Functionalization of 3-Chlorobenzaldehyde

Kristine Aksjonova,[a] Sergey Belyakov,[a] Edvards Liepinsh,[a] Arne Boman,[b] Torbjorn Lundstedt,[b] Per Lek,[b] Peteris Trapencieris*[a]

[a] Latvian Institute of Organic Synthesis, Aizkraukles 21, 1006 Riga, Latvia

[b] AcurePharma AB, Ulleråkersvägen 38, 75643 Uppsala, Sweden
E-mail: peteris@osi.lv

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Abstract: 2-Substituted 3-chlorobenzaldehydes were prepared from the corresponding 2-(3-chlorophenyl)-1,3-dioxolanes using an *ortho*-lithiation strategy. The 6-chloro-2-formylbenzamide exists only in a ring form, but 6-chloro-2-formylbenzoic acid esters were isolated in both forms as open chain and cyclic tautomers. 7-Chloro-3-hydroxy-3*H*-isobenzofuran-1-one reacted with nucleophilic reagents at the carbonyl or quaternary carbon depending on the character of nucleophile.

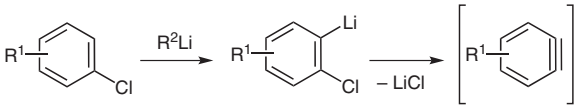
Key words: 3-chlorobenzaldehyde, 2,3-dihydroisoindol-1-ones, 3*H*-isobenzofuran-1-ones, directed *ortho*-lithiation, ring-chain tautomers

One of the aims of advanced organic synthesis is still the formation of regiospecific substituted benzene rings. Polysubstituted benzenes are used in many areas of pharmaceutical and agricultural chemistry as versatile intermediates.[1]

We have demonstrated a general synthesis of 2-modified 3-chlorobenzaldehydes via *ortho*-lithiation[2] of cyclic acetal **1**. So far, Comins and co-workers reported in situ protection of aromatic aldehydes via the formation of α-aminoalkoxides using *n*-BuLi and TMEDA.[3] Carter and co-workers showed that aromatic aldimines could be *ortho*-lithiated and trapped with electrophiles and the products were converted to the corresponding benzaldehyde derivatives.[4] Still the dimethyl acetals are more often used as aldehyde protecting group in *ortho*-lithiation reaction.[5] In 1999, Yus and co-workers described naphthalene-catalyzed lithiation of 2-(chlorophenyl)-1,3-dioxolanes by chlorine–lithium exchange.[6]

The aldehyde group was protected with ethylene glycol, because dioxolane ring has lower reactivity to alkyllithium reagents and oxygen atoms could coordinate with lithium ion. Thus, acetal functionality works as the lithiation-directing group (LDG). The acetal group is considered to have a poor *ortho*-directing capacity, but can be easily transformed into the corresponding aldehydes by acid hydrolysis. On the other hand, chlorine atom is an electron-accepting group and it raises the acidity of hydrogen atom in 2-position.

Chlorine atom may cause difficulties connected with decreased stability of unsubstituted 2-chlorophenyllithiums (R^1 = H) toward elimination of LiCl at –90 °C[7] or –42 °C[3] to form the intermediate benzyne (Scheme 1).



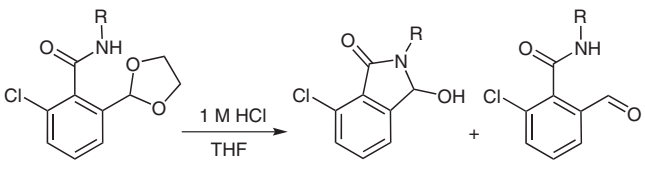
Scheme 1 Benzyne formation

The elimination temperature is highly dependent on the overall electronic effects induced in the ring by the substituents. Mortier and co-workers[7c,d] have shown the elimination of LiCl in 2-chlorobenzoic acid between –50 and –30 °C. Meyers and co-workers[7a] have described a benzyne generation from (3-chlorophenyl)oxazoline at 0 °C.

In our experiments, the elimination of LiCl did not proceed at –78 °C. At the same temperature, free 3-chlorobenzaldehyde did not form benzyne.[3] Therefore, directed *ortho*-metalation of 2-(3-chlorophenyl)-1,3-dioxolane (**1**) was achieved by treatment with 1.5 equivalents of *n*-BuLi in THF at –78 °C. The resulting orange lithiated species easily reacted with a variety of electrophiles to give the *ortho*-substituted products **2a**–**i**. Some limitations of the reaction were observed. Thus, *ortho*-carboxylic- and *ortho*-methylsulfonyl-substituted 2-(3-chlorophenyl)-1,3-dioxolanes **2j**,**k** were not obtained directly, but 2-fluorobenzaldehyde acetal **2i** was formed in low (19%) yield (Table 1). The low yield of 2-fluorination is explained due to spacial disturbances of used *N*-fluoro electrophile.

Newly formed acetals **2** were selectively deprotected under acidic conditions (aq 1 M HCl in THF) at reflux temperature to give the corresponding aldehydes **3** (Table 2).

The acetal protecting group of *N*-alkyl-2-formylbenzamides **2f**,**h** was cleaved in acidic media, but expected aldehydes **3f**,**h** were not obtained. Instead, the hydroxylactams **4f**,**h** were always isolated (Scheme 2).



2f R = Et
2h R = H

4f (67%)
4h (59%)

3f,**h** (0%)

Scheme 2 Cleavage of *N*-alkyl-2-formylbenzamides acetal protecting group

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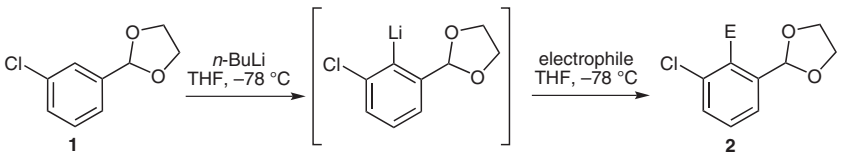
Table 1 Synthesis of 2-Substituted 3-Chlorobenzaldehyde Acetals



Product	Electrophile	E	Yield (%)
2a	I_2	I	56
2b	MeI	Me	60 (1:1)[a]
2c	MeSSMe	MeS	66
2d	$ClCO_2Et$	CO_2Et	68
2e	$ClCON(Me)_2$	$CON(Me)_2$	32
2f	EtN=C=O	CONHEt	42
2g	PrN=C=O	CONHPr	44
2h	TMSN=C=O	$CONH_2$	53
2i	$(PhSO_2)_2NF$	F	19 (10:3)[a]
2j	CO_2	CO_2H	–
2k	MsCl	Ms	–

[a] Ratio (product **2**:starting material **1**) detected by ^1H NMR analysis.

Open chain tautomers were characterized by IR and NMR spectroscopy. Ring structure of hydroxyisoindolinone **4f** was based on the X-ray crystallography (Figure 1). *N*-Alkyl-3-chloro-2-amidobenzaldehydes **3** exist only as the cyclic tautomers **4**.

