$ = 5.5 Hz, 2 H), 7.48 (d, J = 8.4 Hz, 1 H), 7.33 (d, J = 8.4 Hz, 1 H), 7.00 (tm, J = 8.8 Hz, 2 H), 4.15–4.05 (m, 2 H), 4.05–3.95 (m, 2 H)
7d	Cl	Cl	F	H	SO_2Cl	–78	74	169–170 (2-propanol)	$C_{15}H_{10}Cl_3FO_4S$ (411.67)	C 43.77, H 2.45, Cl 25.84, S 7.79	C 44.01, H 2.44, Cl 25.50, S 7.59	1384 (S=O) 1192 (S=O)	8.04 (d, J = 8.8 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 1 H), 7.30 (ddm, J = 7.3, $^4J_{H,F}$ = 5.1 Hz, 2 H), 7.01 (tm, J = 8.7 Hz, 2 H), 4.31–4.18 (m, 2 H), 3.92–3.79 (m, 2 H)
6e	Cl	Cl	CH_3O	H	COOH	–78	80	121–122 (EtOAc/ hexane, 2:5)	$C_{17}H_{14}Cl_2O_5$ (369.20)	C 55.31, H 3.82, Cl 19.21	C 55.55, H 3.87, Cl 18.95	1716 (C=O)	7.47 (d, J = 8.4 Hz, 1 H), 7.43 (d, J = 8.8 Hz, 2 H), 7.34 (d, J = 8.4 Hz, 1 H), 6.84 (d, J = 8.8 Hz, 2 H), 4.15–4.04 (m, 2 H), 4.03–3.92 (m, 2 H), 3.77 (s, 3 H)
7e	Cl	Cl	CH_3O	H	SO_2Cl	–78	73	173–175 (ethanol)	$C_{16}H_{13}Cl_3O_5S$ (423.70)	C 45.36, H 3.09, Cl 25.10, S 7.57	C 45.78, H 3.18, Cl 25.30, S 7.33	1386 (S=O) 1191 (S=O)	8.03 (d, J = 8.9 Hz, 1 H), 7.83 (d, J = 8.9 Hz, 1 H), 7.23 (d, J = 8.9 Hz, 2 H), 6.84 (d, J = 8.9 Hz, 2 H), 4.29–4.17 (m, 2 H), 3.89–3.77 (m, 2 H), 3.80 (s, 3 H)

