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Manufacturing Synthesis of 5-Substituted Phthalides

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Abstract:

A manufacturing synthesis of 5-chlorophthalide has been elaborated. The key step of the procedure is ortho-lithiation of 4-chloro-*N*,*N*-diisopropylbenzamide, followed by formylation with dimethyl formamide. Reduction of the formyl moiety and subsequent ring closure, which can be carried out also in one pot, led to 5-chlorophthalide in high overall yield. The procedure has also been successfully adapted for the synthesis of the 5-fluoro and 5-trifluoromethyl analogues. The compounds thus obtained are useful building blocks in the synthesis of various heterocyclic ring systems.

Introduction

Phthalide (2-benzofuran-1(3*H*)-one) skeleton is a common motif in drugs and drug candidates. Besides the several hundreds of phthalide derivatives in preclinical development worldwide, this fact is best demonstrated by two marketed drugs: the antiarthritic agent talniflumate[1−3] and the immunosuppressant drug mycophenolate mofetil.[4,5] Furthermore, 5-substituted phthalide intermediates are used in the manufacturing process of the blockbuster antidepressant drug citalopram[6,7] and its optically active congener escitalopram.[8]

At our laboratory, we were interested in a viable manufacturing synthesis of 5-chlorophthalide (**1a**, Scheme 1). Phthalides are useful intermediates for the synthesis of more complex heterocyclic compounds[9] and several methods have been developed for their synthesis.[10,11] The classical approach to phthalides is based on phthalic acid derivatives (phthalic anhydride, phthalimide) and involves substitutions on the aromatic ring, transformations of the primarily introduced aromatic substituents and selective reduction of one of the carboxylic functions. Various combinations of this chemistry have been described in the literature for the synthesis of compound **1a**. Thus, 4-nitrophthalimide, obtained by nitration of phthalimide,[12,13] was hydrogenated to give 4-aminophthalimide, which was further reduced with zinc dust in aqueous sodium hydroxide solution to afford 5-aminophthalide (Scheme 1, route A).[14] Alternatively, these two steps can be performed in one-pot (route B).[12,15] Then, diazotization of the amino compound, followed by Sandmeyer reaction led to the desired compound **1a**.[16] Although this is the best classical procedure for the synthesis of compound **1a**, it is not efficient enough for manufacture. The alternative methods, such as reduction of 4-chlorophthalic anhydride[17] with zinc dust in acidic medium[18] or with sodium borohydride in DMF[19] leading to significant amounts of regioisomeric byproduct (route C), or the synthesis[20] starting from 4-chloro-2-methylbenzoic acid[21] (route D) are not satisfactory even at laboratory scale.

As an alternative approach, a variety of phthalides was obtained by directed ortho-lithiation methodology. A proper choice of the directing group and the electrophilic reagent results in ortho-disubstituted compounds suitable for further transformation to the required phthalides. Thus, ortho-carboxylation via ortho-lithiation of benzylic alcohols and subsequent cyclization furnishes the corresponding phthalides[22,23] (Scheme 2, route A).

