Unexpected Smiles Rearrangement During Borane Reduction of 2-Aryloxy-2-methylpropionamides

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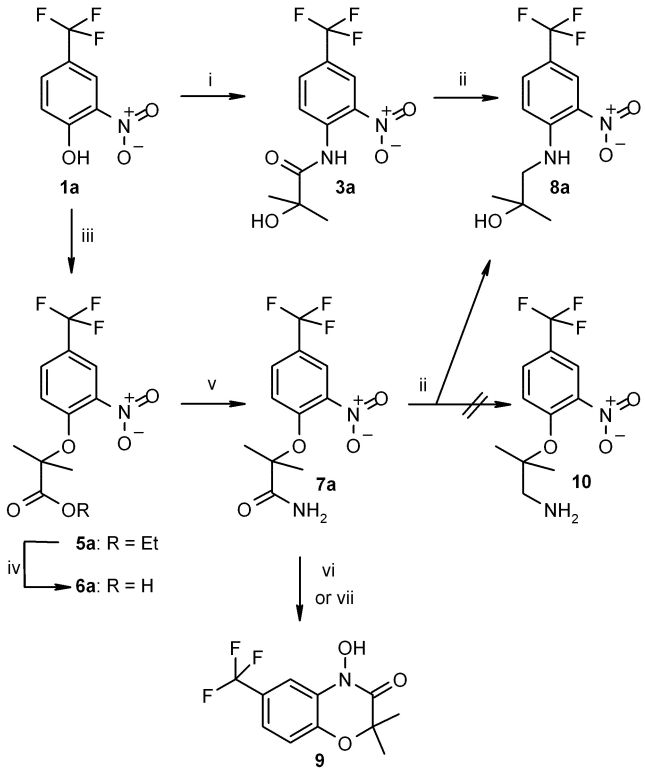
Abstract: 2-Nitrophenols spontaneously rearrange during alkylation with 2-bromo-2-methylpropionamide in the presence of cesium carbonate in acetonitrile to the corresponding 2-hydroxy-2-methyl-*N*-(2-nitrophenyl)propionamides. Upon reduction of 2-aryloxy-2-methylpropionamides, which were obtained from 2-nitrophenols in three steps, with borane dimethyl sulfide complex in THF, a Smiles rearrangement was observed as well leading to 2-methyl-1-phenylaminopropan-2-ols. Both approaches give access to valuable 2-nitro substituted aniline derivatives.

Key words: Smiles rearrangement, reduction, amide, amine, borane/dimethyl sulfide complex

In the course of a medicinal chemistry program we were interested in the synthesis of substituted nitrobenzene derivatives bearing sterically hindered aminoalkoxy groups. Since the alkylation of phenols with 2-bromo-2-methylpropionamide (**2**)[1,2] and the reduction of amides to the corresponding amines[3] are well known reactions in the literature, we expected to gain compounds like **10** in a two-step procedure starting from commercially available phenols. Usually, for the conversion of phenols to 2-aryloxy-2-methylpropionamides sodium hydride was used at elevated temperature,[1,2] but unexpected difficulties were encountered under these conditions. We investigated alternative bases for their suitability for this particular alkylation using 2-nitro-4-trifluoromethylphenol (**1a**) as model system and found that cesium carbonate reacts smoothly in acetonitrile at 78 °C leading to a product with the expected mass after work-up and purification. However, the ^{1}H NMR spectrum was not in accordance with the desired compound **7a**, which we synthesized later via an alternative strategy, but could be assigned to compound **3a** (Scheme 1). The spectrum displays two exchangeable H-atoms with a significant difference in their chemical shifts [δ = 11.46 (NH), 6.23 (OH)]. This clearly indicates that the isolated structure corresponds to compound **3a** and that a rearrangement has occurred under the applied alkylation conditions. This rearrangement, which is known as Smiles rearrangement, typically is performed in DMF, HMPA, or DMF/DMPU in the presence of sodium hydride at 100 °C and has been used several times in the past for the preparation of anilines from the corresponding phenols.[1,2,4] We assume that the activation of the aromatic system by the nitro group is responsible for the rearrangement already taking place at lower temperature under less basic conditions. Recently, a mechanism for this particular rearrangement has been proposed, which supports this assumption.[1,4] It includes a nucleophilic attack of the amide anion and the subsequent formation of a spiro aromatic anion, which is stabilized by electron-withdrawing groups.