Table 2. *(continued)*

	R^1	R^2	R^3	R^4	E	*T* [°C]	Yield [%]	M.p. [°C]	Empirical formula	Elemental analysis Calcd.	Found	IR (KBr): $\tilde{\nu}$ [cm^{-1}]	^1H NMR: δ [ppm]
6f	Cl	Cl	CH_3O	Cl	COOH	–78	74	159–160 (EtOAc/ hexane, 1:1)	$C_{17}H_{13}Cl_3O_5$ (403.65)	C 50.59, H 3.25, Cl 26.35	C 50.27, H 3.10, Cl 26.12	1714 (C=O)	7.57 (d, *J* = 2.3 Hz, 1 H), 7.48 (d, *J* = 8.5 Hz, 1 H), 7.33 (d, *J* = 8.5 Hz, 1 H), 7.31 (dd, *J* = 8.7, *J* = 2.3 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 1 H), 4.12–4.08 (m, 2 H), 4.00–3.96 (m, 2 H), 3.87.(s, 3 H)
7f	Cl	Cl	CH_3O	Cl	SO_2Cl	–78	67	87–88 (2-propanol)	$C_{16}H_{12}Cl_4O_5S$ (458.15)	C 41.95, H 2.64, Cl 30.95, S 7.00	C 41.86, H 2.43, Cl 30.98, S 6.89	1382 (S=O) 1193 (S=O)	8.02 (d, *J* = 8.7 Hz, 1 H), 7.85 (d, *J* = 8.7 Hz, 1 H), 7.36 (d, *J* = 2.2 Hz, 1 H), 7.14 (dd, *J* = 8.7, *J* = 2.2 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 1 H), 4.28–4.24 (m, 2 H), 3.88 (s, 3 H), 3.83–3.79 (m, 2 H)
6g	Cl	H	H	H	COOH	–78	60	144–146 (EtOAc/ hexane, 3:7)	$C_{16}H_{13}ClO_4$ (304.73)	C 63.06, H 4.30, Cl 11.63	C 62.73, H 4.24, Cl 11.50	1720 (C=O)	11.09 (br. s, 1 H), 7.60–7.54 (m, 2 H), 7.40–7.35 (m, 2 H), 7.34–7.25 (m, 4 H), 4.09–4.04 (m, 2 H), 4.04–3.99 (m, 2 H)
7g	Cl	H	H	H	SO_2Cl	–78	67	140–141 (2-propanol)	$C_{15}H_{12}Cl_2O_4S$ (359.23)	C 50.15, H 3.37, Cl 19.74, S 8.93	C 50.11, H 3.30, Cl 19.91, S 8.75	1378 (S=O) 1188 (S=O)	8.10 (dd, *J* = 7.3, *J* = 2.2 Hz, 1 H), 7.72 (dd, *J* = 7.3, *J* = 2.2 Hz, 1 H), 7.65 (t, *J* = 7.3 Hz, 1 H), 7.33 (s, 5 H), 4.37–4.19 (m, 2 H), 3.94–3.76 (m, 2 H)
6h	Cl	H	Cl	H	COOH	–78	75	153–155 (EtOAc/ hexane, 1:10)	$C_{16}H_{12}Cl_2O_4$ (339.18)	C 56.66, H 3.57, Cl 20.91	C 56.91, H 3.66, Cl 20.87	1710 (C=O)	7.49 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 7.8 Hz, 1 H), 7.31 (t, *J* = 7.8 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 4.12–4.04 (m, 2 H), 4.03–3.95 (m, 2 H)
7h	Cl	H	Cl	H	SO_2Cl	–78	58	120–122 (methanol)	$C_{15}H_{11}Cl_3O_4S$ (393.68)	C 45.77, H 2.82, Cl 27.02, S 8.14	C 45.86, H 3.00, Cl 26.81, S 7.91	1387 (S=O) 1193 (S=O)	8.07 (dd, *J* = 7.3, *J* = 2.2 Hz, 1 H), 7.72 (dd, *J* = 8.0, *J* = 2.2 Hz, 1 H), 7.66 (t, *J* = 7.7 Hz, 1 H), 7.34–7.22 (m, 4 H), 4.32–4.20 (m, 2 H), 3.90–3.78 (m, 2 H)
6i	Cl	H	F	H	COOH	–78	74	158–159 (EtOAc/ hexane, 1:3)	$C_{16}H_{12}ClFO_4$ (322.72)	C 59.55, H 3.75, Cl 10.99	C 59.82, H 3.72, Cl 10.68	1684 (C=O)	7.53 (ddm, *J* = 8.8, $^4J_{H,F}$ = 5.5 Hz, 2 H), 7.41 (dd, *J* = 7.3, *J* = 2.6 Hz, 1 H), 7.40–7.29 (m, 2 H), 7.00 (tm, *J* = 8.8 Hz, 2 H), 4.16–4.06 (m, 2 H), 4.05–3.95 (m, 2 H)
7i	Cl	H	F	H	SO_2Cl	–78	57	136–138 (2-propanol)	$C_{15}H_{11}Cl_2FO_4S$ (377.22)	C 47.76, H 2.94, Cl 18.80, S 8.50	C 47.67, H 3.01, Cl 18.68, S 8.46	1379 (S=O) 1189 (S=O)	8.08 (dd, *J* = 7.0, *J* = 2.2 Hz, 1 H), 7.72 (dd, *J* = 8.1, *J* = 2.2 Hz, 1 H), 7.65 (t, *J* = 7.7 Hz, 1 H), 7.31 (ddm, *J* = 8.8, $^4J_{H,F}$ = 5.5 Hz, 2 H), 7.00 (tm, *J* = 8.8 Hz, 2 H), 4.31–4.23 (m, 2 H), 3.87–3.79 (m, 2 H)
6j	Cl	H	CH_3O	H	COOH	–78	60	145–146 (EtOAc/ hexane, 1:1)	$C_{17}H_{15}ClO_5$ (334.76)	C 61.00, H 4.52, Cl 10.59	C 61.23, H 4.43, Cl 10.60	1742 (C=O)	7.45 (d, *J* = 8.9 Hz, 2 H), 7.41–7.36 (m, 2 H), 7.31 (dd, *J* = 8.4, *J* = 7.2 Hz, 1 H), 6.84 (d, *J* = 8.9 Hz, 2 H), 4.11–4.06 (m, 2 H), 4.02–3.77 (m, 2 H), 3.77 (s, 3 H)