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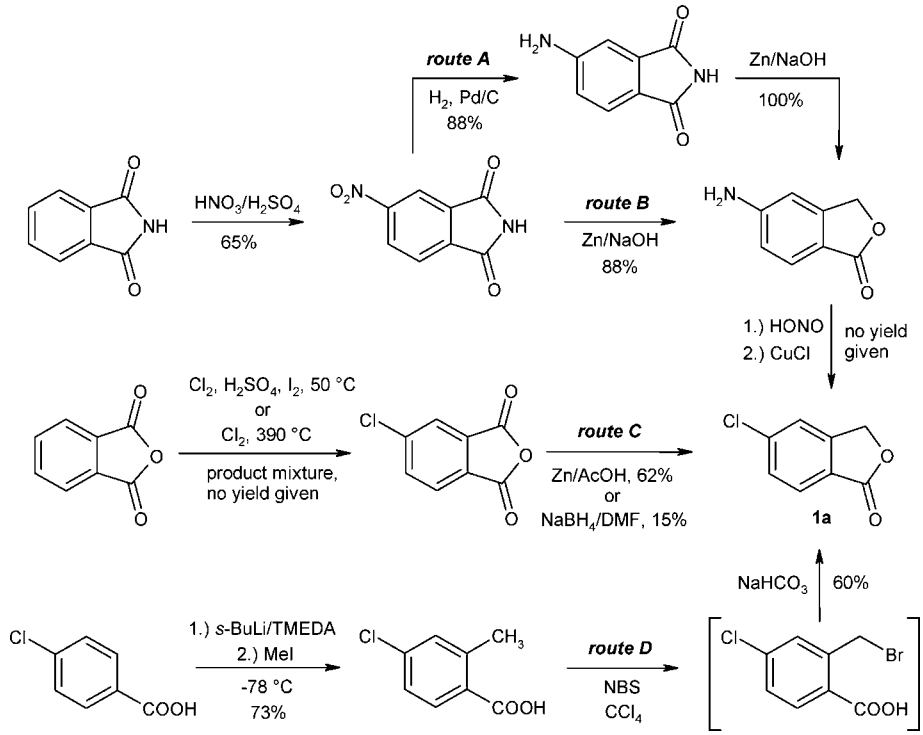
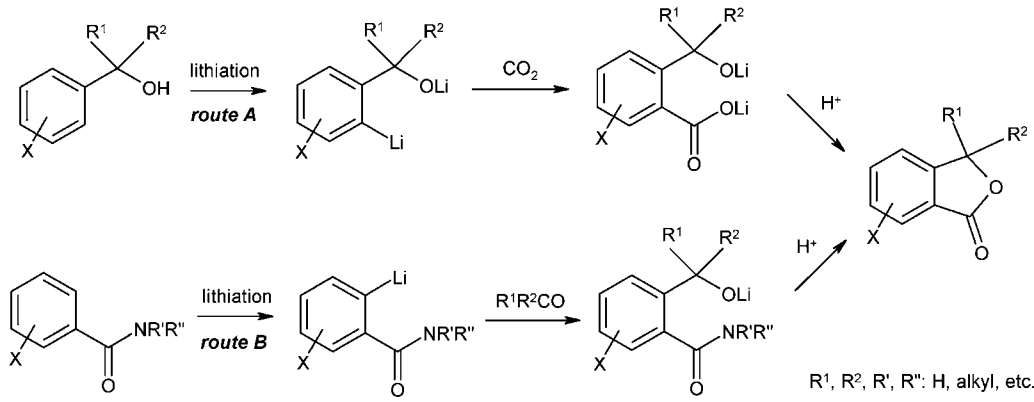
Scheme 1. **Literature procedures leading to 5-chlorophthalide**



Scheme 2. **Directed ortho-lithiation methodologies for the synthesis of phthalides**



However, since some derivatives of benzoic acids (e.g., various amides, dihydrooxazoles) proved to be much more powerful directors in ortho-lithiation reactions than hydroxymethyl groups, mostly they are used as starting materials for the synthesis of phthalides. Ortho-lithiation of suitable benzoic acid derivatives, followed by introduction of the optionally substituted hydroxymethyl moiety and subsequent acidic treatment lead to phthalides (Scheme 2, route B).[10,20,24−26]

Hauser discovered that *N*-methylbenzamide underwent *N*- and ortho-metalation with butyllithium, in contrast to *N*,*N*-dimethylbenzamide, which had been known to react in an addition reaction with lithium reagents to form ketones.[27] 4-Chloro-*N*-phenylbenzamide was lithiated with 2 equiv of butyllithium in THF at −70 °C and the dilithio intermediate was treated with *N*-alkyl-4-piperidinones to give 3,3-spiro-disubstituted-5-chlorophthalides in low yield (Scheme 3).[26]

From industrial point of view, the disadvantage of the use of secondary benzamides as starting compounds for the synthesis of phthalide **1** lies in the requirement of 2 equiv of butyllithium for metalation and the possible insolubility of the intermediate dianions.[28]

Gschwend[29] and Meyers[30] reported that 2-aryl-4,4-dimethyl-4,5-dihydro-1,3-oxazoles[31] can be ortho-metalated with butyllithium and treated with electrophilic reagents, leading after hydrolysis to ortho-substituted benzoic acids. Ortho-metalation

