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Application of Organolithium and Related Reagents in Synthesis, Part X [1]. Metallation-Electrophilic Substitution Sequence of Secondary Chlorobenzamides

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Summary. The lithiation (*Bu*^{n}Li/*THF*) of 2-chloro- (**1**), 3-chloro- (**2**) and 4-chlorobenzanilides (**3**) and the subsequent reactions of the corresponding bis-lithiated anilides **4**–**6** with electrophiles (*Me*I, $CH_2=CH-CH_2Br$, Me_3SiCl, *Me*CHO, *o*-*Me*OC_6H_4CHO, *p*-*Me*OC_6H_4CHO, Me_2NCHO and *p*-*Me*$OC_6H_4CONMe_2$) towards the synthesis of the *ortho* substituted chlorobenzoesic acids derivatives **12**–**14** have been described. The effect of the chlorine substituent upon the generation and stability of the bis-lithiated chloro-anilides **4**–**6** has been studied. It has been found that the bis-lithiated chloro-anilide **5** derived from *m*-chloro-benzanilide (**2**) at a temperature above −30°C converts into the corresponding benzyne **9**. The anilide moiety (masking group) of the formed *ortho*-substituted chlorobenzanilides appeared to be effectively removable on acid-driven hydrolysis.

Keywords. Secondary chlorobenzamides; Lithation; Electrophilic substitution; *ortho*-Substituted chlorobenzoesic acids; Phthalides; 2,3-Dihydro-1*H*-iso-indolin-1-ones; 3,4-Dihydroisocoumarins.

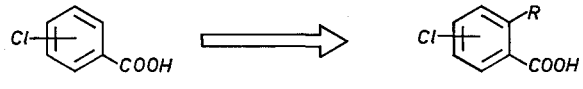
Anwendungen von Organolithium und verwandten Reagenzien in organischen Synthesen, 10. Mitt. [1]: Metallierung und nachfolgende elektrophile Substitution sekundärer Chlorbenzamide

Zusammenfassung. Die Lithiierung (*Bu*^{n}Li/*THF*) der 2-Chlor- (**1**), 3-Chlor- (**2**) and 4-Chlorbenzanilide (**3**) und nachfolgende Reaktion der entsprechenden doppellithiierten Anilide **4**–**6** mit elektrophilen Reagenzien (*Me*I, $CH_2=CH-CH_2Br$, Me_3SiCl, *Me*CHO, *o*-*Me*OC_6H_4CHO, *p*-*Me*OC_6H_4CHO, Me_2NCHO und *p*-*Me*$OC_6H_4CONMe_2$) zur Synthese von *ortho*-substituierten Benzoesäurederivaten **12**–**14** wird beschrieben. Der Einfluß des Chlorsubstituierten auf die Bildung und Stabilität der doppellithiierten Chloranilide **4**–**6** wurde untersucht. Es wurde festgestellt, daß das doppellithiierte, vom *m*-Chlorbenzanilid erhaltene Chloranilid **5** bei Temperaturen über −30°C das entsprechende Arin **9** bildet. Der Anilidrest (eine maskierende Gruppe) der gebildeten *ortho*-substituierten Chloranilide kann durch saure Hydrolyse abgespalten werden.

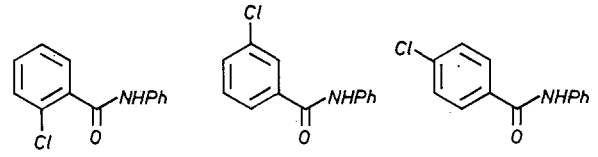
Introduction

The formation of the regiospecifically *ortho* metallated aromatic compounds is a convenient route to polysubstituted aromatics. Because of the high selectivity and

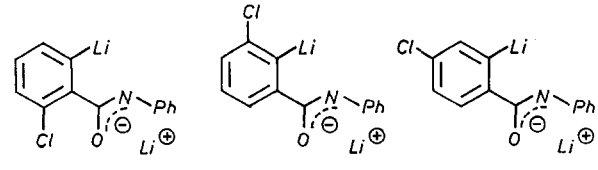
the wide range of further transformations the process is often used in organic synthesis [2–10]. In the course of our work on the aromatic lithiation–electrophilic substitution sequence [1, 11] of secondary carboxamides (masked carboxylic acids), we have now studied, to what extent the transformation of chloro-benzoic acids (**A**) into their *ortho*-substituted derivatives (**B**) (carbon–carbon bond formed) shows a preparative applicability. In the *ortho* lithiation of aromatic carboxylic acids, secondary amide [6, 11], tertiary amide [10] and oxazoline [12] groups are widely used for protection of the carboxylic moiety. In the literature only two examples of the lithiation of masked chloro-benzoic acids have been reported. It has been shown that N,N-diethyl-chloro-benzamides [5] and 2-(3-chlorophenyl)-4,4-dimethyl-2-oxazoline [12] are lithiated *ortho* to the masked carboxylic function. To our knowledge the lithiation of the secondary amides of chloro-benzoic acids has never been investigated. In this paper, we report a systematic study on the lithiation–electrophilic substitution sequence of the secondary chloro-benzamides and the subsequent removal of the masking moiety. We have identified all the products and have attempted to establish the conditions necessary to obtain the maximum yield from the process. It has been demonstrated [11 c] that amongst the secondary carboxamides the N-phenylamides (anilides) are the most powerful directing groups and that the anilide function should be considered the best choice for direct metallation of the masked carboxylic acids. For this reason, we investigated the lithiation of the chloro-benzanilides **1–3**.