Scheme 1 *Reagents and conditions*: i) Cs_2CO_3, CsI, 2-bromo-2-methylpropionamide (**2**), MeCN, 78 °C, 3 h; ii) $BH_3{\cdot}SMe_2$, THF, 60–70 °C, 1–1.5 h; iii) Cs_2CO_3, 2-bromo-2-methylpropionic acid ethyl ester (**4**), MeCN, reflux, 24–78 h; iv) KOH, EtOH, reflux, 1–4 h; v) a) $SOCl_2$, toluene, reflux, 1.5–2 h; b) toluene, NH_3, r.t., 1 h; vi) $SnCl_2{\cdot}2H_2O$, EtOH, 70 °C, 1 h; vii) H_2, Pd/C, THF.

The required starting material **7a** for the reduction to the desired compound **10** could be obtained by an alternative synthetic strategy. Hence, the commercially available phenol **1a** was readily alkylated with 2-bromo-2-methylpropionic acid ethyl ester (**4**) and cesium carbonate in acetonitrile under reflux to the ester **5a**, which was subsequently saponified with potassium hydroxide in eth-

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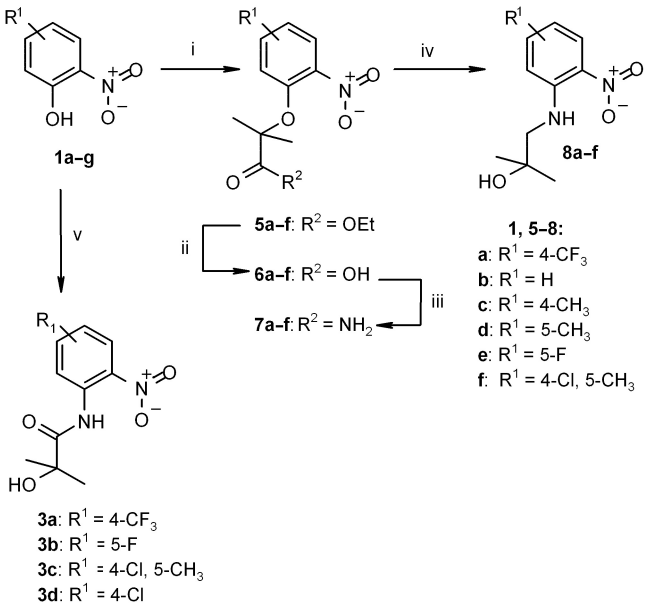
anol to the corresponding acid **6a**. Conversion of **6a** to the amide **7a** was accomplished with thionyl chloride and ammonia in toluene in a two-step procedure without isolating the acyl chloride intermediate. Borane/dimethyl sulfide complex was selected as reducing agent for the reduction of the amide **7a** to the desired amine **10**, since the reduction of a closely related structure had been published.[3] When **7a** was treated with this reagent in THF, the main reaction product showed the expected mass. Surprisingly, the ^{1}H NMR spectrum was not in accordance with the desired compound **10**. Chemical shifts and coupling patterns, especially of the exchangeable H-atoms, unambiguously showed that the isolated product could be assigned to compound **8a**. This indicates that two distinct reactions - a reduction and rearrangement - occurred even under the mild reaction conditions. Although the reaction was monitored accurately via HPLC, it remained unclear in which order both reactions took place. Since the utilized reagent has an acidic character it is likely that the reduction occurs prior to a nucleophilic attack of the generated aliphatic amine to yield the rearranged product **8a**. Additionally, the structural assignment could be confirmed due to the fact that the reduction of the rearranged product **3a** under identical reduction conditions afforded the same result. The NMR spectra of the products obtained by reduction of **7a** and **3a** were identical. In order to see whether this unexpected rearrangement is restricted to highly activated aromatic systems bearing an additional electron withdrawing residue besides the nitro group, like in **7a**, other phenols **1b–f** were treated accordingly as depicted in Scheme 2.