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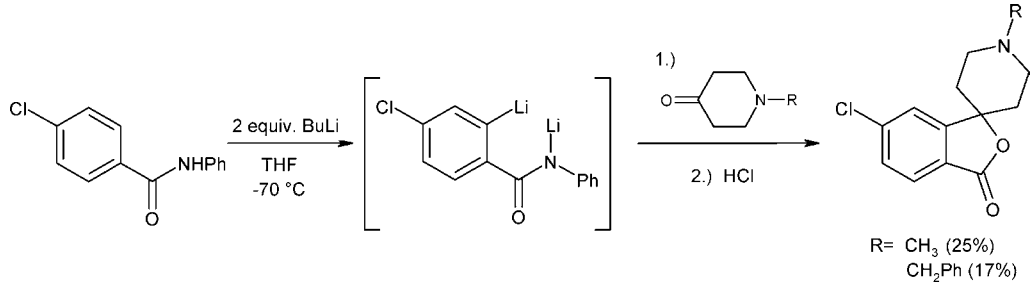
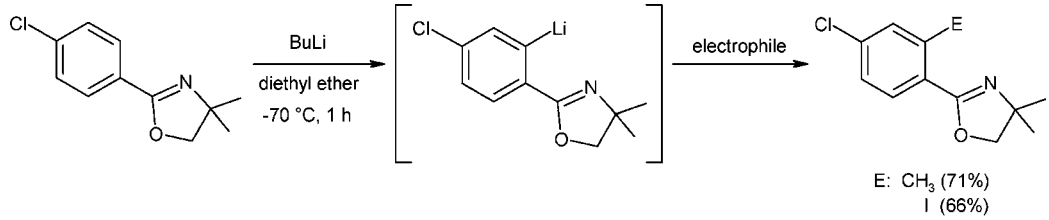
(31) 2-Aryloxazolines were prepared from benzoyl chloride with the appropriate amino alcohol, followed by cyclization of the amide with thionyl chloride.

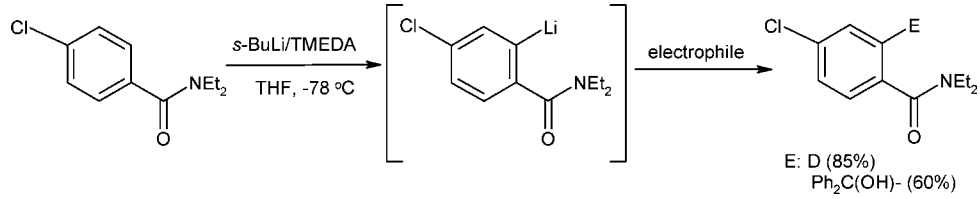
Scheme 3. **Lithiation of 4-chloro-*N*-phenylbenzamide**



Scheme 4. **Application of the 4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl directing group**



Scheme 5. **Lithiation of 4-chloro-*N,N*-diethylbenzamide**



of 2-(4-chlorophenyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole was carried out with butyllithium at −70 °C in diethyl ether[29] (Scheme 4).

Using this methodology, phthalides were prepared from the corresponding 4-fluorophenyl- and 4-(trifluoromethyl)phenyl derivatives.[32−35] The lithiations were carried out with butyllithium, mostly at low temperature (−42 °C, −78 °C), presumably in order to avoid the addition of the lithium reagent to the C═N double bond. Considering this and the relatively circuitous synthesis of 2-aryl-4,4-dimethyl-4,5-dihydro-1,3-oxazoles,[36] we decided to search for an alternative approach.

Thanks to the works of Beak[37] and Snieckus,[25] directed ortho-metalation chemistry of *N,N*-diethylbenzamides has found numerous synthetic applications. Comparative studies demonstrated the superiority of the *N,N*-diethylcarbamoyl group to the dihydrooxazole in its ability to direct ortho-lithiation.[38] The optimal reaction conditions for the ortho-lithiation of *N,N*-diethylbenzamides require *s*-butyllithium/TMEDA for the metalation at −78 °C in THF. Lithiation of the 4-chloro-*N,N*-diethylbenzamide under these conditions occurred adjacent to the amide group (Scheme 5).[39]

Results and Discussion

We intended to elaborate a safe and robust manufacturing process of phthalide **1a**. Therefore, use of highly inflammable *s*-butyllithium and *tert*-butyllithium, as the reagents in the manufacture, was undesirable. Furthermore, because of its better industrial applicability, it was our fixed intention — if there is only one opportunity — to use hexyllithium as the reagent instead of butyllithium. For this purpose, a suitable tertiary benzamide starting compound had to be found for a high-yielding phthalide production via ortho-lithiation reaction using this lithiating agent.

In a detailed study on tertiary amides in directed ortho-lithiation, Beak demonstrated that in the case of *N,N*-diisopropylbenzamides, ortho-lithiation could be achieved with butyllithium/TMEDA at −78 °C.[39] However, lithiation of our potential starting compound 4-chloro-*N,N*-diisopropylbenzamide (**2a**, Scheme 6) has only been described with *tert*-butyllithium at −78 °C in THF.[40]

After all this, it was a revelation to find that 4-chloro-*N,N*-diisopropylbenzamide (**2a**) could be smoothly lithiated simply with butyllithium adjacent to the amide moiety. By benefiting from this successful key reaction step, herein we report on the simple manufacturing synthesis of 5-chlorophthalide (**1a**). It has

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Scheme 6. **Manufacturing synthesis of 5-substituted phthalides**