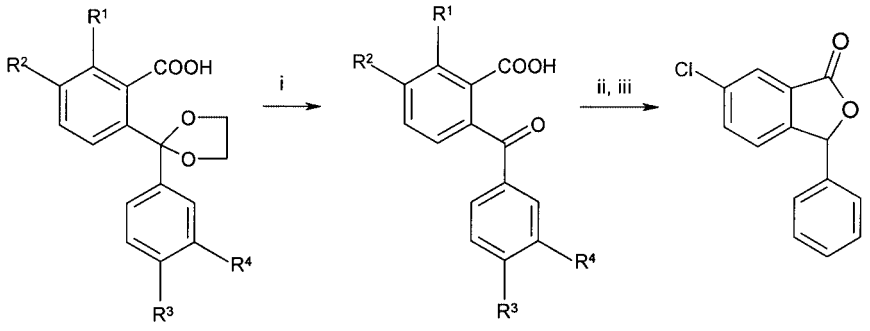
Table 2. *(continued)*

	R^1	R^2	R^3	R^4	E	*T* [°C]	Yield [%]	M.p. [°C]	Empirical formula	Elemental analysis Calcd.	Found	IR (KBr): $\tilde{\nu}$ [cm^{-1}]	^1H NMR: δ [ppm]
7j	Cl	H	CH_3O	H	SO_2Cl	–78	58	141–143 (2-propanol)	$C_{16}H_{14}Cl_2O_5S$ (389.26)	C 49.37, H 3.63, Cl 18.22, S 8.24	C 49.39, H 3.83, Cl 18.00, S 8.61	1389 (S=O) 1192 (S=O)	8.07 (dd, *J* = 7.3, *J* = 2.2 Hz, 1 H), 7.70 (dd, *J* = 8.1, *J* = 2.2 Hz, 1 H), 7.63 (t, *J* = 8.0 Hz, 1 H), 7.25 (d, *J* = 8.8 Hz, 2 H), 6.84 (d, *J* = 8.8 Hz, 2 H), 4.31–4.20 (m, 2 H), 3.86–3.75 (m, 2 H), 3.79 (s, 3 H)
6k	Cl	H	H	CH_3O	COOH	–78	64	158–159 (EtOAc/ hexane, 1:3)	$C_{17}H_{15}ClO_5$ (334.76)	C 61.00, H 4.52, Cl 10.59	C 60.87, H 4.59, Cl 10.40	1723 (C=O)	7.38 (dd, *J* = 7.7, *J* = 1.2 Hz, 1 H), 7.37 (dd, *J* = 8.1, *J* = 1.2 Hz, 1 H), 7.30 (t, *J* = 7.9 Hz, 1 H), 7.24 (t, *J* = 8.1 Hz, 1 H), 7.18–7.14 (m, 2 H), 6.84 (ddd, *J* = 8.2, *J* = 2.7, *J* = 0.9 Hz, 1 H), 4.09–4.06 (m, 2 H), 4.06–4.03 (m, 2 H), 3.78 (s, 3 H)
7k	Cl	H	H	CH_3O	SO_2Cl	–78	54	106–108 (EtOAc/ hexane, 1:3)	$C_{16}H_{14}Cl_2O_5S$ (389.26)	C 49.37, H 3.63, Cl 18.22, S 8.24	C 49.57, H 3.51, Cl 18.11, S 8.73	1380 (S=O) 1191 (S=O)	8.08 (dd, *J* = 7.9, *J* = 1.6 Hz, 1 H), 7.70 (dd, *J* = 7.9, *J* = 1.6 Hz, 1 H), 7.64 (t, *J* = 7.9 Hz, 1 H), 7.24 (t, *J* = 7.8 Hz, 1 H), 6.92–6.84 (m, 3 H), 4.29–4.25 (m, 2 H), 3.86–3.82 (m, 2 H), 3.79 (s, 3 H)
6l	Cl	CH_3O	H	H	COOH	–78	34	166–168 (diethyl ether)	$C_{17}H_{15}ClO_5$ (334.76)	C 61.00, H 4.52, Cl 10.59	C 60.63, H 4.67, Cl 10.48	1745 (C=O)	7.60–7.51 (m, 2 H), 7.43–7.24 (m, 4 H), 6.92 (d, *J* = 8.8 Hz, 1 H), 4.09–4.04 (m, 2 H), 4.04–3.99 (m, 2 H), 3.90 (s, 3 H)