Scheme 2 *Reagents and conditions:* i) Cs_2CO_3, 2-bromo-2-methylpropionic acid ethyl ester (**4**), MeCN, reflux, 24–78 h; ii) KOH, EtOH, reflux, 1–4 h; iii) a) $SOCl_2$, toluene, reflux, 1.5–2 h; b) toluene, NH_3, r.t., 1 h; iv) BH_3·SMe_2, THF, 60–70 °C, 1–1.5 h; v) Cs_2CO_3, CsI, 2-bromo-2-methylpropionamide (**2**), MeCN, 78 °C, 1–3 h.

Hence, **1b–f** were alkylated, saponified, and converted to the respective amides **7b–f** as described for **7a**. All of these amides were reduced and rearranged upon treatment with borane/dimethyl sulfide complex in THF, even those bearing electron-donating methyl groups like **5c** or **5d**. In addition, we tried to investigate the reactivity of the corresponding aniline derivative of **7a** under the known rearrangement conditions. However, these attempts failed, because the reduction of **7a** using well known reaction conditions for the nitro group reduction (stannous chloride or hydrogenation) always led to the formation of the 1,4-benzoxazinone **9**.[5]

In summary, we have described a one-pot alkylation and Smiles rearrangement procedure for 2-nitrophenols. 2-Aryloxy-2-methylpropionamides, which were obtained from 2-nitrophenols in three steps, rearrange spontaneously to 2-methyl-1-phenylaminopropan-2-ols during reduction with borane/dimethyl sulfide complex in THF. Both approaches give access to valuable 2-nitro substituted aniline derivatives.

All solvents and reagents were obtained from commercial suppliers and were used without further purification. Petroleum ether used had a boiling range of 50–70 °C. 2-Bromo-2-methylpropionamide (**2**) was prepared according to the procedure described in the literature.[1] ^{1}H NMR spectra were recorded on a Bruker AM 250 spectrometer or a Bruker DRX 500 spectrometer, respectively, using DMSO-d_6 as solvent. Chemical shifts are reported in parts per million (δ) relative to DMSO as internal reference. High-resolution mass spectra were recorded on a VG Analytical 7070E spectrometer (EI). Column chromatography was carried out on Merck Silica Gel 60 (0.063–0.2 mm).

2-Hydroxy-2-methyl-*N*-(2-nitro-4-trifluoromethylphenyl)propionamide (3a); Typical Procedure

To a solution of 2-nitro-4-trifluoromethylphenol (**1a**; 100 mg, 0.48 mmol) and 2-bromo-2-methylpropionamide (**2**; 105 mg, 0.63 mmol) in MeCN (1.5 mL) were added Cs_2CO_3 (236 mg, 0.73 mmol) and CsI (13 mg, 0.05 mmol). The resulting suspension was stirred at 78 °C for 3 h, cooled, and diluted with EtOAc. The organic layer was washed successively with H_2O, aq 2 N NaOH, H_2O, and brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (12 g silica gel, eluent: Et_2O–petroleum ether, 3:2) to yield **3a** (74 mg, 53%) as a yellow oil, which crystallized upon standing.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.46 (s, 1 H, NH), 8.78 (d, 1 H, ^3J = 9 Hz, 6′-H), 8.45 (d, 1 H, ^4J = 2 Hz, 3′-H), 8.14 (dd, 1 H, ^3J = 9 Hz, ^4J = 2 Hz, 5′-H), 6.23 (s, 1 H, OH), 1.39 (s, 6 H, 2 CH_3).