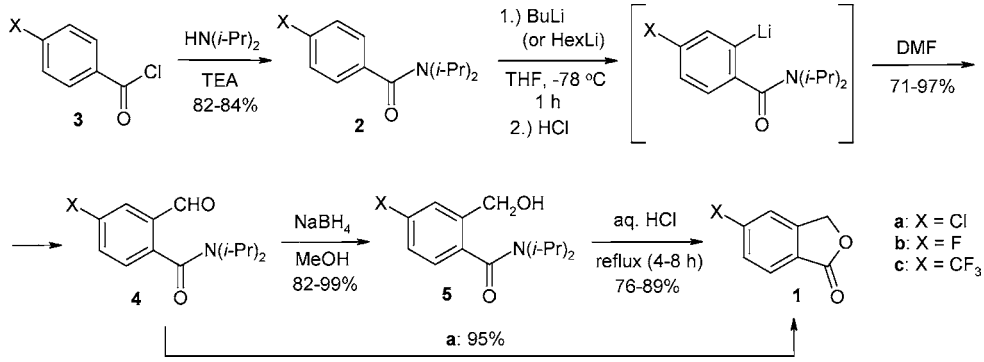

Table 1. **Yields of the reaction steps (%)**

	3 → 2	2 → 4	4 → 5	5 → 1
a	82	84 (86[a])	82	76 95 (92[b])
b	84	97	97	86
c	82	71	99	89

[a] Scaled-up reaction (starting from 239.7 g of **2a**). [b] Scaled-up reaction (starting from 230.0 g of **4a**).

been shown that the corresponding 5-fluoro- and 5-trifluoromethylphthalide (**1b**,**c**) could also be obtained under the same conditions.

4-Chloro-*N*,*N*-diisopropyl-benzamide (**2a**) was obtained from the corresponding acid chloride **3a**, by reacting it with diisopropylamine in the presence of triethylamine (TEA). Contrary to its diethyl analogue, **2a** is a solid, easy-to-handle compound. It was lithiated with butyllithium in THF, by maintaining the temperature in the range of −78 °C to −50 °C during the addition of the reagent (Scheme 6). Subsequent treatment with DMF afforded formyl derivative **4a** in good yield. Sodium borohydride reduction of the formyl group gave the corresponding hydroxymethyl derivative **5a**. The alternative one-step method, lithiation of benzamide **2a** followed by hydroxymethylation with paraformaldehyde provided compound **5a** only in poor yield when compared with the overall yield of the two-step sequence. Acidic treatment of hydroxymethyl derivative **5a** led to the desired phthalides **1a**. It has been demonstrated that the corresponding 5-fluoro- (**1b**) and 5-trifluoromethyl-phthalides (**1c**) could be obtained analogously under the same conditions (Scheme 6). Yields of the individual reaction steps are summarized in Table 1.

For practical reasons mentioned above, the synthesis of phthalide **1a** has been further modified. Lithiation with hexyllithium instead of butyllithium under the same conditions and subsequent formylation gave similar results. Sodium borohydride reduction of the formyl derivative **4a** followed by acidic cyclization, without isolation of the hydroxymethyl intermediate, afforded phthalide **1a** in 95% yield (Table 1).

Conclusion

In conclusion, the new synthesis elaborated at our laboratory provides a convenient access to target compound 5-chlorophthalide (**1a**). Literature processes described for the synthesis of **1a** suffer from several disadvantages. Classical methods usually include numerous reaction steps and, due to modest regioselectivity, the yields are either low or, in certain cases, not reported in the literature. Moreover, considering the environmental impact, industrial application of these processes is to be avoided e.g. because of the use of carbon tetrachloride or that of the large (4−5 equiv) excess of elemental zinc. Alternative approaches in the literature, based on ortho-lithiation, apply circuitously accessible starting materials or hazardous lithiating agents. Using the new method described here, **1a** can be synthesised in two steps from the easily available benzamide **2a**, in high overall yield (80%). The methodology is appropriate for industrial scale-up, and it has successfully been adopted for the analogous synthesis of 5-fluoro and 5-trifluoromethyl congeners **1b**,**c**. The compounds thus obtained are useful building blocks in the synthesis of various heterocyclic ring systems.

Experimental Section

All melting points were determined on a Büchi B-540 capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker IFS-113v FT spectrometer in KBr pellets or in neat. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Inova 500 (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively), Bruker Avance III (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively) or Varian Gemini 200 (200 and 50 MHz for ^{1}H and ^{13}C NMR spectra, respectively) spectrometer. DMSO-d_6 or $CDCl_3$ was used as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. Elemental analyses were performed on a Vario EL III analyzer. The reactions were followed by analytical thin layer chromatography on silica gel 60 F_{254}. All reagents were purchased from commercial sources.