7l	Cl	CH_3O	H	H	SO_2Cl	–78	50	188–190 (ethanol)	$C_{16}H_{14}Cl_2O_5S$ (389.26)	C 49.37, H 3.63, Cl 18.22, S 8.24	C 49.30, H 3.60, Cl 18.00, S 8.34	1386 (S=O) 1194 (S=O)	8.04 (d, *J* = 8.8 Hz, 1 H), 7.33 (m, 5 H), 7.28 (d, *J* = 8.8 Hz, 1 H), 4.27–4.22 (m, 2 H), 4.01 (s, 3 H), 3.85–3.80 (m, 2 H)
6m	Cl	CH_3O	Cl	H	COOH	–78	36	166–168 (EtOAc/ hexane, 3:7)	$C_{17}H_{14}Cl_2O_5$ (369.20)	C 55.31, H 3.82, Cl 19.21	C 55.24, H 3.84, Cl 19.28	1743 (C=O)	7.47 (d, *J* = 8.8 Hz, 2 H), 7.30 (d, *J* = 8.8 Hz, 1 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 1 H), 4.09–4.03 (m, 2 H), 4.03–3.97 (m, 2 H), 3.91 (s, 3 H)
7m	Cl	CH_3O	Cl	H	SO_2Cl	–78	70	163–164 (ethanol)	$C_{16}H_{13}Cl_3O_5S$ (423.70)	C 45.36, H 3.09, Cl 25.10, S 7.57	C 45.79, H 3.13, Cl 24.84, S 7.51	1389 (S=O) 1194 (S=O)	8.03 (d, *J* = 8.8 Hz, 1 H), 7.28 (s, 4 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 4.30–4.20 (m, 2 H), 4.04 (s, 3 H), 3.87–3.77 (m, 2 H)
6n	H	Cl	Cl	H	COOH	–10	48	175–176 (EtOAc/ hexane, 1:1)	$C_{16}H_{12}Cl_2O_4$ (339.18)	C 56.66, H 3.57, Cl 20.91	C 57.10, H 3.50, Cl 20.68	1690 (C=O)	7.56 (d, *J* = 2.2 Hz, 1 H), 7.52 (d, *J* = 8.4 Hz, 1 H), 7.43 (dd, *J* = 8.4, *J* = 2.2 Hz, 1 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.8 Hz, 2 H), 4.17–4.04 (m, 2 H), 4.04–3.91 (m, 2 H)
7n	H	Cl	Cl	H	SO_2Cl	–10	76	146–148 (acetone)	$C_{15}H_{11}Cl_3O_4S$ (393.68)	C 45.77, H 2.82, Cl 27.02, S 8.14	C 45.84, H 2.94, Cl 26.80, S 7.92	1381 (S=O) 1176 (S=O)	8.28 (d, *J* = 2.2 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.73 (dd, *J* = 8.4, *J* = 2.2 Hz, 1 H), 7.27 (s, 4 H), 4.29–4.16 (m, 2 H), 4.08–3.95 (m, 2 H)