2-Hydroxy-2-methyl-*N*-(5-fluoro-2-nitrophenyl)propionamide (3b)

From 5-fluoro-2-nitrophenol (**1e**; 100 mg, 0.64 mmol), 2-bromo-2-methylpropionamide (**2**; 137.5 mg, 0.83 mmol), Cs_2CO_3 (311 mg, 0.96 mmol), CsI (16 mg, 0.06 mmol), and MeCN (1 mL); 2 h, 78 °C; purification: column chromatography (12 g silica gel, eluent: CH_2Cl_2–petroleum ether, 9:1); yield: 63 mg (41%); yellow oil (crystallized upon standing).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.55 (s, 1 H, NH), 8.49 (dd, 1 H, $^3J_{H,F}$ = 11.7 Hz, ^4J = 2.9 Hz, 6′-H), 8.33 (dd, 1 H, ^3J = 9.4 Hz, $^4J_{H,F}$ = 6.1 Hz, 3′-H), 7.18 (m, 1 H, 4′-H), 6.22 (s, 1 H, OH), 1.38 (s, 6 H, 2 CH_3).

2-Hydroxy-2-methyl-*N*-(4-chloro-5-methyl-2-nitrophenyl)propionamide (3c)
From 4-chloro-5-methyl-2-nitrophenol (**1f**; 200 mg, 1.07 mmol), 2-bromo-2-methylpropionamide (**2**; 195 mg, 1.17 mmol), Cs_2CO_3 (521 mg, 1.6 mmol), CsI (28 mg, 0.11 mmol), and MeCN (4 mL); 1 h, 78 °C; purification: column chromatography (12 g silica gel, eluent: Et_2O–petroleum ether, 3:2); yield: 92 mg (32%); yellow oil (crystallized upon standing).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.24 (s, 1 H, NH), 8.57 (s, 1 H, 6′-H), 8.2 (s, 1 H, 3′-H), 6.14 (s, 1 H, OH), 2.42 (s, 3 H, CH_3), 1.39 (s, 6 H, 2 CH_3).

2-Hydroxy-2-methyl-*N*-(4-chloro-2-nitrophenyl)propionamide (3d)
From 4-chloro-2-nitrophenol (**1g**; 100 mg, 0.58 mmol), 2-bromo-2-methylpropionamide (**2**; 105 mg, 0.63 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), CsI (15 mg, 0.06 mmol), and MeCN (1 mL); 1 h, 78 °C; purification like compound **3b**; yield: 92 mg (62%); yellow oil (crystallized upon standing).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.18 (s, 1 H, NH), 8.78 (d, 1 H, ^3J = 9.2 Hz, 6′-H), 8.45 (d, 1 H, ^4J = 2.6 Hz, 3′-H), 8.14 (dd, 1 H, ^3J = 9.2 Hz, ^4J = 2.6 Hz, 5′-H), 6.13 (s, 1 H, OH), 1.37 (s, 6 H, 2 CH_3).

2-Methyl-2-[2-nitro-4-(trifluoromethyl)phenoxy]propionic Acid Ethyl Ester (5a); Typical Procedure
To a solution of 2-nitro-4-(trifluoromethyl)phenol (**1a**; 5.0 g, 24.14 mmol) in MeCN (25 mL) was added Cs_2CO_3 (11.8 g, 36.22 mmol). 2-Bromo-2-methylpropionic acid ethyl ester (**4**; 5 mL, 33.58 mmol) dissolved in MeCN (10 mL) was added and the reaction mixture was refluxed for 24 h. The mixture was cooled, filtered, and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc and the organic layer was washed subsequently with H_2O and brine. The organic layer was dried (Na_2SO_4) and concentrated to give **5a** (8.5 g, 97%) as a pale-brown oil.

2-Methyl-2-(2-nitrophenoxy)propionic Acid Ethyl Ester (5b)
From 2-nitrophenol (**1b**; 0.50 g, 3.59 mmol), Cs_2CO_3 (1.76 g, 5.39 mmol), 2-bromo-2-methylpropionic acid ethyl ester (**4**; 0.69 mL, 4.67 mmol), and MeCN (4 mL); 78 h, reflux; yield: 0.48 g (53%); yellow oil.