(A) (B)



(1) (2) (3)



(4) (5) (6)

Results and Discussion

From the bases used for the lithiation *n*-butyllithium (*Bu*^{n}Li) in tetrahydrofuran (*THF*) as solvent was selected as the system most frequently used.

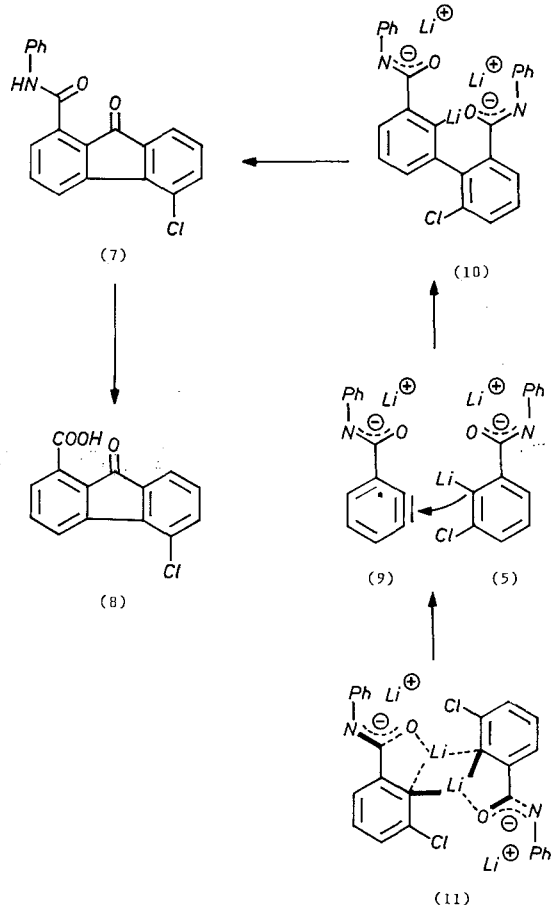
A different behaviour of the chloroanilides **1–3** studied in the lithiation (*Bu*^{n}Li/

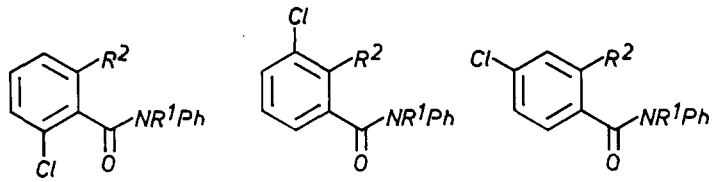
THF), towards converting them into the corresponding bis-lithiated anilides **4**–**6** was observed, as explained in the present paper. Thus, the *m*-chloro-anilide **2** was effectively converted at low temperature (anilide/−78°C/*Bu*^{n}Li/0.5 h) into the bis-lithiated anilide **5**, which appeared to be unstable if the reaction solution was allowed to warm up (see below). On the other hand, in the cases of the *o*- and *p*-chloro-anilides **1** and **3**, the effective generation of the bis-lithiated anilides **4** and **6** required an increase of temperature for the lithiation (anilide/−72°C/*Bu*^{n}Li/0.5 h → 20°C/1 h). The formation of the lithiated anilides was confirmed by the subsequent reactions of these species with electrophiles.

When the bis-lithiated *m*-chloro-anilide **5** was allowed to warm in its *THF* solution, and no trap (electrophile) was added, the reaction product was the fluorenone **7** in 72% yield. The structure of **7** was confirmed by the convergent synthesis of the corresponding acid **8** (s. Exp. Part and formula scheme).

This interesting process was presumed to involve addition of the bis-lithiated anilide **5** to the benzyne **9** (formed via LiCl elimination [12, 13] at the temperature above −30°C from the lithiated species). In the regioselective formation of the adduct **10**, which arose from the self-attack of **5** at the C^3-position of the benzyne **9** is in contrast to the general rule of the nucleophillic addition to benzynes containing an electrondonating group [13] (e.g. CON*Ph*$^-$, a structurally negatively charged group [14].