Similar results with ring-chain tautomerism were observed in *o*-formylbenzoic amides existing as the ring tautomers, that is, hydroxylactam.[8–11] Formation of the ring form was stimulated in conditions with rising electrophilicity of aldehyde group and increased nucleophilic character of nitrogen atom. Amides of *o*-formylated benzoic acids are shown to exist only in the cyclic form by IR and NMR spectroscopy.[8,10,11] The presence of hydrogen bond between two molecules of cyclic tautomers (Scheme 3) was proved by IR spectroscopy.[10]

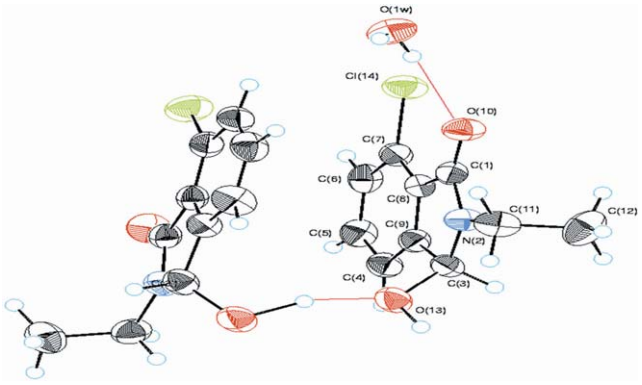
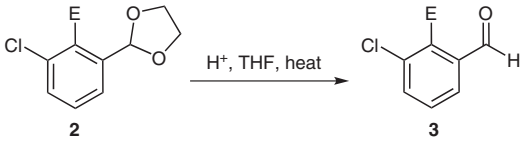
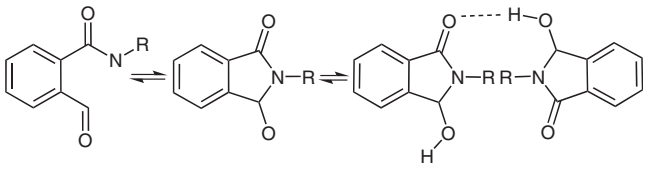


Figure 1 ORTEP view of **4f** showing 50% probability displacement ellipsoids and atom labeling scheme

Table 2 Cleavage of the Acetal Protecting Group



Product	E	Yield (%)
3a	I	54
3c	MeS	82
3d	CO_2Et	65
3e	$CON(Me)_2$	15



Scheme 3 Ring-chain tautomerism and association of 2-formylbenzamides

The *N*-alkyl-2-formylbenzamides **2f**,**h** were refluxed in acidic media in polar protic solvents EtOH (Scheme 4) and MeOH (Scheme 5). In this case, nucleophilic substitution occurred to give products **5** and **6** in moderate to high yields. In all the cases aldehydes were not detected.

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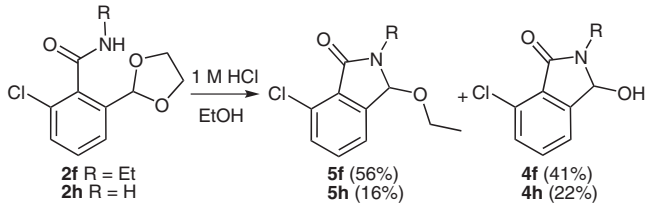
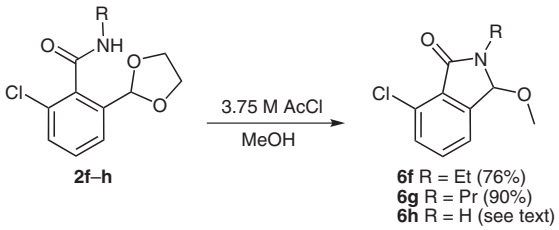


Scheme 4 Nucleophilic substitution of EtOH in isoindolinones



Scheme 5 Nucleophilic substitution of MeOH in isoindolinones

When EtOH was used as a solvent, additional hydroxylactams **4** together with alkoxylactams **5** were isolated. Less nucleophilic 2-chloro-6-(1,3-dioxolan-2-yl)benzamide (**2h**) gave a mixture of hydroxylactam **4h** and ethoxylactam **5h** in smaller yields than benzamide **2f** (Scheme 4).

Reaction of amides **2f** and **2g** in MeOH in acidic medium produced methoxy derivatives **6f** and **6g** in high yields (76% and 90%, Scheme 5). An X-ray crystal structure (Figure 2) was obtained for 7-chloro-2-ethyl-3-methoxy-2,3-dihydro-1*H*-isoindol-1-one (**6f**).

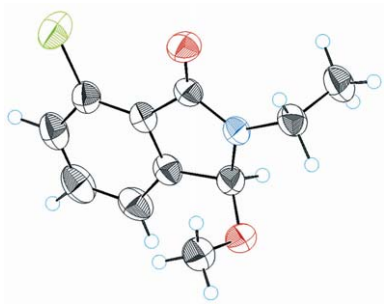
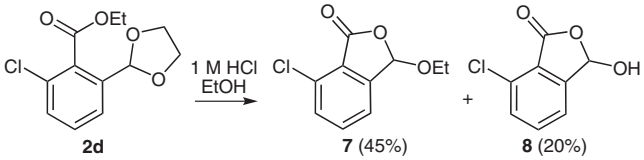


Figure 2 ORTEP view of **6f** showing 50% probability displacement ellipsoids and atom-labeling scheme

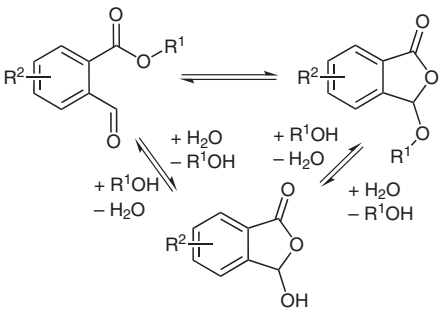
In the case of 2-chloro-6-(1,3-dioxolan-2-yl)benzamide (**2h**), a mixture of 3 compounds, 3-methoxylactam **6h**, 2-chloro-6-dimethoxymethylbenzoic acid methyl ester, and traces of 2-chloro-6-formylbenzoic acid methyl ester were detected by ^{1}H NMR spectroscopy. Similar phenomenon with the intramolecular cyclization was observed for acetal **2d**. Thus, after removal of acetal function in EtOH and chromatographic separation only lactone type substances **7** and **8** were isolated (Scheme 6).

o-Formylbenzoic acids and esters exist as both tautomers, stable in neutral conditions. Transformations from tautomeric chain to ring form occur in acidic or basic media or



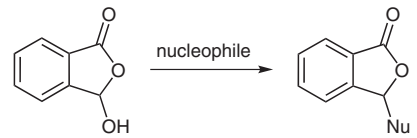
Scheme 6 Reaction of ethyl 2-chloro-6-(1,3-dioxolan-2-yl)benzoate (**2d**) with EtOH in acidic conditions

at elevated temperatures. Thus, esterification of carboxylic acid with alcohols in the presence of acidic catalysts (Fisher–Speier esterification) gives a mixture of isomers (Scheme 7).[9] Ratios of products depend on the time of reaction (thermodynamic and kinetic control).