4-Chloro-*N*,*N*-diisopropylbenzamide (2a). A mixture of diisopropylamine (67 mL, 48.4 g, 480 mmol) and triethylamine (67 mL, 48.6 g, 480 mmol) was added to a solution of 4-chlorobenzoyl chloride (**3a**, 40.9 mL, 55.8 g, 319 mmol) in toluene (600 mL). After stirring for 24 h at ambient temperature, toluene (100 mL) and water (200 mL) were added. The organic layer was separated, washed with an aqueous solution of hydrochloric acid (5 w/w%, 150 mL) and brine (150 mL), dried over $MgSO_4$, and evaporated. The residue was triturated with hexane (100 mL), and the crystalline product was collected by

filtration to give **2a** (62.5 g, 82%) as colorless crystals. Mp 92−93 °C (hexane), lit.[41] mp 85−87 °C.

***N,N*-Diisopropyl-4-fluorobenzamide (2b).**[42] This compound was prepared analogously to **2a**, starting from **3b** (28.7 g, 204 mmol) to give **2b** (38.6 g, 84%) as colorless crystals. Mp 95−96 °C (hexane). IR (KBr, cm^{-1}): 1620. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.31 (dd, $J = 8.8$, 5.5 Hz, 2H), 7.06 (t, $J = 8.8$ Hz, 2H), 3.68 (br s, 2H), 1.34 (br s, 12H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.4 (d, $J = 242.3$ Hz), 160.1, 134.9 (d, $J = 3.4$ Hz), 137.6 (d, $J = 8.4$ Hz), 115.2 (d, $J = 21.7$ Hz), 48.1 (br), 20.5 ppm. Elemental analysis for $C_{13}H_{18}FNO$ (223.29): calculated C 69.93, H, 8.13, N 6.27%; found C 69.59, H 8.21, N 6.19%.

***N,N*-Diisopropyl-4-(trifluoromethyl)benzamide (2c).**[42] This compound was prepared analogously to **2a**, starting from **3c** (39.6 g, 190 mmol) to give **2c** (42.6 g, 82%) as colorless crystals. Mp 64−65 °C (hexane). IR (KBr, cm^{-1}): 1630. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, $J = 8.1$ Hz, 2H), 7.42 (d, $J = 8.1$ Hz, 2H), 3.64 (br s, 2H), 1.51 (br s, 6H), 1.20 (br s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4, 142.3, 130.7 (q, $J = 32.9$ Hz), 125.9, 125.54 (q, $J = 3.8$ Hz), 123.9 (q, $J = 272.2$ Hz), 50.6 (br), 46.0 (br), 20.6 ppm. Elemental analysis for $C_{14}H_{18}F_3NO$ (273.30): calculated C 61.53, H 6.64, N 5.13%; found C 61.09, H 6.65, N 5.12%.

4-Chloro-*N,N*-diisopropyl-2-formylbenzamide (4a). *Method A.* Butyllithium (75.6 mL of a 2.5 M solution in hexane, 190 mmol) was added to a solution of **2a** (37.6 g, 156 mmol) in THF (360 mL) at −78 °C. After stirring for 1 h at −78 °C, DMF (16.1 mL, 15.3 g, 208 mmol) was added, while the temperature of the mixture rose to −50 °C. After warming to ambient temperature, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (350 mL) and extracted with ethyl acetate (350 and 2 × 120 mL). The organic layer was washed with brine (250 mL), dried over $MgSO_4$, and evaporated. The residue was triturated with a mixture of hexane (120 mL) and ethyl acetate (15 mL). The crystalline product was collected by filtration to give 35.1 g (84%) of **4a** as colorless crystals. Mp 116−117 °C (hexane/EtOAc). IR (KBr, cm^{-1}): 1703, 1628. ^1H NMR (DMSO-d_6, 500 MHz): δ 9.96 (s, 1H), 7.99 (d, $J = 2.2$ Hz, 1H), 7.79 (dd, $J = 8.2$, 2.2 Hz, 1H), 7.41 (d, $J = 8.2$ Hz, 1H), 3.60 (m, 1H), 3.46 (m, 1H), 1.48 (m, 6H), 1.05 (m, 6H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 190.4, 166.6, 138.7, 134.2, 133.8, 133.5, 130.4, 128.2, 51.0, 45.1, 20.2, 20.1 ppm. Elemental analysis for $C_{14}H_{18}ClNO_2$ (267.76): calculated C 62.80, H 6.78, N 5.23, Cl 13.24%; found C 62.42, H 6.73, N 5.20, Cl 13.34%.