2-Methyl-2-(4-methyl-2-nitrophenoxy)propionic Acid Ethyl Ester (5c)
From 4-methyl-2-nitrophenol (**1c**; 0.50 g, 3.27 mmol), Cs_2CO_3 (1.60 g, 4.9 mmol), 2-bromo-2-methylpropionic acid ethyl ester (**4**; 0.63 mL, 4.25 mmol), and MeCN (4 mL); 24 h, reflux; yield: 0.51 g (58%); yellow oil.

2-Methyl-2-(5-methyl-2-nitrophenoxy)propionic Acid Ethyl Ester (5d)
From 5-methyl-2-nitrophenol (**1d**; 0.50 g, 3.27 mmol), Cs_2CO_3 (1.60 g, 4.9 mmol), 2-bromo-2-methylpropionic acid ethyl ester (**4**; 0.63 mL, 4.25 mmol), and MeCN (4 mL); 24 h, reflux; yield: 0.46 g (53%); yellow oil.

2-Methyl-2-(5-fluoro-2-nitrophenoxy)propionic Acid Ethyl Ester (5e)
From 5-fluoro-2-nitrophenol (**1e**; 0.50 g, 3.27 mmol), Cs_2CO_3 (1.60 g, 4.9 mmol), 2-bromo-2-methylpropionic acid ethyl ester (**4**; 0.63 mL, 4.25 mmol), and MeCN (4 mL); 24 h, reflux; yield: 0.48 g (56%); yellow oil.

2-Methyl-2-(4-chloro-5-methyl-2-nitrophenoxy)propionic Acid Ethyl Ester (5f)
From 4-chloro-5-methyl-2-nitrophenol (**1f**; 0.50 g, 2.67 mmol), Cs_2CO_3 (1.30 g, 4 mmol), 2-bromo-2-methylpropionic acid ethyl ester (**4**; 0.52 mL, 3.47 mmol), and MeCN (4 mL); 24 h, reflux; yield: 0.38 g (47%); yellow oil.

2-Methyl-2-[2-nitro-4-(trifluoromethyl)phenoxy]propionic Acid (6a); Typical Procedure
Compound **5a** (6.43 g, 17.21 mmol) was dissolved in a solution of KOH in EtOH (44 mL, 0.5 N) and refluxed for 1 h. The reaction mixture was evaporated to dryness, the residue was dissolved in H_2O (20 mL), and extracted with EtOAc. The aqueous layer was acidified with conc. aq HCl (pH 4) and extracted with EtOAc (3 ×). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated to give **6a** (5.06 g, 98%) as a yellow oil.

2-Methyl-2-(2-nitrophenoxy)propionic Acid (6b)
From compound **5b** (468 mg, 1.85 mmol) and KOH in EtOH (3.7 mL, 1 N); 2 h, reflux; purification: column chromatography [12 g silica gel, eluent: CH_2Cl_2–MeOH (1–5%)]; yield: 200 mg (48%); brown oil.

2-Methyl-2-(4-methyl-2-nitrophenoxy)propionic Acid (6c)
From compound **5c** (476 mg, 1.78 mmol) and KOH in EtOH (3.56 mL, 1 N); 2 h, reflux; yield: 420 mg (99%); orange oil (crystallized upon standing).

2-Methyl-2-(5-methyl-2-nitrophenoxy)propionic Acid (6d)
From compound **5d** (358 mg, 1.34 mmol) and KOH in EtOH (2.68 mL, 1 N); 3 h, reflux; purification: column chromatography [35 g silica gel, eluent: CH_2Cl_2–MeOH (2–5%)]; yield: 240 mg (75%); brown oil.

2-Methyl-2-(5-fluoro-2-nitrophenoxy)propionic Acid (6e)
From compound **5e** (469 mg, 1.71 mmol) and KOH in EtOH (3.43 mL, 1 N); 2 h, reflux; purification: column chromatography [35 g silica gel, eluent: CH_2Cl_2–MeOH (1–3%)]; yield: 350 mg (83%); pale-brown oil.