Although the observed regiospecific formation of the biphenyl **10** cannot be unequivocally explained, it may be assumed that at low temperature the dimeric species **11** [15] was formed, which





(12) (13) (14)

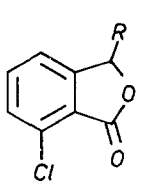
a, $R^1 = R^2 = Me$
b, $R^1 = H$; $R^2 = CH_2\text{-}CH{=}CH_2$
c, $R^1 = H$; $R^2 = SiMe_3$
d, $R^1 = H$; $R^2 = CH(OH)Me$
e, $R^1 = H$; $R^2 = CH(OH)C_6H_4OMe\text{-}o$
f, $R^1 = H$; $R^2 = CH(OH)C_6H_4OMe\text{-}p$
g, $R^1 = H$; $R^2 = CHO$
h, $R^1 = H$; $R^2 = COC_6H_4OMe\text{-}p$

at an increased temperature (−30°C) in part eliminated LiCl to generate the benzyne **9** coordinated with the unchanged bis-lithiated anilide **5**, and this complex forced the aryl group at the C^3-position of the benzyne.

A wide range of electrophiles was employed to react with the lithiated species. The bis-lithiated anilides **4**−**6** reacted with *Me*I (3 mol equivalents), $CH_2{=}CH-CH_2Br$ (3 mol equivalents), Me_3SiCl, *Me*CHO, *o*-*Me*OC_6H_4CHO, *p*-*Me*OC_6H_4CHO, Me_2NCHO and *p*-*Me*$OC_6H_4CONMe_2$ to give a single product in every case: di-methylated anilides **12a**−**14a**, allylated anilides **13b** and **14b**, which could be used for further transformations without purification (see below); unexpectedly the reaction of the bis-lithiated anilide **4** with allylbromide failed; further the silylated compounds **12c**−**14c**, hydroxy products **12d**−**14d**, **12e**−**14e**, **12f**−**14f**, and the formyl-derivatives **12g**−**14g**. In the cases when the lithiated species were reacted with N,N-dimethyl-4-methoxybenzamide, only the bis-lithiated anilide **6** gave the expected product **14h**. Attempted reactions of the bis-lithiated anilides **4** and **5** with N,N-dimethyl-4-methoxybenzamide failed. This could be accounted for by the extreme instability of the formed adducts of the lithiated species across the carbonyl group of N,N-dimethylbenzamide and/or the impeding of their formation arising from a steric hindrance caused by the chlorine substituent of the bis-lithiated anilides **4** and **5** [1, 11c]. The hydroxy products, without isolation on acid-driven cyclization, yielded the corresponding lactones (phthalides) **15a**, **16a**, **17a**, **15b**, **16b**, **17b**, **15c**, **16c**, and **17c**. The formylated and benzoylated derivatives upon hydrolytic workup, spontaneously cyclized into the isoindolinones **18**, **19**, **20a**, and **20b**.

The described methodology for introducing an alkyl substituent at the *ortho* position to the anilide function of chlorobenzoic acids shows considerable versatility for the regiospecific synthesis of tri-substituted benzenes. This, together with the effective removal of the anilide moiety on acid hydrolysis or reductive cleavage to the carboxylic acids and other functional groups should allow the access to a wide variety of benzenes.

Thus, the methylated chloro-anilides **13a** and **14a** upon their reaction with boiling sulphuric acid (58% $-H_2SO_4$) afforded quantitatively the corresponding methylated acids **22** and **23**. The anilide **12a** appeared to be practically inert towards



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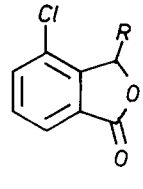

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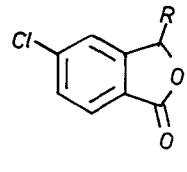
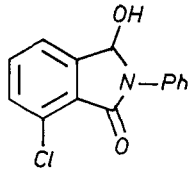


(17)

a, R = Me
b, R = C_6H_4OMe-o
c, R = C_6H_4OMe-p



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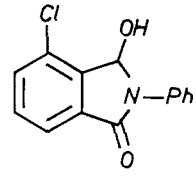

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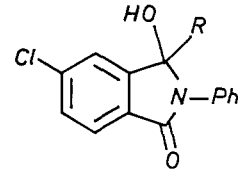
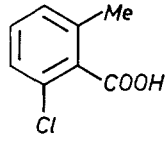


(20)

a, R = H
b, R = C_6H_4OMe-p



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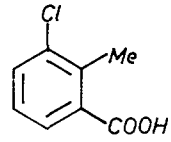