Method B. The reaction was carried out similarly to *Method A*, starting from **2a** (35.3 g, 147 mmol) and using hexyllithium (82.6 mL, 2.3 M solution in hexane, 190 mmol) as the lithiating agent to give **4a** (32.2 g, 82%). Mp 115−117 °C.

Scaled-Up Process. Butyllithium (482 mL of a 2.5 M solution in hexane, 1.20 mol) was added to a solution of **2a** (239.7 g, 1.00 mol) in THF (2290 mL) at −78 °C. After stirring for 1.5 h at this temperature, DMF (102.6 mL, 96.8 g, 1.30 mol) was added in one portion, while the temperature of the mixture rose to −45 °C. After warming to −15 °C, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (750 mL) and then water (100 mL), and extracted with ethyl acetate (1000 and 2 × 150 mL). The organic layer was washed with brine (1000 mL), dried over a mixture of $MgSO_4$ (110 g) and charcoal (10 g), and evaporated. The residue was triturated with hexane (250 mL). The crystalline product was collected by filtration and washed with hexane (100 mL) to give 230.0 g (86%) of **4a** as colorless crystals.

***N,N*-Diisopropyl-4-fluoro-2-formylbenzamide (4b).** This compound was prepared analogously to **4a**, starting from **2b** (27.8 g, 124.5 mmol). The residue obtained after the final evaporation was triturated with hexane (100 mL), and the crystalline product was collected by filtration to give 30.1 g (97%) of **4b** as colorless crystals. Mp 101−102 °C (hexane/EtOAc). IR (KBr, cm^{-1}): 1708, 1618. ^1H NMR (DMSO-d_6, 200 MHz): δ 9.96 (s, 1H), 7.74 (dd, $J = 9.2$, 2.4 Hz, 1H), 7.59 (td, $J = 8.2$, 2.8 Hz, 1H), 7.45 (dd, $J = 8.5$, 5.5 Hz, 1H), 3.60 (m, 1H), 3.48 (m, 1H), 1.48 (m, 6H), 1.05 (m, 6H) ppm. ^{13}C NMR (DMSO-d_6, 50 MHz): δ 190.3 (d, $J = 1.9$ Hz), 166.7, 161.7, (d, $J = 247.3$ Hz), 137.0 (d, $J = 3.8$ Hz), 134.3 (d, $J = 6.1$ Hz), 128.7 (d, $J = 7.6$ Hz), 121.5 (d, $J = 21.7$), 116.6 (d, $J = 22.1$ Hz), 51.0, 45.2, 20.3, 20.1 ppm. Elemental analysis for $C_{14}H_{18}FNO_2$ (251.30): calculated C 66.91, H 7.22, N 5.57%; found C 66.74, H 7.13, N 5.53%.

***N,N*-Diisopropyl-2-formyl-4-(trifluoromethyl)benzamide (4c).** This compound was prepared analogously to **4a**, starting from **2c** (38.8 g, 142 mmol). The residue obtained after the final evaporation was triturated with hexane (100 mL), the crystalline product was collected by filtration to give **4c** (30.5 g, 71%) as colorless crystals. Mp 78−79 °C (hexane). IR (KBr, cm^{-1}): 1702, 1629. ^1H NMR ($CDCl_3$, 500 MHz): δ 10.12 (s, 1H), 8.20 (d, $J = 1.3$ Hz, 1H), 7.87 (dd, $J = 8.1$, 1.3 Hz, 1H), 7.44 (d, $J = 8.1$ Hz, 1H), 3.59 (m, 1H), 3.53 (m, 1H), 1.61 (d, $J = 7$ Hz, 6H), 1.13 (d, $J = 6.4$ Hz, 6H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.0, 166.8, 144.0, 132.7, 131.3 (q, $J = 33.7$ Hz), 130.6, (q, $J = 3.4$ Hz), 126.6, (q, $J = 3.9$ Hz), 123.2, (q, $J = 272.5$ Hz), 51.4, 46.4, 20.5, 20.3 ppm. Elemental analysis for $C_{15}H_{18}F_3NO_2$ (301.31): calculated C 59.79, H 6.02, N 4.65%; found C 59.55, H 6.11, N 4.59%.