2-Methyl-2-(4-chloro-5-methyl-2-nitrophenoxy)propionic Acid (6f)
From compound **5f** (312 mg, 1.04 mmol) and KOH in EtOH (2.07 mL, 1 N), 4 h, reflux; purification: column chromatography [35 g silica gel, eluent: CH_2Cl_2–MeOH (2–7%)]; yield: 220 mg (78%); pale-yellow oil (crystallized upon standing).

2-Methyl-2-[2-nitro-4-(trifluoromethyl)phenoxy]propionamide (7a); Typical Procedure
Compound **6a** (168 mg, 0.57 mmol) was refluxed in toluene (3 mL) containing $SOCl_2$ (0.52 mL) for 2 h and concentrated in vacuo. The residue was co-evaporated with toluene (2 × 5 mL) and dissolved in toluene (2 mL). This solution was added dropwise to a vigorously stirred emulsion of NH_4OH (32%, 80 μL) in toluene (2 mL) at 0–5 °C. The reaction mixture was allowed to warm to r.t., stirred for 1 h, and concentrated in vacuo. The residue was dissolved in EtOAc and the EtOAc layer was washed successively with 1 M aq NaOH solution, 1 M aq HCl, H_2O, and brine. The organic layer was dried (Na_2SO_4) and concentrated to give **7a** (150 mg, 90%) as a pale-brown oil.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.30 (d, 1 H, ^4J = 2.2 Hz, 3′-H), 7.99 (dd, 1 H, ^3J = 9 Hz, ^4J = 2.2 Hz, 5′-H), 7.66 (s, 1 H, NH_2), 7.42 (s, 1 H, NH_2), 7.22 (d, 1 H, ^3J = 9 Hz, 6′-H), 1.55 (s, 6 H, 2 CH_3).

2-Methyl-2-(2-nitrophenoxy)propionamide (7b)
From compound **6b** (170 mg, 0.75 mmol), $SOCl_2$ (0.69 mL), and toluene (3 mL); reflux, 2 h; NH_4OH (32%, 105 μL) in toluene (2 mL), 1 h; yield: 150 mg (89%); brown oil (crystallized upon standing).

2-Methyl-2-(4-methyl-2-nitrophenoxy)propionamide (7c)
From compound **6c** (416 mg, 1.74 mmol), $SOCl_2$ (1.6 mL), and toluene (3 mL); reflux, 2 h; NH_4OH (32%, 242 μL) in toluene (2 mL), 1 h; yield: 390 mg (94%); yellow oil (crystallized upon standing).

2-Methyl-2-(5-methyl-2-nitrophenoxy)propionamide (7d)
From compound **6d** (243 mg, 1.02 mmol), $SOCl_2$ (0.92 mL), and toluene (3 mL); reflux, 1.5 h; NH_4OH (32%, 141 μL) in toluene (2 mL), 1 h; yield: 230 mg (95%); brown oil (crystallized upon standing).

2-Methyl-2-(5-fluoro-2-nitrophenoxy)propionamide (7e)
From compound **6e** (302 mg, 1.24 mmol), $SOCl_2$ (1.13 mL), and toluene (3 mL); reflux, 2 h; NH_4OH (32%, 173 μL) in toluene (2 mL), 1 h; yield: 130 mg (43%); yellow oil.

2-Methyl-2-(4-chloro-5-methyl-2-nitrophenoxy)propionamide (7f)
From compound **6f** (215 mg, 0.79 mmol), $SOCl_2$ (0.71 mL), and toluene (3 mL); reflux, 1.5 h; NH_4OH (32%, 109 μL) in toluene (2 mL), 1 h; yield: 210 mg (98%); yellow oil (crystallized upon standing).