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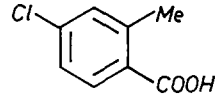

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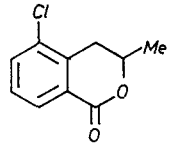

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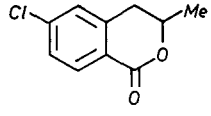

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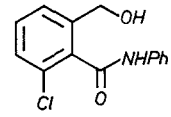

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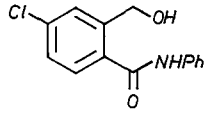

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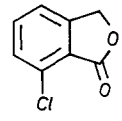

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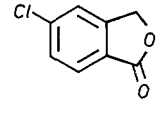

(29)

the hydrolysis (under the conditions used). The acid **21** was formed with a low yield (~ 10%). In the cases of the allylated anilides **13b** and **14b** hydrolysis (58% $-H_2SO_4$) did not give the benzoic acids, but produced the lactones (3,4-dihydro-isocoumarins) **24** and **25** in good yields. The treatment of the isoindolinones **18** and **20g** with KBH_4 in *Me*OH gave the hydroxymethylo-anilides **26** and **27** which on acid-driven cyclizatin were converted into the corresponding lactones (phthalides) **28** and **29**. Attempted reactions of the isoindolinone **19** with KBH_4 in *Me*OH

or with $LiAlH_4$ in *THF* failed. It has been found that the silylated chloro-anilides **12c–14c** in the presence of KF in boiling *Me*OH were quantitatively proto-desilylated. This indicates that the introduction of the trimethylsilyl group at the *ortho* position to the anilide function of the chloro-anilides **1–3** may be recognized as a good blocking [16] and readily removable group.

Experimental Part

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. A Zeiss-Jena Specord 71-IR spectrometer was used for the IR spectra, and a Varian EM-360 or a Tesla BS-467 NMR-spectrometer for the ^{1}H-NMR spectra. Compounds were purified until observed as single spots on TLC (Kieselgel GF-254 type 68). The chloro-anilides **1–3** were obtained by known methods. *n*-Butyllithium (Aldrich) was titrated before use.

General Procedure for the Metallation–Electrophilic Substitution of the Chloro-anilides **1**, **2**, *and* **3**

To the anilide (0.01 mol) in *THF* (25 ml) at −78°C *Bu*^{n}Li (0.022 mol) was added dropwise. The solution was held at −78°C for 0.5 h. In the case of the chloro-anilide **1** or **3** the mixture was warmed up to room temperature and kept at this temperature for 1 h, and then recooled to −78°C. To the solution of the lithiated species at −78°C an electrophile: *Me*I (0.033 mol), $CH_2=CH-CH_2Br$ (0.033 mol), Me_3SiCl (0.022 mol), *Me*CHO (0.033 mol), *o*-*Me*OC_6H_4CHO (0.011 mol), *p*-*Me*-OC_6H_4CHO (0.011 mol), Me_2NCHO (0.022 mol) or *p*-*Me*$OC_6H_4CONMe_2$ (0.011 mol) in *THF* (20 ml) was added. The mixture–after 1 h at −78°C–was allowed to reach room temperature and was stirred under this condition for 1 h, and then water (10 ml) was added. The reaction mixture, after evaporation of a part of *THF*, was extracted with $CHCl_3$ (3 × 50 ml), the layers were separated and the organic one, after washing with 10% HCl, was dried ($MgSO_4$). From the organic layer the solvent was removed and the residue chromatographed by column chromatography (silica gel-benzene, chloroform and chloroform : ether = 8 : 2) giving products **12a–14a**, **13b**, **14b**, **12c–14c**, **17b**, **17c**, **20a**, and **20b**, which were purified by distillation or crystallization. The allylated anilides **13b** and **14b** were used for the hydrolysis without further purification. The water layer after acidification (*pH* ~ 1) with hydrochloric acid was extracted with $CHCl_3$ (3 × 50 ml) and the layers were separated with the organic being dried ($MgSO_4$). Then the solvent was removed and the residue chromatographed by column chromatography (silica gel–benzene, chloroform and chloroform : ether = 8 : 2) giving products **15a–17a**, **15b**, **16b**, **15c**, **16c**, **18**, and **19**, which were purified by crystallization. The yields of the reactions, the physical properties, the IR and ^{1}H-NMR data, and the analytical data are given below.