Scheme 7 Ring-chain tautomerism of formylbenzene-carboxylic acids and esters

Wheeler and co-workers[12] and Kagan[13] reported the presence of phthalaldehydic acid in the 3-hydroxyphthalide form both in solid state and in aqueous solution. Wheeler and co-workers[12] described phthalaldehydic acid reactions with a variety of alcohols forming 3-alkoxyphthalides (Scheme 8). Analogous is the reaction with mercaptans or thiophenols. With less hindered primary alkylamines and ammonia, 3,3′-iminodiphthalides were obtained as the only products. Sterically hindered primary alkylamines gave 3-alkylaminophthalides. The corresponding 3-amidophthalides were obtained from alkyl and aryl acid amides. Similarly 3-hydroxyphthalide reacts with urea or substituted ureas, alkyl carbamates, and carboxylic acid anhydrides (Scheme 8).[12]



Scheme 8 Reaction of phthalaldehydic acid with nucleophiles

Heating 7-chloro-3-hydroxy-2-benzofuran-1(3*H*)-one (**8**) in EtOH gave 7-chloro-3-ethoxyphthalide (**7**) as the product of nucleophilic substitution in the 3-position (Scheme 9).

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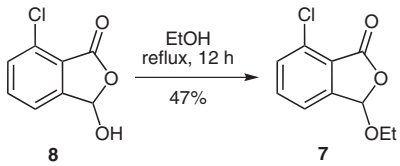


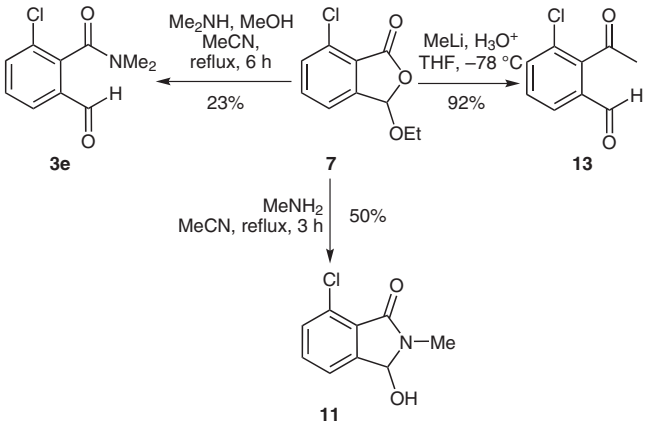
Scheme 9 Reaction of 7-chloro-3-hydroxy-2-benzofuran-1(3*H*)-one (**8**) with EtOH

Depending on the solvent used different products were obtained with primary amines. In polar nucleophilic solvent, a mixture of 3-alkoxylactam **10**, 3-alkylaminolactam **9**, and 3-hydroxylactam **11** together with unreacted starting material was obtained (Scheme 10).

Weaker nucleophiles such as *N*-methylurea did not react with 7-chloro-3-hydroxy-2-benzofuran-1(3*H*)-one (**8**) at position C3, but gave the product **12** (Scheme 10) after opening of lactone ring with subsequent lactam ring formation.

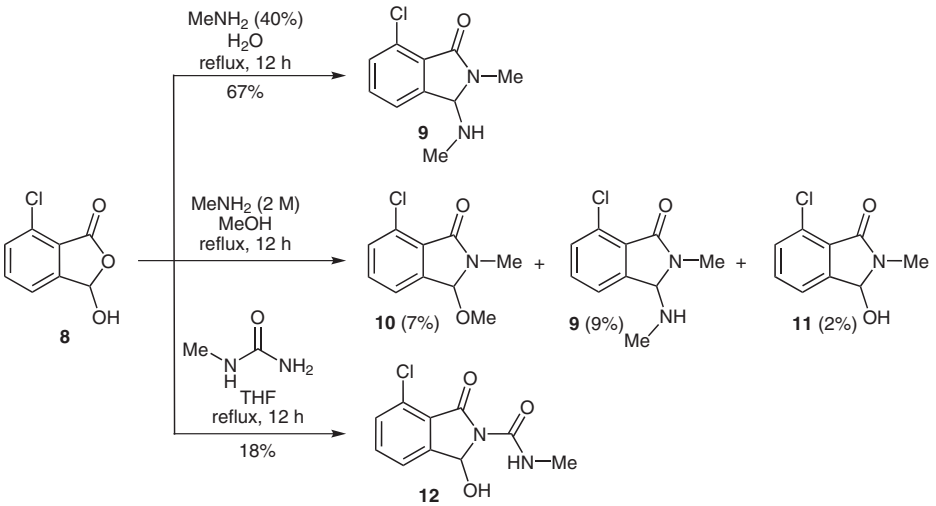
The reactivity of 3-ethoxyphthalide **7** with different nucleophiles is shown in Scheme 11. Thus, reaction with methylamine gave the 3-hydroxylactam **11** in good yield (50%). Another *ortho*-substituted aldehyde, 2-acetyl-3-chlorobenzaldehyde (**13**), was obtained by treating lactone **7** with MeLi in high isolated yield (92%). Reaction with dimethylamine was more complex and aldehyde **3e** was isolated in low yield (23%).

In summary, a simple and efficient procedure of directed *ortho*-lithiation of 3-chlorobenzaldehyde has been demonstrated to provide trisubstituted benzaldehydes regiospecifically. When a deprotection of acetal functionality in substituted benzamides was performed, incompatibility of amide and aldehyde groups in the reaction products was shown; intramolecular cyclization took place and cyclic amide products were isolated.



Scheme 11 Reaction of 7-chloro-3-ethoxy-2-benzofuran-1(3*H*)-one (with nucleophiles

All nonaqueous reactions were performed under dry conditions in the atmosphere of argon, unless otherwise specified. Commercial grade reagents and anhyd solvents were used as received from suppliers and no attempts were made to purify or to dry these components further. TLC was performed using silica gel 60 F254 (Merck) plates. Visualization of TLC plates was made with short wave (254 nm) UV light. Flash column chromatography was carried out using silica gel 0.035–0.070 mm (Merck). ^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained on 200 and 400 MHz NMR spectrometers (Varian Mercury 200 and Varian Mercury Plus 400) and are reported in ppm δ values, using TMS as an internal reference. Microanalyses were performed using a Carlo Erba-106 elemental analyzer. Melting points were determined in capillary tubes using a Gallenkamp apparatus. IR spectra were recorded on Perkin-Elmer IR spectrometer. For compounds **4f** and **6f** diffraction data were collected on a Bruker-Nonius KappaCCD diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The crystal structures of **4f** and **6f** were solved by the direct method and refined by full-matrix least squares. All non-hydrogen atoms were refined anisotropically. For further details, see Supporting Information and crystallographic data for **4f** and **6f**.[14]



Scheme 10 Reaction of phthalaldehydic acid **8** with N-nucleophiles

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2-(3-Chlorophenyl)-1,3-dioxolane (1)[6]
[CAS # 64380-53-6]

A mixture of the commercially available 3-chlorobenzaldehyde (52.8 g, 376 mmol), ethylene glycol (32 mL, 564 mmol), and a catalytic amount of *p*-TsOH (50 mg) in toluene (50 mL) was refluxed in a Dean–Stark apparatus for 14 h. The solvent was evaporated and the residue was condensed (62–67 °C/0.15 mbar) to give the title compound as a colorless liquid; yield: 64.6 g (93%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.06 (m, 4 H, CH_2CH_2), 5.79 (s, 1 H, CH), 7.29–7.40 (m, 3 H, H-4, 5, 6), 7.46–7.53 (m, 1 H, H-2).