Table 2. *(continued)*

	R^1	R^2	R^3	R^4	E	*T* [°C]	Yield [%]	M.p. [°C]	Empirical formula	Elemental analysis Calcd.	Found	IR (KBr): $\tilde{\nu}$ [cm^{-1}]	^1H NMR: δ [ppm]
6o	H	Cl	H	H	COOH	0	34	178–179 (EtOAc)	$C_{16}H_{13}ClO_4$ (304.73)	C 63.06, H 4.30, Cl 11.63	C 62.98, H 4.29, Cl 11.49	1703 (C=O)	7.59 (d, *J* = 2.2 Hz, 1 H), 7.49 (d, *J* = 8.5 Hz, 1 H), 7.48–7.45 (m, 2 H), 7.42 (dd, *J* = 8.5, *J* = 2.2 Hz, 1 H), 7.36–7.31 (m, 3 H), 4.14–4.09 (m, 2 H), 4.05–4.00 (m, 2 H)
7o	H	Cl	H	H	SO_2Cl	0	69	138–140 (ethanol)	$C_{15}H_{12}Cl_2O_4S$ (359.23)	C 50.15, H 3.37, Cl 19.74, S 8.93	C 49.75, H 3.31, Cl 19.93, S 8.86	1384 (S=O) 1143 (S=O)	8.29 (d, *J* = 2.2 Hz, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.72 (dd, *J* = 8.4, *J* = 2.2 Hz, 1 H), 7.32 (s, 5 H), 4.32–4.20 (m, 2 H), 4.06–3.94 (m, 2 H)
6p[a]	H	Cl	CH_3O	H	COOH	–20	Isolated as the benzophenone **9p**, see Exp. Sect.						
7p	H	Cl	CH_3O	H	SO_2Cl	–20	40	136–138 (ethanol)	$C_{16}H_{14}Cl_2O_5S$ (389.26)	C 49.37, H 3.63, Cl 18.22, S 8.24	C 49.65, H 3.72, Cl 17.98, S 8.46	1382 (S=O) 1176 (S=O)	8.29 (d, *J* = 2.2 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.70 (dd, *J* = 8.4, *J* = 2.2 Hz, 1 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 4.30–4.18 (m, 2 H), 4.04–3.92 (m, 2 H), 3.78 (s, 3 H)
6q	H	Cl	H	CH_3O	COOH	–20	53	149–150 (ethanol)	$C_{17}H_{15}ClO_5$ (334.76)	C 61.00, H 4.52, Cl 10.59	C 60.61, H 4.55, Cl 10.21	1712 (C=O)	7.61 (d, *J* = 2.2 Hz, 1 H), 7.46 (d, *J* = 8.4 Hz, 1 H), 7.40 (dd, *J* = 8.4, *J* = 2.2 Hz, 1 H), 7.32–7.20 (m, 1 H), 7.08–6.98 (m, 2 H), 6.87 (ddd, *J* = 8.4, *J* = 2.6, *J* = 0.7 Hz, 1 H), 4.20–4.09 (m, 2 H), 4.08–3.97 (m, 2 H), 3.78 (s, 3 H)
7q	H	Cl	H	CH_3O	SO_2Cl	–20	55	117–118 (2-propanol)	$C_{16}H_{14}Cl_2O_5S$ (389.26)	C 49.37, H 3.63, Cl 18.22, S 8.24	C 49.17, H 3.71, Cl 18.10, S 8.18	1379 (S=O) 1188 (S=O)	8.28 (d, *J* = 2.2 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 1 H), 7.70 (dd, *J* = 8.4, *J* = 2.2 Hz, 1 H), 7.23 (t, *J* = 8.0 Hz, 1 H), 6.93 (t, *J* = 2.1 Hz, 1 H), 6.89 (ddd, *J* = 7.7, *J* = 1.7, *J* = 0.9 Hz, 1 H), 6.86 (ddd, *J* = 8.2, *J* = 2.6, *J* = 0.9 Hz, 1 H), 4.27–4.21 (m, 2 H), 4.05–3.97 (m, 2 H), 3.78 (s, 3 H)
6r[b]	H	Cl	CH_3O	CH_3O	COOH	–20	Isolated as the benzophenone **9r**, see Exp. Sect.						
7r	H	Cl	CH_3O	CH_3O	SO_2Cl	–20	45	140–142 (ethanol)	$C_{17}H_{16}Cl_2O_6S$ (419.28)	C 48.70, H 3.85, Cl 16.91, S 7.65	C 48.99, H 3.90, Cl 16.49, S 7.50	1389 (S=O) 1189 (S=O)	8.30 (d, *J* = 2.2 Hz, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 7.70 (dd, *J* = 8.4, *J* = 2.2 Hz, 1 H), 7.07 (d, *J* = 1.8 Hz, 1 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 6.69 (dd, *J* = 8.4, *J* = 1.8 Hz, 1 H), 4.28–4.20 (m, 2 H), 4.04–3.96 (m, 2 H), 3.87 (s, 3 H), 3.85 (s, 3 H)
7s	H	Cl	F	H	SO_2Cl	–50	10	174–176 (methanol)	$C_{15}H_{11}Cl_2FO_4S$ (377.22)	C 47.76, H 2.94, Cl 18.80, S 8.50	C 47.33, H 3.06, Cl 18.60, S 8.40	1383 (S=O) 1177 (S=O)	8.29 (d, *J* = 2.2 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 7.74 (dd, *J* = 8.4, *J* = 2.2 Hz, 1 H), 7.31 (ddm, *J* = 8.8, $^4J_{H,F}$ = 5.3 Hz, 2 H), 6.99 (tm, *J* = 8.8 Hz, 2 H), 4.30–4.17 (m, 2 H), 4.08–3.95 (m, 2 H)

[a] 59% of the starting compound was recovered. [b] 52% of the starting compound was recovered.



Scheme 3

^{1}H NMR spectra provided the chemical shift, multiplicity and integration data for the assignment of the structures. The structure of **6o** was proved by its transformation to phthalide **10** via the benzophenone derivative **9o** (Scheme 3).

Conclusions

The *ortho*-lithiation methodology described in this paper is an efficient route to highly substituted *ortho*-functionalized benzophenone ketals, which may be used in the construction of condensed heterocycles by *ortho* cyclization. The intramolecular competition of phenyl rings with different substitution patterns makes benzophenone ketals interesting substrates for the study of *ortho*-directing ability and the long-range effects of various substituents in lithiation reactions.

Experimental Section

General Remarks: All melting points were determined with a Büchi 535 capillary melting point apparatus and are uncorrected. IR spectra were obtained with a Bruker IFS-113v FT spectrometer in KBr pellets. ^{1}H NMR spectra were recorded in $CDCl_3$ (unless stated otherwise) with a Varian Gemini-200 or Inova-500 spectrometer using TMS as the internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. Elemental analyses were performed with a Perkin−Elmer 2400 analyzer.