2,N-Dimethyl-6-chloro-benzanilide (**12a**)

Yield 96%; b.p. 235–245°C at 0.4 mm Hg (bulb to bulb), m.p. 87–89°C (hexane). Calculated for $C_{15}H_{14}ClNO$: C 69.3, H 5.4, Cl 13.6, N 5.4; found: C 69.0, H 5.4, Cl 13.8, N 5.6. IR (KBr, cm^{-1}): 1 660 (C=O). NMR ($CDCl_3$, δ): 7.6–6.8 (8 H, m, *Ar*-H), 3.4 (2.4 H, s, N*Me*-H), 2.2 (2.4 H, s, *ArMe*-H), 3.1 (0.6 H, s, N*Me*-H), 2.4 (0.6 H, s, *ArMe*-H). The compound **12a** was obtained as a mixture of the two stable rotamers. The ratio of them was determined by NMR spectroscopy utilizing the peak areas of the methyl protons.

2,N-Dimethyl-3-chloro-benzanilide (**13a**)

Yield 92%; b.p. 235–245°C at 0.6 mm Hg (bulb to bulb). Calculated for $C_{15}H_{14}ClNO$: C 69.3, H 5.4, Cl 13.6, N 5.4; found: C 69.0, H 5.4, Cl 13.0, N 5.3. IR (KBr, cm^{-1}): 1 650 (C=O). ^{1}H-NMR ($CDCl_3$, δ): 7.5–6.6 (8 H, m, *Ar*-H), 3.4 (3 H, s, N*Me*-H), 2.3 (3 H, s, *ArMe*-H).

2,N-Dimethyl-4-chloro-benzanilide (**14 a**)

Yield 84%; b.p. 234–242°C at 0.4 mm Hg (bulb to bulb), m.p. 56–58°C (hexane). Calculated for $C_{15}H_{14}ClNO$: C 69.3, H 5.4, Cl 13.6, N 5.4; found: C 69.7, H 5.4, Cl 13.4, N 5.3. IR (KBr, cm^{-1}): 1 640 (C=O). NMR ($CDCl_3$, δ): 7.4–6.7 (8 H, m, *Ar*-H), 3.4 (3 H, s, N*Me*-H), 2.2 (3 H, s, *ArMe*-H).

6-Chloro-2-trimethylsilyl-benzanilide (**12 c**)

Yield 67%; m.p. 169–171°C (toluene). Calculated for $C_{16}H_{18}ClNOSi$: C 63.2, H 6.0, Cl 11.6, N 4.6; found: C 63.5, H 5.9, Cl 11.3, N 4.6. IR (KBr, cm^{-1}): 1 660 (C=O). NMR ($CDCl_3$, δ): 8.0–7.0 (9 H, m, NH–H and *Ar*-H), 0.4 (9 H, s, SiMe_3-H).

3-Chloro-2-trimethylsilyl-benzanilide (**13 c**)

Yield 87%; m.p. 165–167°C (heptane). Calculated for $C_{16}H_{18}ClNOSi$: C 63.2, H 6.0, Cl 11.6, N 4.6; found: C 63.1, H 6.0, Cl 11.5, N 4.5. IR (KBr, cm^{-1}): 1 650 (C=O). NMR ($CDCl_3$, δ): 8.0–7.3 (9 H, m, NH–H and *Ar*-H), 0.6 (9 H, s, SiMe_3-H).

4-Chloro-2-trimethylsilyl-benzanilide (**14 c**)

Yield 76%; m.p. 204–206°C (benzene : hexane = 1 : 3). Calculated for $C_{16}H_{18}ClNOSi$: C 63.2, H 6.0, Cl 11.6, N 4.6; found: C 63.2, H 5.9, Cl 11.6, N 4.5. IR (KBr, cm^{-1}): 1 660 (C=O). NMR ($CDCl_3$, δ): 7.9–7.4 (9 H, m, NH–H and *Ar*-H), 0.5 (9 H, s, SiMe_3-H).

7-Chloro-3-methylphthalide (**15 a**)

Yield 49%; m.p. 99–101°C (heptane). Calculated for $C_9H_7ClO_2$: C 59.2, H 3.8, Cl 19.4; found: C 59.6, H 3.8, Cl 19.3. IR (KBr, cm^{-1}): 1 770 (C=O). NMR ($CDCl_3$, δ): 7.9–7.2 (3 H, m, *Ar*-H), 5.5 (1 H, q, J=6 Hz, CH–H), 1.6 (3 H, d, J=6 Hz, *Me*-H).

4-Chloro-3-methylpthalide (**16 a**)

Yield 95%; m.p. 69.5–71.5°C (hexane). Calculated for $C_9H_7ClO_2$: C 59.2, H 3.8, Cl 19.4; found: C 59.2, H 3.6, Cl 19.5. IR (KBr, cm^{-1}): 1 760 (C=O). NMR ($CDCl_3$, δ): 7.8–7.2 (3 H, m, *Ar*-H), 5.5 (1 H, q, J=6 Hz, CH-H), 1.7 (3 H, d, J=6 Hz, *Me*–H).