MS (EI, 70 eV): *m*/*z* (%) = 73.1 (50), 89.1 (25), 112.0 (25), 125.0 (12), 139.0 (47), 183.0 (100), 184.0 (30, $[M]^+$).

***Ortho*-Functionalization of 3-Chlorophenyl Acetal 1; General Procedure**
A solution of 2-(3-chlorophenyl)-1,3-dioxolane (**1**; 1.84 g, 10.0 mmol) in anhyd THF (20 mL) was cooled to –78 °C. Then, a hexane solution of 2.5 M *n*-BuLi (6.0 mL, 15.0 mmol) was added dropwise and the resulting red-brown solution was stirred for 45 min at this temperature. To this solution was added the electrophile (1.2–5.0 equiv). The mixture was warmed to –20 °C and sat. aq NH_4Cl (10 mL) was added. The mixture was extracted with MTBE (50 mL) and the organic layer was separated, washed with H_2O (2 × 25 mL) and brine (25 mL), and dried (Na_2SO_4). The residue obtained after filtration and evaporation of the solvent in vacuo was purified by flash chromatography on silica gel (hexane–EtOAc).

2-(3-Chloro-2-iodophenyl)-1,3-dioxolane (2a)
A solution of **1** (6.74 g, 36.5 mmol) in anhyd THF (40 mL) was cooled to –78 °C. Then, a hexane solution of 2.5 M *n*-BuLi (22 mL, 54.8 mmol) was added dropwise and the resulting red-brown solution was stirred for 45 min at this temperature. To this solution was added a solution of I_2 (27.8 g, 109.5 mmol) in THF (100 mL). The mixture was warmed to –20 °C and sat. aq $Na_2S_2O_3$ (50 mL) was added. After workup, the yellow oil obtained was purified by flash chromatography on silica gel (hexane–EtOAc, 10:1) affording the product as a colorless oil; yield: 6.40 g (56%).

IR (film): 3367, 3067, 1729, 1419, 1369, 1149, 1101–1091, 944, 788 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.00–4.10 (m, 4 H, CH_2CH_2), 5.99 (s, 1 H, CH), 7.28–7.36 (m, 1 H_{arom}), 7.40–7.52 (m, 2 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 60.5, 101.8, 106.9, 125.2, 129.1, 130.0, 139.6, 142.3.

MS (EI, 70 eV): *m*/*z* (%) = 73.1 (80), 182.0 (20), 309.0 (100, $[M]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_8ClIO_2$: 310.9336; found: 310.9316.

2-(3-Chloro-2-methylphenyl)-1,3-dioxolane (2b)
A solution of **1** (1.84 g, 10.0 mmol) in anhyd THF (20 mL) was cooled to –78 °C. Then, a hexane solution of 2.5 M *n*-BuLi (6.0 mL, 15.0 mmol) was added dropwise and the resulting red-brown solution was stirred for 45 min at this temperature. To this solution was added MeI (3.1 mL, 50.0 mmol). After workup, the yellow oil obtained was purified by flash chromatography on silica gel (hexane–EtOAc, 10:1) affording the product as a colorless oil; yield: 1.62 g (60%) (~1:1 mixture with starting material).

IR (film): 3343, 1723, 1444, 1385, 1267, 1149, 1097, 1018, 958, 787 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 3.97–4.18 (m, 4 H, CH_2CH_2), 5.97 (s, 1 H, CH), 7.09–7.19 (m, 1 H_{arom}), 7.34–7.52 (m, 2 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.4, 65.3, 101.8, 124.3, 126.5, 129.8, 134.7, 135.3, 137.6.

2-[3-Chloro-2-(methylsulfanyl)phenyl]-1,3-dioxolane (2c)
A solution of **1** (4.62 g, 25.0 mmol) in anhyd THF (40 mL) was cooled to –78 °C. Then, a hexane solution of 2.5 M *n*-BuLi (15 mL, 37.5 mmol) was added dropwise and the resulting red-brown solution was stirred for 45 min at this temperature. To this solution was added Me_2S_2 (11 mL, 125 mmol). After workup, the yellow oil obtained was purified by flash chromatography on silica gel (hexane–EtOAc, 10:1) affording the product as a colorless oil; yield: 3.81 g (66%).

IR (film): 3066, 1729, 1689, 1575, 1419, 1369, 1148, 1111, 964, 791 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, SCH_3), 4.01–4.20 (m, 4 H, CH_2CH_2), 6.46 (s, 1 H, CH), 7.32 (d, *J* = 7.8 Hz, 1 H_{arom}), 7.49 (dd, *J* = 7.8, 1.5 Hz, 1 H_{arom}), 7.56 (dd, *J* = 7.8, 1.5 Hz, 1 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.2, 65.5, 101.8, 125.0, 129.5, 130.7, 134.4, 140.5, 143.3.

MS (EI, 70 eV): *m*/*z* (%) = 73.1 (20), 108.0 (20), 138.0 (35), 171.0 (45), 182.0 (85), 215.0 (100), 230.0 (5, $[M]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{11}ClO_2S$: 231.0247; found: 231.0224.

Ethyl 2-Chloro-6-(1,3-dioxolan-2-yl)benzoate (2d)
A solution of **1** (13.9 g, 75.0 mmol) in anhyd THF (50 mL) was cooled to –78 °C. Then, a hexane solution of 2.5 M *n*-BuLi (45 mL, 113 mmol) was added dropwise and the resulting red-brown solution was stirred for 45 min at this temperature. To this solution was added ethyl chloroformate (36.0 mL, 375 mmol). After workup, the colorless oil obtained was purified by flash chromatography on silica gel (hexane–EtOAc, 10:1) affording the product as a colorless oil; yield: 9.96 g (68%).

IR (film): 3422, 1734, 1445, 1271, 1153, 1124, 1095, 1062, 797 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.99 (s, 4 H, CH_2CH_2), 4.43 (q, *J* = 7.2 Hz, 2 H, OCH_2), 6.03 (s, 1 H, CH), 7.29–7.43 (m, 2 H_{arom}), 7.48 (dd, *J* = 7.1, 1.8 Hz, 1 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 61.7, 65.1, 101.3, 124.8, 130.0, 130.2, 131.4, 132.4, 137.9, 166.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{13}ClO_4$: 279.0400; found: 279.0435.

2-Chloro-6-(1,3-dioxolan-2-yl)-*N*,*N*-dimethylbenzamide (2e)
A solution of **1** (1.84 g, 10.0 mmol) in anhyd THF (20 mL) was cooled to –78 °C. Then, a hexane solution of 2.5 M *n*-BuLi (6.0 mL, 15.0 mmol) was added dropwise and the resulting red-brown solution was stirred for 45 min at this temperature. To this solution was added *N*,*N*-dimethylchloroformamide (2.8 mL, 30.0 mmol). After workup, the yellow oil obtained was purified by flash chromatography on silica gel (hexane–EtOAc, 19:1–16:1) affording the product as a yellowish oil, yield: 810 mg (32%).