3,3′,4-Trichlorobenzophenone (3b): A mixture of 1,2-dichlorobenzene (14.8 mL, 19.4 g, 0.132 mol), 3-chlorobenzoyl chloride (16.9 mL, 23.1 g, 0.132 mol) and anhydrous aluminium chloride (17.7 g, 0.132 mol) was stirred at 120 °C for 3 h. The reaction mixture was poured onto crushed ice (300 g), the solid product was filtered, washed with water and recrystallized from 2-propanol (220 mL) to give the title compound (20.8 g, 55%), m.p. 119−120 °C. ^{1}H NMR (500 MHz, 25 °C): δ = 7.88 (d, *J* = 1.9 Hz, 1 H), 7.75 (t, *J* = 1.7 Hz, 1 H), 7.64−7.58 (m, 2 H), 7.61 (dd, *J* = 8.3, *J* = 1.9 Hz, 1 H), 7.58 (d, *J* = 8.3 Hz, 1 H), 7.45 (t, *J* = 7.9 Hz, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 1658 cm^{-1} (C=O). $C_{13}H_7Cl_3O$ (285.56): calcd. C 54.68, H 2.47, Cl 37.25; found C 54.80, H 2.37, Cl 37.41.

3,4-Dichloro-4′-fluorobenzophenone (3d): This compound was prepared analogously to **3b** starting from 1,2-dichlorobenzene (12.6 mL, 16.5 g, 0.112 mol), 4-fluorobenzoyl chloride (11.8 mL, 15.9 g, 0.1 mol) and anhydrous aluminium chloride (14.7 g, 0.11 mol) to give the title compound (17.3 g, 64%), m.p. 92−93 °C (2-propanol). ^{1}H NMR (500 MHz, 25 °C): δ = 7.86 (d, *J* = 1.8 Hz, 1 H), 7.82 (ddm, *J* = 8.8, $^4J_{H,F}$ = 5.4 Hz, 2 H), 7.60 (dd, *J* = 8.3, *J* = 1.8 Hz, 1 H), 7.58 (d, *J* = 8.3 Hz, 1 H), 7.19 (tm, *J* = 8.6 Hz, 2 H) ppm. IR (KBr): $\tilde{\nu}$ = 1646 cm^{-1} (C=O). $C_{13}H_7Cl_2FO$ (269.10): calcd. C 58.02, H 2.62, Cl 26.35; found C 57.95, H 2.60, Cl 26.44.

3,3′,4-Trichloro-4′-methoxybenzophenone (3f): 2-Chloroanisole (14.0 mL, 15.7 g, 0.11 mol) was added dropwise to a mixture of anhydrous aluminium chloride (14.6 g, 0.11 mol) and dichloromethane (30 mL) maintaining the temperature below 20 °C. After stirring for 5 min, 3,4-dichlorobenzoyl chloride (21.0 g, 0.1 mol) was added maintaining the temperature below 20 °C. After stirring for an additional 30 min, the reaction mixture was poured onto crushed ice (140 g). The organic layer was separated, dried and the solvents were evaporated. The crude solid was recrystallized from acetone (150 mL) to give the title compound (24.2 g, 77%), m.p. 145−146 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 7.90 (d, *J* = 2.1 Hz, 1 H), 7.84 (d, *J* = 8.2 Hz, 1 H), 7.83 (d, *J* = 2.1 Hz, 1 H), 7.75 (dd, *J* = 8.5, *J* = 2.1 Hz, 1 H), 7.66 (dd, *J* = 8.2, *J* = 2.1 Hz, 1 H), 3.98 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1655 cm^{-1} (C=O). $C_{14}H_9Cl_3O_2$ (315.59): calcd. C 53.28, H 2.87, Cl 33.70; found C 53.52, H 2.75, Cl 33.53.

4′-Chloro-3,4-dimethoxybenzophenone (3r): This compound was prepared analogously to **3f** starting from 1,2-dimethoxybenzene (14.0 mL, 15.2 g, 0.11 mol), 4-chlorobenzoyl chloride (12.7 mL, 17.5 g, 0.1 mol) and anhydrous aluminium chloride (20.0 g, 0.15 mol) to give the title compound (14.6 g, 53%), m.p. 111−112 °C (ethanol). ^{1}H NMR (200 MHz, 25 °C): δ = 7.71 (d, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 1.8 Hz, 1 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.34 (dd, *J* = 8.2, *J* = 1.8 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1644 cm^{-1} (C=O). $C_{15}H_{13}ClO_3$ (276.73): calcd. C 65.11, H 4.74, Cl 12.81; found C 65.10, H 4.77, Cl 12.64.

Synthesis of 1,3-Dioxolanes 4. General Procedure: A solution of benzophenone (1.0 mol), ethylene glycol (200 mL, 222.6 g, 3.6 mol) and *p*-toluenesulfonic acid (2.0 g, 0.01 mol) in toluene (600 mL)

was refluxed in a Dean−Stark apparatus for 40 h. The reaction mixture was washed with aqueous sodium hydrogen carbonate solution (5%, 200 mL) and water (2 × 200 mL), dried ($MgSO_4$) and the solvents were evaporated. The residue was recrystallized or distilled in vacuo. For yields, boiling or melting points, solvents of recrystallization, elemental analyses and ^1H NMR spectroscopic data of the ketals see Table 1.