5-Chloro-3-methylphtlalide (**17 a**)

Yield 66%; m. p. 99–101°C (ethanol). Calculated for $C_9H_7ClO_2$: C 59.2, H 3.8, Cl 19.4; found: C 58.9, H 3.8, Cl 19.1. (KBr, cm^{-1}): 1 770 (C=O). NMR ($CDCl_3$, δ): 8.0–7.3 (3 H, m, *Ar*-H), 5.5 (1 H, q, J=6 Hz, CH–H), 1.6 (3 H, d, J=6 Hz, *Me*-H).

7-Chloro-3-(2'-methoxyphenyl)-phthalide (**15 b**)

Yield 63%; m. p. 150–152°C (ethanol). Calculated for $C_{15}H_{11}ClO_3$: C 65.6, H 4.0, Cl 12.9; found: C 65.6, H 3.9, Cl 12.8. IR (KBr, cm^{-1}): 1 780 (C=O). NMR ($CDCl_3$, δ): 7.7–6.7 (8 H, m, CH–H and *Ar*-H), 3.8 (3 H, s, O*Me*-H).

4-Chloro-3-(2'-methoxyphenyl)-phthalide (**16 b**)

Yield 66%; m.p. 160–162°C (acetone). Calculated for $C_{15}H_{11}ClO_3$: C 65.6, H 4.0, Cl 12.9; found: C 65.4, H 4.0, Cl 12.9. IR (KBr, cm^{-1}): 1 780 (C=O). NMR ($CDCl_3$, δ): 8.0–6.7 (8 H, m, CH–H and *Ar*-H), 3.7 (3 H, s, O*Me*-H).

5-Chloro-3-(2'-methoxyphenyl)-phthalide (**17 b**)

Yield 51%; m.p. 110–112°C (ethanol). Calculated for $C_{15}H_{11}ClO_3$: C 65.6, H 4.0, Cl 12.9; found: C 66.0, H 4.1, Cl 12.9. IR (KBr, cm^{-1}): 1 780 (C=O). NMR ($CDCl_3$, δ): 8.0–6.6 (8 H, m, CH–H and *Ar*-H), 3.8 (3 H, s, O*Me*-H).

7-Chloro-3-(4'-methoxyphenyl)-phthalide (**15c**)

Yield 74%; m.p. 99–101°C (ethanol). Calculated for $C_{15}H_{11}ClO_3$: C 65.6, H 4.0, Cl 12.9; found: C 64.6, H 3.9, Cl 12.8. IR (KBr, cm^{-1}): 1770 (C=O). NMR ($CDCl_3$, δ): 7.7–6.7 (7H, m, *Ar*-H), 6.2 (1H, br. s, CH–H), 3.7 (3H, s, O*Me*-H).

4-Chloro-3-(4'-methoxyphenyl)-phthalide (**16c**)

Yield 76%; m.p. 147–148.5°C (ethanol). Calculated for $C_{15}H_{11}ClO_3$: C 65.6, H 4.0, Cl 12.9; found: C 65.6, H 3.9, Cl 12.6. IR (KBr, cm^{-1}): 1780 (C=O). NMR ($CDCl_3$, δ): 8.0–6.7 (7H, m, *Ar*-H), 6.4 (1H, br. s, CH–H), 3.7 (3H, s, O*Me*-H).

5-Chloro-3-(4'-methoxyphenyl)-phthalide (**17c**)

Yield 64%; m.p. 185–186°C (ethanol). Calculated for $C_{15}H_{11}ClO_3$: C 65.6, H 4.0, Cl 12.9; found: C 65.7, H 4.1, Cl 12.9. IR (KBr, cm^{-1}): 1770 (C=O). NMR ($CDCl_3$, δ): 8.0–6.7 (7H, m, *Ar*-H), 6.3 (1H, br. s, CH–H), 3.8 (3H, s, O*Me*-H).

7-Chloro-3-hydroxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (**18**)

Yield 71%; m.p. 154–156°C (benzene). Calculated for $C_{14}H_{10}ClNO_2$: C 64.7, H 3.9, Cl 13.6, N 5.4; found: C 64.5, H 3.8, Cl 13.5, N 5.1. IR (KBr, cm^{-1}): 1680 (C=O). NMR (*DMSO-d_6*, δ): 8.0–7.2 (8H, m, *Ar*-H), 7.1–6.3 (2H, m, CH–H and OH–H).

4-Chloro-3-hydroxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (**19**)

Yield 75%; m.p. 164–166°C (benzene). Calculated for $C_{14}H_{10}ClNO_2$: C 64.7, H 3.9, Cl 13.6, N 5.4; found: C 64.7, H 3.9, Cl 13.6, N 5.1. IR (KBr, cm^{-1}): 1690 (C=O). NMR ($CDCl_3$, δ): 8.0–7.0 (3H, m, *Ar*-H), 6.8–6.1 (2H, m, CH–H and OH–H).