IR (film): 3421, 1641, 1506, 1399, 1089, 944, 770 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.82 (s, 3 H, NCH_3), 3.15 (s, 3 H, NCH_3), 3.89–4.21 (m, 4 H, CH_2CH_2), 5.85 (s, 1 H, CH), 7.28–7.44 (m, 2 H_{arom}), 7.54 (dd, *J* = 7.2, 1.7 Hz, 1 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.4, 37.9, 65.3, 65.6, 101.1, 125.0, 129.6, 130.0, 130.5, 135.3, 136.7, 167.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{14}ClNO_3$: 256.0740; found: 256.0699.

2-Chloro-6-(1,3-dioxolan-2-yl)-*N*-ethylbenzamide (2f)
A solution of **1** (4.62 g, 25.0 mmol) in anhyd THF (30 mL) was cooled to –78 °C. Then, a hexane solution of 2.5 M *n*-BuLi (18.8 mL, 30.0 mmol) was added dropwise and the resulting red-brown solution was stirred for 45 min at this temperature. To this solution was added isocyanatoethane (3.0 mL, 37.5 mmol). The residue obtained after filtration and evaporation of the solvent in vacuo was

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crystallized from hexane–EtOAc to afford the product as a white powder; yield: 2.66 g (42%); mp 119–121 °C.

IR (Nujol): 3250, 2970–2835, 1660, 1645 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.3 Hz, 3 H, CH_3), 3.45–3.61 (m, 2 H, NCH_2), 3.96–4.18 (m, 4 H, CH_2CH_2), 5.88 (br s, 2 H, NH and CH), 7.29–7.45 (m, 2 H_{arom}), 7.54 (dd, *J* = 7.3, 1.7 Hz, 1 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.4, 29.6, 60.3, 95.9, 119.5, 124.8, 125.2, 126.1, 130.9, 131.7, 160.5.

Anal. Calcd for $C_{11}H_{12}ClNO_3$: C, 56.37; H, 5.52; N, 5.48. Found: C, 56.00; H, 5.39; N, 5.52.

2-Chloro-6-(1,3-dioxolan-2-yl)-*N*-propylbenzamide (2g)
A solution of **1** (462 mg, 2.50 mmol) in anhyd THF (7 mL) was cooled to –78 °C. Then, a hexane solution of 1.6 M *n*-BuLi (1.3 mL, 3.00 mmol) was added dropwise and the resulting red-brown solution was stirred for 45 min at this temperature. To this solution was added 1-isocyanatopropane (0.71 mL, 7.50 mmol). The residue obtained after filtration and evaporation of the solvent in vacuo was crystallized from hexane–EtOAc to afford the product as a white powder, yield: 295 mg (44%); mp 118–119 °C.

IR (Nujol): 3267, 3072, 1641, 1554, 1307, 801 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.00 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.65 (sext, *J* = 7.2 Hz, 2 H, CH_2CH_3), 3.44 (q, *J* = 7.2 Hz, 2 H, NCH_2), 3.90–4.19 (m, 4 H, CH_2CH_2), 5.87 (s, 1 H, CH), 7.28–7.47 (m, 2 H_{arom}), 7.53 (dd, *J* = 7.3, 1.6 Hz, 1 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.4, 22.7, 41.7, 65.5, 101.1, 124.7, 130.1, 130.4, 131.2, 136.1, 136.9, 165.8.

Anal. Calcd for $C_{11}H_{12}ClNO_3$: C, 57.89; H, 5.98; N, 5.19. Found: C, 57.46; H, 5.84; N, 5.46.

2-Chloro-6-(1,3-dioxolan-2-yl)benzamide (2h)
A solution of **1** (1.84 g, 10.0 mmol) in anhyd THF (20 mL) was cooled to –78 °C. Then, a hexane solution of 1.6 M *n*-BuLi (5.2 mL, 12.0 mmol) was added dropwise and the resulting red-brown solution was stirred for 45 min at this temperature. To this solution was added trimethylsilyl isocyanate (4.0 mL, 30.0 mmol). The residue obtained after filtration and evaporation of the solvent in vacuo was crystallized from hexane–EtOAc to afford the product as a white powder; yield: 1.21 g (53%); mp 100–103 °C.

IR (Nujol): 3327, 3187, 1668, 1609, 1368, 1091 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.96–4.20 (m, 4 H, CH_2CH_2), 5.90–6.20 (br s, 2 H, NH_2), 5.95 (s, 1 H, CH), 7.31–7.47 (m, 2 H_{arom}), 7.54 (dd, *J* = 7.3, 1.8 Hz, 1 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 65.5, 101.1, 124.9, 130.3, 130.6, 131.0, 135.0, 136.8, 167.9.

Anal. Calcd for $C_{11}H_{12}ClNO_3$: C, 52.76; H, 4.43; N, 6.15. Found: C, 53.02; H, 4.41; N, 6.26.

2-(3-Chloro-2-fluorophenyl)-1,3-dioxolane (2i)
A solution of **1** (1.84 g, 10.0 mmol) in anhyd THF (20 mL) was cooled to –78 °C. Then, a hexane solution of 1.6 M *n*-BuLi (7.5 mL, 12.0 mmol) was added dropwise and the resulting red-brown solution was stirred for 45 min at this temperature. To this solution was added $(PhSO_2)_2NF$ (3.78 g, 12.0 mmol). After workup, the colorless oil obtained was purified by flash chromatography on silica gel (hexane–EtOAc, 10:1–10:3) affording the product as a colorless oil; yield: 380 mg (19%) (mixed with ~15% of starting material).

IR (film): 3438, 2375, 1470, 1364, 1178, 1098, 944, 787 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 3.96–4.20 (m, 4 H, CH_2CH_2), 6.08 (s, 1 H, CH), 7.03–7.15 (m, 1 H_{arom}), 7.30–7.50 (m, 2 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 65.5, 98.8, 124.4, 124.5, 126.0, 126.1, 131.3, 158.0.

^{19}F NMR (200 MHz, $CDCl_3$): δ = –122.1 (t, *J* = 6.5 Hz).

3-Chloro-2-iodobenzaldehyde (3a)
To a solution of **2a** (5.82 g, 18.7 mmol) in THF (20 mL) was added aq 1 M HCl (20 mL) and the mixture was refluxed for 2 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (30 mL) and the organic layer was separated, washed with H_2O (2 × 20 mL) and brine (20 mL), and dried (Na_2SO_4). Filtration and evaporation of the solvent in vacuo gave a solid, which was recrystallized from hexane as colorless needles; yield: 2.70 g (54%); mp 73–75 °C.

IR (Nujol): 3062, 2809, 2370, 1700, 1685, 1409, 1230, 1138, 753 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.41 (t, *J* = 7.8 Hz, 1 H_{arom}), 7.67–7.78 (m, 2 H_{arom}), 10.13 (s, 1 H, CHO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 105.1, 128.0, 129.5, 134.5, 138.1, 140.6, 196.0.