Lithiation of 1,3-Dioxolanes 4. General Procedure: Butyllithium (6 mL of a 2.5 M solution in hexane, 0.015 mol) was added to a solution of **4** (0.010 mol) in THF (10 mL) under argon and the mixture was stirred for 2 h (for the temperature of lithiation see Table 2). The resulting suspension of **5** was treated with the appropriate electrophile to give compounds **6**, **7** and **8**, respectively.

Carboxylation of Lithio Derivatives 5. General Procedure: A suspension of the lithio derivative **5**, prepared as described above, 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. The crystalline product was filtered to give **6** as colourless crystals. For the yields, melting points, solvents of recrystallization, elemental analyses, IR and ^1H NMR spectroscopic data see Table 2.

Chlorosulfonation of Lithio Derivatives 5. General Procedure: A suspension of the lithio derivative **5**, prepared as described above, was added to a stirred solution of sulfur dioxide (3.2 g, 0.05 mol) in THF (10 mL). The mixture was stirred at ambient temperature for 12 h and the solid product (lithium sulfinate) was filtered. Sulfuryl chloride (1.6 mL, 2.7 g, 0.02 mol) in hexane (5 mL) was added to the suspension of the solid in hexane (30 mL) at 0 °C. After stirring at 0 °C for 30 min, the solvent was evaporated, water (50 mL) was added to the residue and the mixture was stirred for 30 min. The crystalline product was filtered to give **7** as colourless crystals. For the yields, melting points, solvents of recrystallization, elemental analyses, IR and ^1H NMR spectroscopic data see Table 2.

5-[2-(4-Chlorophenyl)-1,3-dioxolan-2-yl]-2-fluorobenzoic Acid (8a): The crude product mixture, obtained after lithiation and carboxylation of ketal **4s** according to the general procedure, was recrystallized from EtOAc/hexane (1:3) to give **8a** (0.48 g, 15%) as colourless crystals, m.p. 159−160 °C (EtOAc/hexane, 1:3). ^1H NMR (500 MHz, 25 °C): δ = 8.17 (dd, $^4J_{H,F}$ = 7.0, J = 2.4 Hz, 1 H), 7.67 (ddd, J = 8.6, $^4J_{H,F}$ = 4.5, J = 2.4 Hz, 1 H), 7.44 (d, J = 8.7 Hz, 2 H), 7.32 (d, J = 8.7 Hz, 2 H), 7.13 (dd, $^3J_{H,F}$ = 10.4, J = 8.6 Hz, 1 H), 4.11−3.96 (m, 4 H) ppm. IR (KBr): $\tilde{\nu}$ = 1686 cm^{-1} (C=O). $C_{16}H_{12}ClFO_4$ (322.72): calcd. C 59.55, H 3.75, Cl 10.99; found C 59.99, H 3.88, Cl 10.60.

5-[2-(4-Chlorophenyl)-1,3-dioxolan-2-yl]-2-fluorobenzenesulfonyl Chloride (8b): Ketal **4s** was lithiated and chlorosulfonated according to the general procedure. A 1:2 mixture of sulfonyl chlorides **7s** and **8b** was formed, as determined by ^1H NMR measurements on the basis of the intensity ratio of the signals corresponding to the aromatic proton between the chlorine and chlorosulfonyl substituent in **7s** (δ = 8.29 ppm) and between the ketal group and the chlorosulfonyl substituent in **8b** (δ = 8.15 ppm). The crude product mixture was recrystallized from methanol to give **7s** (0.38 g, 10%); for data see Table 2. The mother liquor was concentrated, and the residue was triturated with a mixture of hexane (10 mL) and EtOAc (1 mL). The resulting solution was decanted and the solvents evaporated to give **8b** (0.3 g, 8%) as an oil, contaminated with **7s** (5%, as determined by ^1H NMR). ^1H NMR (500 MHz, 25 °C): δ = 8.15 (dd, $^4J_{H,F}$ = 6.6, J = 2.2 Hz, 1 H), 7.80 (ddd, J = 8.7, $^4J_{H,F}$ = 4.5, J = 2.2 Hz, 1 H), 7.43 (d, J = 8.6 Hz, 2 H), 7.34 (d, J = 8.6 Hz, 2 H), 7.27 (t, J = 9.1 Hz, 1 H), 4.15−4.04 (m, 4 H) ppm. IR (film): $\tilde{\nu}$ = 1377, 1182 cm^{-1} (S=O). $C_{15}H_{11}Cl_2FO_4S$ (377.22): calcd. C 47.76, H 2.94, Cl 18.80, S 8.50; found C 47.87, H 3.05, Cl 19.01, S 8.40.