5-Chloro-3-hydroxy-2-phenyl-2,3-dihydro-1H-isoindol-1-one (**20a**)

Yield 77%; m.p. 196-198°C (benzene). Calculated for $C_{14}H_{10}ClNO_2$: C 64.7, H 3.9, Cl 13.6, N 5.4; found: C 65.2, H 3.8, Cl 13.6, N 5.4. IR (KBr, cm^{-1}): 1680 (C=O). NMR (*DMSO-d_6*, δ): 7.8–6.1 (10H, m, *Ar*-H, CH–H and OH–H).

5-Chloro-3-hydroxy-3-(4'-methoxyphenyl)-2-phenyl-2,3-dihydro-1H-isoindol-1-one (**20b**)

Yield 74%; m.p. 163–165°C (ethanol). Calculated for $C_{21}H_{16}ClNO_3$: C 68.9, H 4.4, Cl 9.7, N 3.8; found: C 68.9, H 4.4, Cl 9.3, N 3.6. IR (KBr, cm^{-1}): 1680 (C=O). NMR (*DMSO-d_6*, δ): 7.9–6.5 (12H, m, *Ar*-H), 3.5 (3H, s, O*Me*-H), 3.2 (1H, s, OH–H).

5-Chloro-9-oxo-1-fluorenanilide (**7**)

To the anilide **2** (2.32 g, 0.01 mol) in *THF* (25 ml) at −78°C *Bu*^{n}Li (0.022 mol) was added dropwise. The solution was held at −78°C for 0.5 h. Then the solution was allowed to warm up to room temperature, where it was kept for 1 h; then water (20 ml) was added. The reaction mixture, after evaporation of the solvents, was extracted with $CHCl_3$ (3 × 50 ml) and the layers were separated with the organic one being dried ($MgSO_4$). From the organic layer the solvent was removed and the residue chromatographed by column chromatography (silica gel–chloroform) giving fluorenone **7** (1.2 g, 72%) m.p. 192–194°C (ethyl acetate). Calculated for $C_{20}H_{12}ClNO_2$: C 71.9, H 3.6, Cl 10.6, N 4.2; found: C 71.6, H 3.5, Cl 10.6, N 3.9. IR (KBr, cm^{-1}): 1680 (C=O), 1690 (C=O). NMR (*DMSO-d_6*, δ): 11.8 (1H, br. s, NH–H), 8.7–6.7 (11H, m, *Ar*-H).

5-Chloro-9-oxo-1-fluorencarboxylic Acid (**8**)

(a) A mixture of **7** (0.33 g, 0.001 mol) in acetic acid (3 ml), water (0.6 ml) and conc. H_2SO_4 (0.8 ml) was refluxed for 10 h, then cooled and poured onto ice and water (90 ml). The precipitated solid was dissolved in Na_2CO_3 and impurities were filtered off. The filtrate was acidified with hydrochloric

acid. The precipitated solid crystallized from ethanol as yellow crystals of acid **8** (0.23 g, 90%), m.p. 228–230°C. Calculated for $C_{14}H_7ClO_3$: C 65.0, H 2.7, Cl 13.7; found: C 65.3, H 2.6, Cl 13.5. IR (KBr, cm^{-1}): 1690 (C=O), 1740 (C=O). NMR (*DMSO-d_6*, δ): 8.5–7.1 (6 H, m, *Ar*-H).

(b) 5-Chloro-9-oxo-1-(2'-oxazolinyl)-fluorene (for preparation and X-ray structure see Ref. [12]) was hydrolized as in point (a) giving acid **8**. M.p., mixed m.p., IR and ^{1}H-NMR spectra indicated acid **8**.

Hydrolysis of the Methylated Anilides **12a**, **13a**, *and* **14a**

The anlide (0.002 mol) was heated to reflux in 58% H_2SO_4 (10 ml) for 6 h. After cooling the reaction mixture was poured onto ice. The precipitated acid was collected and dissolved in $NaHCO_3$ and impurities were filtered off. The filtrate was acidified with hydrochloric acid. The precipitated solid acid was purified by crystallization.

2-Chloro-6-methylbenzoic Acid (**21**)

Yield ~10%; m.p. 104–106°C (water) (Ref. [17], m.p. 108°C). IR (KBr, cm^{-1}): 1700 (C=O). NMR ($CDCl_3$, δ): 11.7 (1 H, br. s COOH–H), 7.5–6.9 (3 H, m, *Ar*-H), 2.4 (3 H, s, *ArMe*-H).