MS (EI, 70 eV): *m*/*z* (%) = 75.1 (65), 110.0 (45), 138.0 (70), 236.9 (20), 265.9 (100, $[M]^+$).

Anal. Calcd for C_7H_4ClIO: C, 31.55; H, 1.51. Found: C, 31.52; H, 1.77.

3-Chloro-2-methylbenzaldehyde (3b)[15]
To a solution of **2b** (560 mg, 2.82 mmol) in THF (15 mL) was added aq 1 M HCl (15 mL) and the mixture was refluxed for 4 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (25 mL) and the organic layer was separated, washed with H_2O (2 × 20 mL) and brine (20 mL), and dried (Na_2SO_4). Filtration and evaporation of the solvent in vacuo afforded the product as a yellowish oil; yield: 278 mg (81%) (mixed with ~30% of starting material).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.72 (s, 3 H, CH_3), 7.27–7.37 (m, 1 H_{arom}), 7.56–7.64 (m, 1 H_{arom}), 7.69–7.77 (m, 1 H_{arom}), 10.28 (s, 1 H, CHO).

MS (EI, 70 eV): *m*/*z* (%) = 125.1 (60), 153.3 (100), 154 (75, $[M]^+$).

3-Chloro-2-(methylsulfanyl)benzaldehyde (3c)[16]
[CAS # 1033574-03-6]

To a solution of **2c** (231 mg, 1.0 mmol) in THF (5 mL) was added aq 1 M HCl (5 mL) and the mixture was refluxed for 5 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (10 mL) and the organic layer was separated, washed with H_2O (2 × 10 mL) and brine (10 mL), and dried (Na_2SO_4). The residue obtained after filtration and evaporation of the solvent in vacuo was purified by flash chromatography on silica gel (hexane–EtOAc, 10:1–10:2) to afford the product as a yellowish oil; yield: 103 mg (82%).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, SCH_3), 7.35–7.46 (m, 1 H_{arom}), 7.71 (dd, *J* = 7.8, 1.6 Hz, 1 H_{arom}), 7.83 (dd, *J* = 7.8, 1.6 Hz, 1 H_{arom}), 10.77 (s, 1 H, CHO).

MS (EI, 70 eV): *m*/*z* (%) = 63.0 (40), 75.0 (80), 108.0 (60), 125.0 (100), 142.9 (40), 157.0 (30), 170.9 (40), 186.0 (100, $[M]^+$).

Ethyl 2-Chloro-6-formylbenzoate (3d)
[CAS # 1049677-64-6]

To a solution of **2d** (2.57 g, 10.0 mmol) in THF (10 mL) was added aq 1 M HCl (10 mL) and the mixture was refluxed for 4 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (25 mL) and the organic layer was separated, washed with H_2O (2 × 20 mL) and brine (20 mL), and dried (Na_2SO_4). The residue obtained after filtration and evaporation of the solvent in vacuo was purified by flash chromatography on silica gel (hexane–EtOAc, 6:1) to afford the product as a colorless oil; yield: 1.39 g (65%).

IR (film): 2981, 1777, 1740, 1705, 1458, 1366, 1267, 1067, 956, 932 cm^{-1}.

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^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.51 (q, *J* = 7.2 Hz, 2 H, OCH_2), 7.54 (t, *J* = 7.7 Hz, 1 H_{arom}), 7.67 (dd, *J* = 7.7, 1.2 Hz, 1 H_{arom}), 7.79 (dd, *J* = 7.7, 1.2 Hz, 1 H_{arom}), 9.97 (s, 1 H, CHO).

MS (EI, 70 eV): *m*/*z* (%) = 75.0 (90), 110.9 (40), 139.0 (100), 167.0 (95), 183.0 (100), 211.9 (10, $[M]^+$).

2-Chloro-6-formyl-*N*,*N*-dimethylbenzamide (3e)
To a solution of **2e** (810 mg, 3.17 mmol) in THF (15 mL) was added aq 1 M HCl (15 mL) and the mixture was refluxed for 4 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (25 mL) and the organic layer was separated, washed with H_2O (2 × 20 mL) and brine (20 mL), and dried (Na_2SO_4). The residue obtained after filtration and concentration of the solvent in vacuo was purified by flash chromatography on silica gel (hexane–EtOAc, 6:1) to afford the product as a yellowish oil; yield: 102 mg (15%).

IR (film): 3303, 3068, 2977, 1768, 1702, 1626, 1603, 1593, 1455, 1210, 1181, 1079, 909, 748 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.83 (s, 3 H, NCH_3), 3.21 (s, 3 H, NCH_3), 7.50 (t, *J* = 7.8 Hz, 1 Harom), 7.67 (dd, *J* = 7.8, 1.1 Hz, 1 H_{arom}), 7.85 (dd, *J* = 7.8, 1.1 Hz, 1 H_{arom}), 9.98 (s, 1 H, CHO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.6, 37.6, 128.9, 130.1, 131.9, 134.2, 134.9, 137.5, 166.0, 189.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{10}ClNO_2$: 212.0478; found: 212.0516.

7-Chloro-2-ethyl-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (4f)
To a solution of **2f** (128 mg, 0.50 mmol) in THF (2.5 mL) was added aq 1 M HCl (2 mL) and the mixture was refluxed for 12 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (2 × 5 mL) and the organic layer was separated, washed with H_2O (2 × 5 mL) and brine (5 mL), and dried (Na_2SO_4). The residue obtained after filtration and evaporation of the solvent in vacuo was purified by flash chromatography on silica gel (hexane–EtOAc, 5:1) to afford the product as a white powder; yield: 66 mg (67%); mp 109–112 °C.

IR (Nujol): 3346, 2977, 1683, 1674, 1608, 1461, 1419, 1203, 1064, 780, 732 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.26–3.51 (m, 2 H, NCH_2), 3.53–3.74 (m, 1 H, CH), 5.72 (d, *J* = 11.2 Hz, 1 H, OH), 7.33 (dd, *J* = 7.4, 1.5 Hz, 1 H_{arom}), 7.42–7.57 (m, 2 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.1, 28.7, 74.9, 116.9, 122.3, 125.5, 126.1, 127.8, 141.3, 160.0.

Anal. Calcd for $C_{10}H_{10}ClNO_2 \cdot 0.5H_2O$: C, 54.43; H, 5.03; N, 6.35. Found: C, 54.51; H, 5.00; N, 6.25.

7-Chloro-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (4h)
To a solution of **2h** (114 mg, 0.50 mmol) in THF (2.5 mL) was added aq 1 M HCl (2 mL) and the mixture was refluxed for 12 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (2 × 5 mL) and the organic layer was separated, washed with H_2O (2 × 5 mL) and brine (5 mL), and dried (Na_2SO_4). The residue obtained after filtration and evaporation of the solvent in vacuo was purified by flash chromatography on silica gel (hexane–EtOAc, gradient from 2:1 to 1:2) to afford the product as a white powder; yield: 54 mg (59%); mp 164–168 °C.