2-Methyl-1-[(2-nitro-4-trifluoromethylphenyl)amino]propan-2-ol (8a); Typical Procedures
*Method A; from **7a***: To a solution of compound **7a** (131 mg, 0.45 mmol) in THF (1.5 mL) was added borane/dimethyl sulfide complex (127 μL, 1.34 mmol) at r.t. and the reaction mixture was stirred for 1 h at 70 °C. The mixture was cooled to 0 °C and cautiously treated with conc. aq HCl (pH 1–2). The mixture was rendered basic with 2 M aq NaOH solution and extracted with EtOAc. The combined organic layers were successively washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (12 g silica gel, eluent: Et_2O–petroleum ether, 2:3) to yield **8a** (87 mg, 70%) as a yellow solid; mp 77 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.59 (t, 1 H, NH), 8.32 (d, 1 H, ^4J = 2.3 Hz, 3′-H), 7.77 (dd, 1 H, ^3J = 9.3 Hz, ^4J = 2.3 Hz, 5′-H), 7.3 (d, 1 H, ^3J = 9.3 Hz, 6′-H), 4.88 (s, 1 H, OH), 3.34 (d, 2 H, ^3J = 5.3 Hz, CH_2), 1.21 (s, 6 H, 2 CH_3).

HRMS: *m*/*z* calcd for $C_{11}H_{13}F_3N_2O_3$: 278.0878; found: 278.0872.

*Method B; from **3a***: To a solution of compound **3a** (35 mg, 0.12 mmol) in THF (1.5 mL) was added borane/dimethyl sulfide complex (35 μL, 0.36 mmol) and the reaction mixture was stirred for 1 h at 60 °C. The mixture was cooled and cautiously treated with conc. aq HCl (pH 1–2). The mixture was rendered basic with 2 M aq NaOH solution and extracted with EtOAc. The combined organic layers were successively washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (12 g silica gel, eluent: Et_2O–petroleum ether, 2:8) to yield **8a** (20 mg, 60%) as a yellow oil (crystallized upon standing).

2-Methyl-1-[(2-nitrophenyl)amino]propan-2-ol (8b)
From compound **7b** (100 mg, 0.45 mmol), borane/dimethyl sulfide complex (127 μL, 1.34 mmol), and THF (1.5 mL); 70 °C, 1 h; purification: column chromatography (12 g silica gel, eluent: Et_2O–petroleum ether, 2:3); yield: 34 mg (36%); yellow solid; mp 81.5 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.31 (t, 1 H, NH), 8.06 (dd, 1 H, ^3J = 8.6 Hz, ^4J = 1.6 Hz, 3′-H), 7.52 (m, 1 H, 5′-H), 7.07 (d, 1 H, ^3J = 8.7 Hz, 6′-H), 6.67 (m, 1 H, 4′-H), 4.81 (s, 1 H, OH), 3.25 (d, 2 H, ^3J = 5.2 Hz, CH_2), 1.21 (s, 6 H, 2 CH_3).

HRMS: *m*/*z* calcd for $C_{10}H_{14}N_2O_3$: 210.1004; found: 210.1004.

2-Methyl-1-[(4-methyl-2-nitrophenyl)amino]propan-2-ol (8c)
From compound **7c** (100 mg, 0.42 mmol), borane/dimethyl sulfide complex (120 μL, 1.26 mmol), and THF (1.5 mL); 65 °C, 1.5 h; purification: column chromatography (12 g silica gel, eluent: Et_2O–petroleum ether, 2:3); yield: 50 mg (53%); red oil.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.22 (t, 1 H, NH), 7.87 (d, 1 H, ^4J = 2.1 Hz, 3′-H), 7.37 (dd, 1 H, ^3J = 8.8 Hz, ^4J = 2.1 Hz, 5′-H), 7.01 (d, 1 H, ^3J = 8.8 Hz, 6′-H), 4.78 (s, 1 H, OH), 3.23 (d, 2 H, ^3J = 5.2 Hz, CH_2), 2.22 (s, 3 H, CH_3), 1.19 (s, 6 H, 2 CH_3).

HRMS: *m*/*z* calcd for $C_{11}H_{16}N_2O_3$: 224.1161; found: 224.1159.