2-Benzoyl-5-chlorobenzoic Acid (9o): A suspension of 5-chloro-2-(2-phenyl-1,3-dioxolan-2-yl)benzoic acid (**6o**) (3.05 g, 0.01 mol) in an aqueous solution of hydrochloric acid (10%, 25 mL) was refluxed for 4 h. The crystalline product was filtered to give **9o** (2.22 g, 85%) as colourless crystals, m.p. 174−175 °C (ethanol) (ref.[32] 172−174 °C). ^1H NMR (200 MHz, 25 °C): δ = 9.11 (br. s, 1 H), 8.03 (d, J = 1.8 Hz, 1 H), 7.63 (dd, J = 8.3, J = 1.8 Hz, 1 H), 7.32 (d, J = 8.3 Hz, 1 H), 7.75−7.48 (m, 4 H), 7.48−7.37 (m, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 1782, 1678 cm^{-1} (C=O). $C_{14}H_9ClO_3$ (260.66): calcd. C 64.50, H 3.48, Cl 13.60; found C 64.39, H 3.47, Cl 13.52.

3-Chloro-6-(4-methoxybenzoyl)benzoic Acid (9p): This compound was prepared analogously to **9o** starting from the crude product obtained after the lithiation and carboxylation of **4p** (see general procedures) to give **9p** (1.21 g, 36% based on **4p**) as colourless crystals, m.p. 177−178 °C (acetonitrile). ^1H NMR (200 MHz, 25 °C): δ = 8.05 (d, J = 2.2 Hz, 1 H), 7.69 (d, J = 8.9 Hz, 2 H), 7.62 (dd, J = 8.1, J = 2.2 Hz, 1 H), 7.31 (d, J = 8.1 Hz, 1 H), 6.90 (d, J = 8.9 Hz, 2 H), 3.87 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1696, 1668 cm^{-1} (C=O). $C_{15}H_{11}ClO_4$ (290.69): calcd. C 61.98, H 3.81, Cl 12.20; found C 61.74, H 3.99, Cl 12.10.

3-Chloro-6-(3,4-dimethoxybenzoyl)benzoic Acid (9r): This compound was prepared analogously to **9o** starting from the crude product obtained after lithiation and carboxylation of **4r** (see general procedures) to give **9r** (1.35 g, 42%, based on **4r**) as colourless crystals, m.p. 241−242 °C (ethanol). ^1H NMR (200 MHz, 25 °C): δ = 8.07 (d, J = 2.2 Hz, 1 H), 7.62 (dd, J = 8.0, J = 2.2 Hz, 1 H), 7.55 (d, J = 2.2 Hz, 1 H), 7.34 (d, J = 8.0 Hz, 1 H), 7.07 (dd, J = 8.4, J = 2.2 Hz, 1 H), 6.80 (d, J = 8.4 Hz, 1 H), 3.94 (s, 3 H), 3.93 (s, 3 H) ppm. IR (KBr): $\tilde{\nu}$ = 1723, 1638 cm^{-1} (C=O). $C_{16}H_{13}ClO_5$ (320.72): calcd. C 59.92, H 4.08, Cl 11.05; found C 59.69, H 4.18, Cl 10.95.

6-Chloro-3-phenylbenzo[*c*]furan-1(3*H*)-one (10): Sodium borohydride (0.59 g, 0.0155 mol) was added to a solution of 2-benzoyl-5-chlorobenzoic acid (**9o**) (0.81 g, 0.0031 mol) in ethanol (7 mL) at ambient temperature. After stirring for 24 h, the solvent was evaporated. Water (10 mL) and aqueous hydrochloric acid (10%, 10 mL) were added to the residue. The crystalline product was collected to give **10** (0.63 g, 63%) as colourless crystals, m.p. 95−96 °C (ethanol) (ref.[33] 88 °C). ^1H NMR (200 MHz, 25 °C): δ = 7.92 (d, J = 2.0 Hz, 1 H), 7.61 (dd, J = 8.2, J = 2.0 Hz, 1 H), 7.44−7.34 (m, 3 H), 7.32−7.20 (m, 3 H), 6.39 (s, 1 H) ppm. IR (KBr): $\tilde{\nu}$ = 1746 cm^{-1} (C=O). $C_{14}H_9ClO_2$ (244.68): calcd. C 68.72, H 3.71, Cl 14.49; found C 68.38, H 3.58, Cl 14.64.

Acknowledgments

The authors are grateful to Dr. Rita Kapiller-Dezsöfi for NMR measurements and helpful discussions. We would also like to thank Mrs. Angéla Veress-Pandur and Miss Mária Vajjon for technical assistance.

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Received May 12, 2004
Early View Article
Published Online September 2, 2004