IR (Nujol): 3345, 3287, 1683, 1465, 1087 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.82 (d, *J* = 9.2 Hz, 1 H, C*H*OH), 6.37 (d, *J* = 9.2 Hz, 1 H, OH), 7.47–7.53 (m, 2 H, H-5, 7), 7.56–7.63 (m, 1 H, H-6), 8.99 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 77.2, 123.2, 127.9, 129.5, 130.9, 133.9, 150.2, 166.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_6ClNO_2$: 184.0165; found: 184.0217.

Anal. Calcd for $C_8H_6ClNO_2$: C, 52.34; H, 3.29; N, 7.63. Found: C, 51.57; H, 3.42; N, 6.97.

7-Chloro-3-ethoxy-2-ethyl-2,3-dihydro-1*H*-isoindol-1-one (5f)
To a solution of **2f** (115 mg, 0.45 mmol) in EtOH (3 mL) was added aq 1 M HCl (2 mL) and the mixture was refluxed for 6 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (7 mL) and the organic layer was separated, washed with H_2O (2 × 5 mL) and brine (10 mL), and dried (Na_2SO_4). The residue obtained after filtration and evaporation of the solvent in vacuo was purified by flash chromatography on silica gel (hexane–EtOAc, gradient from 2:1 to 1:1) to afford the products **5f (**60 mg, 56%) as a yellowish oil and **4f (**40 mg, 41%) as a white powder.

IR (film): 3286, 3080, 2977, 1777, 1725, 1691, 1606, 1464–1385, 1202, 1085, 1063, 797 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.0 Hz, 3 H, CH_3), 1.27 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.87–3.07 (m, 1 H, NCH), 3.11–3.26 (m, 1 H, NCH), 3.34 (sext, *J* = 7.3 Hz, 1 H, OCH), 3.82 (sext, *J* = 7.3 Hz, 1 H, OCH), 5.85 (s, 1 H, CH), 7.40–7.55 (m, 3 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.5, 10.0, 29.8, 52.8, 79.5, 117.6, 123.4, 127.8, 127.9, 128.0, 139.6, 160.5.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{14}NClO_2$: 240.0791; found: 240.0773.

7-Chloro-3-ethoxy-2,3-dihydro-1*H*-isoindol-1-one (5h)
To a solution of **2h** (114 mg, 0.50 mmol) in EtOH (3 mL) was added aq 1 M HCl (2 mL) and the mixture was refluxed for 6 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (7 mL) and the organic layer was separated, washed with H_2O (2 × 5 mL) and brine (10 mL), and dried (Na_2SO_4). The colorless oil obtained after filtration and evaporation of the solvent in vacuo was purified by flash chromatography on silica gel (hexane–EtOAc, gradient from 2:1 to 1:1) to afford products **5h (**17 mg, 16%) and **4h (**20 mg, 22%) as white powders.

Mp 116–120 °C.

IR (Nujol): 3284, 1720, 1606, 1463, 1202, 1120, 1091, 768 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 3 H, CH_3), 3.31–3.39 (m, 1 H, OCH), 3.51–3.60 (m, 1 H, OCH), 5.92 (s, 1 H, CHN), 7.19 (s, 1 H, NH), 7.43–7.56 (m, 3 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.2, 60.7, 82.5, 122.3, 127.9, 131.5, 131.6, 133.4, 145.8, 167.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{10}ClNO_2$: 212.0478; found: 212.0511.

Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.21; H, 4.52; N, 6.17.

7-Chloro-2-ethyl-3-methoxy-2,3-dihydro-1*H*-isoindol-1-one (6f)
Compound **2f** (2.00 g, 7.80 mmol) was dissolved in 3.75 M AcCl–MeOH (15 mL) and the mixture was refluxed for 8 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (2 × 35 mL) and the organic layer was separated, washed with H_2O (2 × 35 mL) and brine (35 mL), and dried (Na_2SO_4). The yellow oil obtained after filtration and evaporation of the solvent in vacuo was purified by flash chromatography on silica gel (hexane–EtOAc, gradient from 5:1 to 5:3) to afford the product **6f** as a white powder; yield: 1.34 g (76%); mp 80–82 °C.

IR (Nujol): 2960–2840, 1780, 1460, 1380, 1355, 1310, 1070, 930 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.1 Hz, 3 H, CH_3), 2.90 (s, 3 H, OCH_3), 3.25–3.35 (m, 1 H, NCH), 3.75–3.90 (m, 1 H, NCH), 5.85 (s, 1 H, CH), 7.45–7.55 (m, 3 H_{arom}).

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^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 34.6, 49.2, 84.9, 122.0, 129.3, 131.5, 131.7, 132.8, 143.0, 160.5.

Anal. Calcd for $C_{11}H_{12}ClO_2$: C, 58.55; H, 5.36; N, 6.21. Found: C, 58.36; H, 5.13; N, 5.91.

7-Chloro-3-methoxy-2-propyl-2,3-dihydro-1*H*-isoindol-1-one (6g)

Compound **2g** (94 mg, 0.35 mmol) was dissolved in 3.75 M AcCl–MeOH (2 mL) and the mixture was refluxed for 12 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (2 × 5 mL) and the organic layer was separated, washed with H_2O (2 × 5 mL) and brine (5 mL), and dried (Na_2SO_4). The residue obtained after filtration and evaporation of the solvent in vacuo was purified by flash chromatography on silica gel (hexane–EtOAc, 2:1) to give the product as a colorless oil; yield: 76 mg (90%).

IR (film): 3078, 2934, 2829, 1708, 1606, 1462, 1407, 1371, 1200, 1088, 1074, 807 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$CH$_2$), 1.50–1.82 (m, 2 H, CH$_2$CH$_3$), 2.89 (s, 3 H, OCH$_3$), 3.11–3.32 (m, 1 H, NCH$_2$), 3.63–3.83 (m, 1 H, NCH$_2$), 5.85 (s, 1 H, CHO), 7.40–7.57 (m, 3 H$_{arom}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6, 21.4, 41.4, 85.3, 110.1, 122.04, 129.2, 131.5, 131.8, 132.8, 143.0, 165.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}ClNO_2$: 240.0791; found: 240.0777.

7-Chloro-3-ethoxy-2-benzofuran-1(3*H*)-one (7) and 7-Chloro-3-hydroxy-2-benzofuran-1(3*H*)-one (8)[17]

To a solution of 2-chloro-6-(1,3-dioxolan-2-yl)benzoate (**2d**; 2.40 g, 9.30 mmol) in EtOH (10 mL) was added aq 1 M HCl (10 mL) and the mixture was refluxed for 12 h. After cooling to r.t., the mixture was neutralized with sat. aq $NaHCO_3$. To the mixture was added EtOAc (25 mL) and the organic layer was separated, washed with H_2O (2 × 20 mL) and brine (20 mL), and dried (Na_2SO_4). Filtration and concentration in vacuo gave a residue, which was washed with MTBE (7 mL) and filtered to afford **8**. The filtrate was concentrated and purified by flash chromatography on silica gel (hexane–EtOAc, gradient from 10:1 to 10:3) to furnish a further amount of **8** and the product **7** as white powders.

7

Yield: 880 mg (45%); mp 102–107 °C.