3-Chloro-2-methylbenzoic Acid (**22**)

Yield 88%; m.p. 162–163°C (benzene) (Ref. [18], m.p. 163°C). IR (KBr, cm^{-1}): 1690 (C=O). NMR (*DMSO-d_6*, δ): 8.0–6.8 (3 H, m, *Ar*-H), 2.3 (3 H, s, *ArMe*-H).

4-Chloro-2-methylbenzoic Acid (**23**)

Yield 95%; m.p. 168–170°C (heptane) (Ref. [18], m.p. 170°C). IR (KBr, cm^{-1}): 1690 (C=O). NMR (*DMSO-d_6*, δ): 7.8–6.8 (3 H, m, *Ar*-H), 2.3 (3 H, s, *ArMe*-H).

Hydrolysis of Allylated Anilides **13b** *and* **14b**. *Synthesis of the 3,4-Dihydro-isocoumarins* **24** *and* **25**

The crude allylated anilide was heated to reflux in 60% H_2SO_4 for 5 h. After cooling the reaction mixture was poured onto ice and extracted with $CHCl_3$ (3 × 50 ml). The layers were separated and the organic one dried ($MgSO_4$). After evaporation of the solvent the resulting crude product was purified by crystallization.

5-Chloro-3-methyl-3,4-dihydroisocoumarin (**24**)

Yield 80%; m.p. 110–111.5°C (hexane). Calculated for $C_{19}H_9ClO_2$: C 61.1, H 4.6, Cl 18.0; found: C 61.2, H 4.6, Cl 17.9. IR (KBr, cm^{-1}): 1720 (C=O). NMR ($CDCl_3$, δ): 8.0 (1 H, dd, J=1.5 and 7 Hz, C^8–H), 7.8–7.1 (2 H, m, C^6 and C^7–H), 5.0–4.3 (1 H, m, CH–H), 3.3–2.6 (2 H, m, CH_2–H), 1.5 (3 H, d, J=6 Hz, *Me*-H).

6-Chloro-3-methyl-3,4-dihydroisocoumarin (**25**)

Yield 74%; m.p. 83–85°C (water) (Ref. [19], m.p. 84–85°C). Calculated for $C_{19}H_9ClO_2$: C 61.1, H 4.6, Cl 18.0; found: C 60.8, H 4.4, Cl 18.2. IR (KBr, cm^{-1}): 1720 (C=O). NMR (*DMSO-d_6*, δ): 8.0–7.0 (3 H, m, *Ar*-H), 4.8–4.1 (1 H, m, CH–H), 3.0–2.6 (2 H, m, CH_2–H), 1.2 (3 H, d, J=6 Hz, *Me*-H).

Conversion of the Isoindolinones **18** *and* **20a** *into the Corresponding Phthalides* **28** *and* **29**

To the solution of isoindolinone (0.002 mol) in methanol (15 ml) KBH_4 (0.22 g, 0.004 mol) was added, and the mixture was refluxed for 1 h. After cooling the next part of KBH_4 (0.22 g, 0.004 mol) was added and refluxing continued for 2 h. Then the solvent was evaporated and water (25 ml) was added. The precipitated solid was collected. The solid was suspended in 15% hydrochloric acid, and heated till boiling for 1 h, and left overnight. The solid was filtered and purified by crystallization.

7-Chlorophthalide (**28**)

Yield 92%; m.p. 142–144°C (ethanol) (Ref. [20], m.p. 145°C). Calculated for $C_8H_5ClO_2$: C 57.0, H 3.0, Cl 21.0; found: C 57.0, H 3.0, Cl 20.7. IR (KBr, cm^{-1}): 1760 (C=O). NMR ($CDCl_3$, δ): 7.8–7.3 (3H, m, *Ar*-H), 5.3 (2H, s, CH_2–H).

5-Chlorophthalide (**29**)

Yield 89%; m.p. 155–157°C (heptane : benzene = 1 : 1) (Ref. [20], m.p. 157°C). Calculated for $C_8H_5ClO_2$: C 57.0, H 3.0, Cl 21.0; found: C 57.2, H 3.0, Cl 20.8. IR (KBr, cm^{-1}): 1760 (C=O). NMR ($CDCl_3$, δ): 7.8–7.3 (3H, m, *Ar*-H), 5.2 (2H, s, CH_2–H).

Proto-Desiliylation of the Silylated Anilides **12c**, **13c**, *and* **14c**

The appropriate silylated anilide (0.001 mol) and 0.3 g of KF in methanol (10 ml) was heated till boiling for 20 h. Then the solvent was removed and the formed residue washed with water to give the anilides **1–3**, which was proved by m.p., mixed m.p., IR, and ^{1}H-NMR spectra.

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