4-Chloro-*N,N*-diisopropyl-2-(hydroxymethyl)benzamide (5a). Sodium borohydride (3.4 g, 88.6 mmol) was added to a solution of **4a** (17.9 g, 66.9 mmol) in methanol (150 mL) and cooled with ice−water bath. After stirring for 5 h, the solvent was evaporated, water (80 mL) was added to the residue, and the mixture was extracted with diethyl ether (3 × 80 mL). The ethereal layer was washed with brine (80 mL), dried over $MgSO_4$ and evaporated. The residue was triturated with diethyl ether and collected by filtration to give **5a** (14.8 g, 82%) as colorless crystals. Mp 81−82 °C (hexane). IR (KBr, cm^{-1}): 3298, 1608. ^1H NMR (DMSO-d_6, 500 MHz): δ 7.52 (d, $J = 2.2$ Hz, 1H), 7.33 (dd, $J = 8.1$, 2.2 Hz, 1H), 7.15 (d, $J = 8.1$ Hz, 1H), 5.34 (t, $J = 5.7$ Hz, 1H), 4.50 (dd, $J = 12.9$, 4.7 Hz, 1H), 4.40 (dd, $J = 13.6$, 5.8 Hz, 1H), 3.52 (m, 2H), 1.44 (m, 6H), 1.06 (m, 6H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 168.0, 141.0, 135.4, 132.8, 126.9, 126.8, 126.4, 59.6, 50.7, 44.9,

(41) Ulibarri, G.; Choret, N.; Bigg, D. C. H. *Synthesis* **1996**, *11*, 1286–1288.

(42) Fong, C. W.; Grant, H. G. *Aust. J. Chem.* **1981**, *34*, 1205–1214. Only ^{13}C NMR spectra of **2b** and **2c** are described.

20.5, 20.4, 20.3, 20.2 ppm. Elemental analysis for $C_{14}H_{20}ClNO_2$ (269.77): calculated C 62.33, H 7.47, N 5.19, Cl 13.14%; found C 62.04, H 7.59, N 5.10, Cl 13.66%.

***N,N*-Diisopropyl-4-fluoro-2-(hydroxymethyl)benzamide (5b).** This compound was prepared analogously to **5a**, starting from **4b** (20.0 g, 79.7 mmol) to give **5b** (19.9 g, 97%) as colorless crystals. Mp 95−96 °C (hexane). IR (KBr, cm^{-1}): 3425, 1617. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.14 (dd, $J = 9.4$, 2.6 Hz, 1H), 7.13 (dd, $J = 8.4$, 5.5 Hz, 1H), 6.97 (~td, $J = 8.4$, 2.7 Hz, 1H), 4.61 (m, 1H), 4.40 (m, 1H), 3.77 (t, $J = 5.4$ Hz, 1H), 3.76 (m, 1H), 3.53 (m, 1H), 1.55 (m, 6H), 1.15 (m, 3H), 1.10 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.3, 162.6 (d, $J = 249.0$ Hz), 141.2 (d, $J = 6.8$ Hz), 133.3 (d, $J = 3.9$ Hz), 126.7 (d, $J = 7.8$ Hz), 116.2 (d, $J = 21.5$ Hz), 114.2 (d, $J = 21.5$ Hz), 63.0 (d, $J = 1.5$ Hz), 51.2, 46.2, 20.9, 20.6, 20.5, 20.4 ppm. Elemental analysis for $C_{14}H_{20}FNO_2$ (253.32): calculated C 66.38, H 7.96, N 5.53%; found C 66.07, H 8.09, N 5.45%.

***N,N*-Diisopropyl-2-hydroxymethyl-4-(trifluoromethyl)-benzamide (5c).** This compound was prepared analogously to **5a**, starting from **4c** (30.0 g, 99.7 mmol) to give **5c** (30.1 g, 99%) as colorless oil. IR (neat, cm^{-1}): 3299, 1611. ^1H NMR (DMSO-d_6, 500 MHz): δ 7.85 (s, 1H), 7.64 (d, $J = 7.9$ Hz, 1H), 7.37 (d, $J = 7.9$ Hz, 1H), 5.46 (t, $J = 5.7$ Hz, 1H), 4.59 (dd, $J = 14.1$, 5.1 Hz, 1H), 4.49 (dd, $J = 14.1$, 6.0 Hz, 1H), 3.58 (m, 1H), 3.47 (m, 1H), 1.47 (m, 6H), 1.08 (m, 6H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 167.7, 140.4 (q, $J = 1.0$ Hz), 139.9, 128.7 (q, $J = 31.7$ Hz), 125.6, 124.3 (q, $J = 272.5$ Hz), 123.8 (q, $J = 3.9$ Hz), 59.6, 50.8, 45.1, 20.4, 20.3, 20.3, 20.1 ppm. Elemental analysis for $C_{15}H_{20}F_3NO_2$ (303.33): calculated C 59.40, H 6.65, N 4.62%; found C 59.17, H 6.73, N 4.56%.