IR (Nujol): 2960–2840, 1780, 1380, 1355, 1310, 1070, 930 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$CH$_2$), 3.80–4.05 (m, 2 H, CH$_2$CH$_3$), 6.31 (s, 1 H, CHO), 7.45–7.68 (m, 3 H, H-4, 5, 6).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.1, 66.1, 100.7, 121.9, 132.2, 133.1, 135.3, 160.1.

Anal. Calcd for $C_{10}H_9ClO_3$: C, 56.49; H, 4.27. Found: C, 56.37; H, 4.25.

8 [CAS # 70097-44-8]

Yield: 350 mg (20%); mp 112–116 °C.

IR (Nujol): 3380, 2920, 2850, 1750, 1735, 1080 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 6.62 (d, *J* = 8.6 Hz, 1 H, CHO), 7.60–7.85 (m, 3 H), 8.23 (d, *J* = 8.6 Hz, 1 H, OH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 96.7, 122.7, 130.6, 131.5, 136.1, 137.6, 150.0, 165.4.

Anal. Calcd for $C_8H_5ClO_3$: C, 52.06; H, 2.73. Found: C, 51.74; H, 2.46.

7-Chloro-2-methyl-3-(methylamino)-2,3-dihydro-1*H*-isoindol-1-one (9)

A mixture of **8** (92 mg, 0.50 mmol) and 40% $MeNH_2$ in H_2O (3 mL) was heated to 80 °C and stirred for 12 h. Concentration in vacuo gave a yellow oil, which was purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 25:1) to give the product as a white powder; yield: 67 mg (64%); mp 112–114 °C.

IR (Nujol): 3340, 3075, 2800, 1709, 1673, 1607, 1462, 1421, 1393, 1199, 1178, 1027, 937, 750 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (s, 3 H, C*H*$_3$NH), 2.08 (br s, 1 H, NH), 3.05 (s, 3 H, CH$_3$N), 5.22 (s, 1 H, CHNH), 7.37–7.53 (m, 3 H, H-4, 5, 6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 27.1, 73.8, 121.6, 129.2, 130.7, 131.0, 132.3, 145.3, 165.6.

Anal. Calcd for $C_{10}H_{11}ClN_2O$: C, 57.02; H, 5.26; N, 13.30. Found: C, 56.86; H, 5.12; N, 12.86.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{11}ClN_2O$: 211.0638; found: 211.0698.

7-Chloro-3-methoxy-2-methyl-2,3-dihydro-1*H*-isoindol-1-one (10) and 7-Chloro-3-hydroxy-2-methyl-2,3-dihydro-1*H*-isoindol-1-one (11)

A mixture of **8** (92 mg, 0.50 mmol) and 2 M $MeNH_2$ in MeOH (3 mL) was warmed to 80 °C and stirred for 12 h. Concentration in vacuo gave a brown oil, which was purified by flash chromatography on silica gel (hexane–EtOAc, gradient from 5:1 to 3:1). Three fractions were collected.

10

Compound **10** was isolated from the first fraction; yield: 7 mg (7%); colorless oil.

IR (film): 3290, 3090, 2980, 1788, 1737, 1681, 1616, 1452, 1392, 1202, 1074, 784 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.91 (s, 3 H, CH$_3$N), 3.08 (s, 3 H, CH$_3$O), 5.73 (s, 1 H, CHO), 7.40–7.56 (m, 3 H, H-5, 6, 7).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.5, 49.2, 86.8, 121.9, 129.1, 131.4, 131.7, 132.8, 142.8, 165.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{10}ClNO_2$: 212.0478; found: 212.0491.

11

Compound **11** was isolated from the second fraction; yield: 3 mg (2%); white powder; mp 133–135 °C.

IR (Nujol): 3290, 2920, 2840, 1685, 1610, 1080 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.01 (s, 3 H, CH$_3$N), 3.55 (d, *J* = 12.0 Hz, 1 H, OH), 5.59 (d, *J* = 12.0 Hz, 1 H, C*H*OH), 7.31 (dd, *J* = 7.5, 1.5 Hz, 1 H, H-6), 7.46 (dd, *J* = 7.5, 7.3 Hz, 1 H, H-5), 7.53 (dd, *J* = 7.3, 1.5 Hz, 1 H, H-4).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.2, 82.4, 122.0, 127.5, 130.9, 131.4, 133.1, 146.2, 165.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_8ClNO_2$: 198.0322; found: 198.0361.

9

Compound **9** was isolated from the third fraction; yield: 10 mg (9%); white powder.

4-Chloro-1-hydroxy-*N*-methyl-3-oxo-1,3-dihydro-2*H*-isoindole-2-carboxamide (12)

A suspension of **8** (92 mg, 0.50 mmol) and *N*-methylurea (41 mg, 0.55 mmol) in THF was refluxed for 12 h. The product precipitated after cooling to r.t. as a white powder; yield: 19 mg (18%); mp 178–181 °C.

IR (Nujol): 3355, 3283, 1773, 1653, 919 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.61 (d, *J* = 4.3 Hz, 3 H, C*H*$_3$NH), 6.24 (d, *J* = 4.3 Hz, 1 H, NH), 6.94 (d, *J* = 9.9 Hz, 1 H, C*H*OH), 7.47 (d, *J* = 9.9 Hz, 1 H, OH), 7.56 (dd, *J* = 7.6, 0.8 Hz, 1 H, H-5), 7.66 (dd, *J* = 8.0, 7.6 Hz, 1 H, H-6), 7.76 (dd, *J* = 8.0, 0.8 Hz, 1 H, H-7).

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^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.8, 83.0, 122.8, 124.0, 131.0, 131.6, 136.2, 149.7, 157.3, 166.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9ClN_2O_3$: 241.0380; found: 241.0421.

2-Acetyl-3-chlorobenzaldehyde (13)

A solution of 7-chloro-3-ethoxy-2-benzofuran-1(3*H*)-one (**7**; 75 mg, 0.35 mmol) in anhyd THF (5 mL) was cooled to –78 °C. Then, a hexane solution of 1.6 M MeLi (0.24 mL, 0.39 mmol) was added dropwise and the resulting orange solution was warmed to –60 °C and aq 1 M HCl (1 mL) was added. The mixture was warmed to r.t. and sat. aq $NaHCO_3$ (3 mL) was added. To the mixture was added EtOAc (7 mL) and the organic layer was separated, washed with H_2O (2 × 5 mL) and brine (10 mL), and dried (Na_2SO_4). Filtration and evaporation of the solvent in vacuo gave a red oil, which was purified by flash chromatography on silica gel (hexane–EtOAc, 3:1) to afford the product as a yellowish oil; yield: 59 mg (92%).

IR (film): 3385, 1771, 1750, 1717, 1699, 1462, 1243, 1186, 1150, 1031, 835, 765 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.59 (s, 3 H, CH_3), 7.54 (dd, *J* = 8.1, 7.4 Hz, 1 H, H-5), 7.66 (dd, *J* = 8.1, 1.2 Hz, 1 H, H-4), 7.79 (dd, *J* = 7.4, 1.2 Hz, 1 H, H-6), 9.93 (s, 1 H, CHO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.1, 130.2, 130.6, 131.2, 134.3, 135.2, 141.5, 190.0, 201.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_7ClO_2$: 183.0213; found: 183.0240.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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