2-Methyl-1-[(5-methyl-2-nitrophenyl)amino]propan-2-ol (8d)
From compound **7d** (97 mg, 0.41 mmol), borane/dimethyl sulfide complex (116 μL, 1.22 mmol), and THF (1.5 mL); 65 °C, 1.5 h; purification: column chromatography (12 g silica gel, eluent: Et_2O–petroleum ether, 2:3); yield: 20 mg (22%); yellow solid; mp 127 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.34 (t, 1 H, NH), 7.96 (d, 1 H, ^4J = 8.8 Hz, 3′-H), 6.88 (d, 1 H, 6′-H), 6.5 (dd, 1 H, ^3J = 8.8 Hz, 4′-H), 4.81 (s, 1 H, OH), 3.24 (d, 2 H, ^3J = 5 Hz, CH_2), 2.3 (s, 3 H, CH_3), 1.21 (s, 6 H, 2 CH_3).

HRMS: *m*/*z* calcd for $C_{11}H_{16}N_2O_3$: 224.1161; found: 224.1159.

2-Methyl-1-[(5-fluoro-2-nitrophenyl)amino]propan-2-ol (8e)
From compound **7e** (100 mg, 0.41 mmol), borane/dimethyl sulfide complex (117 μL, 1.24 mmol), and THF (1.5 mL); 65 °C, 1.5 h; purification: column chromatography (12 g silica gel, eluent: Et_2O–petroleum ether, 2:3); yield: 44 mg (47%); yellow solid; mp 101 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.44 (t, 1 H, NH), 8.17 (dd, 1 H, ^3J = 9.6 Hz, $^4J_{H,F}$ = 6.4 Hz, 3′-H), 6.91 (dd, 1 H, $^3J_{H,F}$ = 12.4 Hz, ^4J = 2.7 Hz, 6′-H), 6.52 (m, 1 H, 4′-H), 4.83 (s, 1 H, OH), 3.25 (d, 2 H, ^3J = 5.3 Hz, CH_2), 1.19 (s, 6 H, 2 CH_3).

HRMS: *m*/*z* calcd for $C_{10}H_{13}FN_2O_3$: 228.0910; found: 228.0913.

2-Methyl-1-[(4-chloro-5-methyl-2-nitrophenyl)amino]propan-2-ol (8f)
From compound **7f** (110 mg, 0.40 mmol), borane/dimethyl sulfide complex (115 μL, 1.21 mmol), and THF (1.5 mL); 65 °C, 1.5 h; purification: column chromatography (12 g silica gel, eluent: Et_2O–petroleum ether, 2:3); yield: 49 mg (47%); yellow solid; mp 123 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.3 (t, 1 H, NH), 8.03 (s, 1 H, 3′-H), 7.13 (s, 1 H, 6′-H), 4.83 (s, 1 H, OH), 3.27 (d, 2 H, ^3J = 5.2 Hz, CH_2), 2.33 (s, 3 H, CH_3), 1.2 (s, 6 H, 2 CH_3).

HRMS: *m*/*z* calcd for $C_{11}H_{15}ClN_2O_3$: 258.0771; found: 258.0767.

4-Hydroxy-2,2-dimethyl-6-trifluoromethyl-4*H*-1,4-benzoxazin-3-one (9)
Method A: To a solution of **7a** (300 mg, 1.03 mmol) in EtOH (3 mL) was added $SnCl_2 \cdot 2H_2O$ (1.16 g, 5.13 mmol) and the reaction mixture was stirred for 1 h at 70 °C. The mixture was cooled, rendered basic with sat. aq $NaHCO_3$ solution and the precipitate was filtered off and washed with EtOH and EtOAc. The filtrate was concentrated in vacuo and extracted with EtOAc. The organic layer was successively washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo to give **9** (226 mg, 84%) as a pale-brown solid; mp 130 °C.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 11.07 (s, 1 H, OH), 7.45–7.35 (m, 2 H, 5-H, 7-H), 7.18 (d, 1 H, 8-H), 1.49 (s, 6 H, 2 CH_3).

Method B: Compound **7a** (200 mg, 0.68 mmol) was hydrogenated at r.t. overnight using Pd/C in THF (10 mL). The mixture was filtered through Kieselguhr and rinsed with THF, and the filtrate was subsequently evaporated. The residue was purified by column chromatography (12 g silica gel, eluent: petroleum ether–EtOAc, 9:1); yield: 125 mg (70%).

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