5-Chloro-2-benzofuran-1(3*H*)-one (1a). *Method A.* A mixture of **5a** (54.7 g, 203 mmol) and aqueous hydrochloric acid (20 w/w%, 410 mL) was refluxed for 4 h. After cooling to ambient temperature it was extracted with dichloromethane (4 × 100 mL). The combined organic layer was extracted with brine (200 mL), dried over $MgSO_4$, and evaporated. The residue was triturated with a mixture (1:1) of hexane and ethyl acetate (100 mL) and collected by filtration to give **1a** (26.0 g, 76%) as colorless crystals. Mp 156−158 °C (EtOH), lit.[12] mp 153.5 °C (EtOH). IR (KBr, cm^{-1}): 1754. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, $J = 8.7$ Hz, 1H), 7.52 (m, 1H), 7.51 (m, 1H), 5.30 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 148.1, 140.7, 129.8, 126.8, 124.2, 122.5, 68.9 ppm. Elemental analysis for $C_8H_5ClO_2$ (168.58): calculated C 57.00, H 2.99, Cl 21.03%; found C 56.91, H 3.03, Cl 21.15%.

Method B. Compound **1a** was also prepared in one pot, starting from formyl derivative **4a** (26.9 g, 0.100 mol) which was dissolved in methanol (225 mL) and treated with sodium borohydride (5.0 g, 0.133 mol) while cooling with ice−water bath. After stirring for 2 h at ambient temperature, water (120 mL) was added, and methanol was evaporated. Concentrated aqueous hydrochloric acid solution (80 mL) was added, and the mixture was refluxed for 6 h. After cooling to room temperature, the crystalline product was collected by filtration and then washed with water (100 mL) and ethanol (20 mL) to give **1a** (16.0 g, 95%) as colorless crystals. Mp 154−155 °C, purity >99% (^1H NMR).

Method B, Scaled-Up Process. Formyl derivative **4a** (230.0 g, 0.86 mol) was dissolved in methanol (1900 mL). Sodium borohydride (42.7 g, 1.13 mol) was added over a period of 90 min, while maintaining the temperature of the reaction mixture between 5−10 °C. After stirring for additional 2 h at ambient temperature, water (1020 mL) was added, and methanol was evaporated. Concentrated aqueous hydrochloric acid solution (685 mL) was added, and the mixture was refluxed for 6 h. After cooling to room temperature, the crystalline product was collected by filtration and then washed with water (3 × 400 mL) and a 2:1 mixture of ethanol and water (2 × 200 mL) to give **1a** (133.4 g, 92%) as colorless crystals. Mp 155−156 °C.

5-Fluoro-2-benzofuran-1(3*H*)-one (1b). This compound was prepared analogously to **1a** (*Method A*), starting from **5b** (19.2 g, 75.7 mmol) to give **1b** (9.80 g, 86%) as colorless crystals. Mp 122−123 °C (hexane/EtOAc), lit.[43] mp 120−121 °C. IR (KBr, cm^{-1}): 1749.

5-Trifluoromethyl-2-benzofuran-1(3*H*)-one (1c). This compound was prepared analogously to **1a** (*Method A*), starting from **5c** (29 g, 95.7 mmol) to give **1c** (17.3 g, 89%) as colorless crystals. Mp 74−75 °C (hexane), lit. mp 70−72 °C,[44] 65−67 °C.[45] IR (KBr, cm^{-1}): 1758. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.07 (d, $J = 8.0$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 7.80 (s, 1H), 5.41 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.4, 146.8, 135.9 (q, $J = 33$ Hz), 129.0, 126.4 (q, $J = 3.5$ Hz), 123.3 (q, $J = 274$ Hz), 119.6, 69.5 ppm. Elemental analysis for $C_9H_5FO_2$ (202.13): calculated C 53.48, H 2.49%; found C 53.28, H 2.48%.

Supporting Information Available

^1H and ^{13}C NMR spectra of new compounds **1a**−**c**, **2b**−**c**, **4a**−**c**, and **5a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(43) Synthesis of **1b** starting from 5-amino-2-benzofuran-1(3*H*)-one is described in ref 14.

(44) Compound **1c** was prepared via hydrolysis of the hardly accessible 2-hydroxymethyl-4-(trifluoromethyl)benzonitrile, see: Bigler, A. J.; Boegesoe, K. P.; Toft, A.; Hansen, V. *Eur. J. Med. Chem.* **1977**, *12*, 289–295.

(45) Compound **1c** was prepared by non-regiospecific lithiation followed by carboxylation and cyclization, starting from *m*-(trifluoromethyl)-benzyl alcohol, see ref 16.