Regiospecific Synthesis of Substituted Nitrofluorenes and Aminofluorenes with the Negishi Coupling Reaction as Key Step

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Received 21 December 1998; revised 13 March 1999

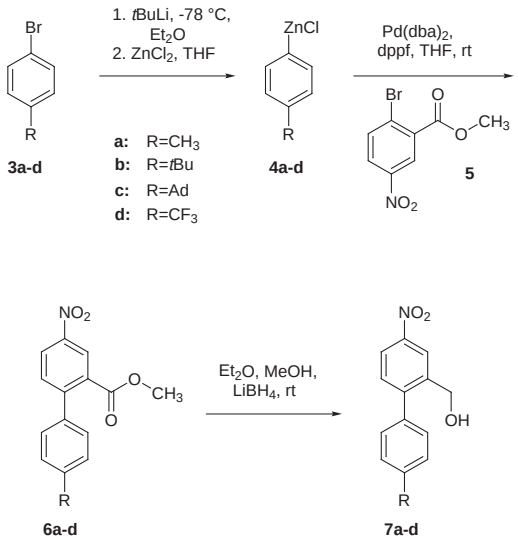
Abstract: A short regiospecific route to 7-alkyl/CF_3 substituted 2-nitrofluorenes and 2-aminofluorenes is described. The synthesis takes advantage of the palladium(0)-catalysed Negishi coupling of methyl 2-bromo-5-nitrobenzoate with aromatic zinc species, followed by chemoselective ester reduction and acid-promoted ring closure.

Key words: palladium(0) catalysis, Negishi reaction, organozinc species, 2-nitrofluorenes, 2-aminofluorenes

Many aromatic amines, aromatic nitro compounds and other *N*-substituted aromatic hydrocarbons are known to be highly mutagenic and carcinogenic.[1] These compounds are widespread environmental contaminants detectable in tobacco smoke, diesel exhaust emissions, fluids used in photocopying machines and grilled food, but they are also important as industrial intermediates for the production of explosives, dyes and pharmaceuticals. Their mutagenic properties arise from metabolic transformations by mammalian and/or bacterial enzymes to aromatic hydroxylamines followed by transformation into electrophilic derivatives like *O*-acyl-*N*-arylhydroxylamines, which form covalent adducts with DNA.[2] Since these adducts disturb DNA replication, mutations occur more frequently than usual. According to recent QSAR (Quantitative Structure Activity Relationship) investigations[3] the mutagenic potential of *N*-substituted aromatic hydrocarbons is both dependent on the structure of the parent aromatic compound as well as the attached substituents. Electronic energies (E_{HOMO}, E_{LUMO}) and especially hydrophobicity (log P value) have been found to be important factors affecting mutagenicity. Although steric influence of substituents has been invoked by some authors[4] these effects have never been studied systematically.

In order to learn more about steric influence on the mutagenicity of such compounds in the Ames test we were interested in the synthesis of various 7-alkyl and -CF_3 substituted derivatives of the highly mutagenic parent compounds 2-nitrofluorene **1e** and 2-aminofluorene **2e**. Since it is known that impurities (e.g. isomers) can falsify Ames test results significantly high purity samples were needed. Previous syntheses of these compounds have utilised Friedel–Crafts alkylation of fluorene[5] followed by electrophilic nitration and reduction.[6] However, nitration and especially alkylation reactions are generally not regiospecific and lead to isomeric mixtures which have to be separated tediously in time consuming procedures in order to achieve the required level of purity. We have therefore developed a short regiospecific route giving access to isomeric pure 7-alkyl and -CF_3 substituted 2-nitrofluorenes and 2-aminofluorenes in overall good yields.[7]

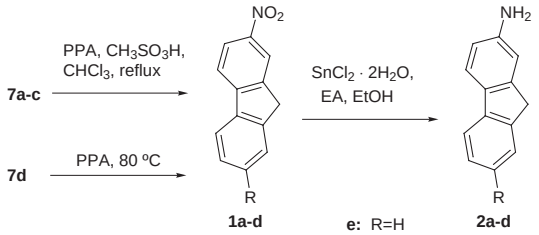
Halide-metal exchange of the substituted bromobenzenes **3a–d** with 2.2 equivalents of *t*-BuLi at –78°C/–100°C in diethyl ether afforded the corresponding lithium species which were transmetallated with anhydrous zinc chloride after exchanging the solvent to THF to give the zincated species **4a–d**[8] (Scheme 1). Cross coupling of **4a–d** with methyl 2-bromo-5-nitrobenzoate **(5)** (prepared by esterification of the commercially available 2-bromo-5-nitrobenzoic acid in 90% yield) at room temperature using $Pd(dba)_2$ (2 mol%) and dppf (2 mol%) as catalyst provided the nitrobiphenyls **6a–d** in 64–76% yield. Chemoselective reduction of the ester function to the alcohols **7a–d**[9] was performed with excess $LiBH_4$ (1.5 – 3 equiv) in a mixed solvent system of diethyl ether/THF and methanol.[10] The possible transformation of the nitro to the amino group was prevented by addition of $LiBH_4$ at 0°C, stirring at this temperature for 1.5 hours and then allowing the mixture to warm up to room temperature.



Scheme 1

Although nitrofluorenes are accessible by Friedel–Crafts cyclization of **7a–d** in the two phase system polyphosphoric acid (PPA)/refluxing $CHCl_3$[7], we found the reaction to

proceed very slowly (e.g. **1b** was synthesized from **7b** in 78% yield by refluxing for 11 days). In contrast modified Eaton conditions[11] (a mixture of PPA, methanesulfonic acid and $CHCl_3$) which allowed to work in homogeneous solution gave the nitrofluorenes **1a–c** in similar yields overnight (Scheme 2). Only compound **7d** containing the strongly deactivating CF_3 group led to completely decomposed material (probably oxidised by methanesulfonic acid). Compound **1d** was obtained in pure PPA at 80°C in moderate yield (44%). Finally, reduction of **1a–d** with $SnCl_2 \cdot 2H_2O$ in refluxing ethyl acetate/EtOH[12] produced the corresponding amines **2a–d** in excellent yields (>90%).



Scheme 2

This method should be applicable for the syntheses of other 7-substituted (e.g. methoxy, fluoro, chloro) 2-nitrofluorenes and 2-aminofluorenes as well.

2-Bromo-5-nitrobenzoic acid, PPA, $LiBH_4$ (2 M in THF) and the substituted bromobenzenes **3a**, **3b**, and **3d,** except 4-(1-adamantyl)-bromobenzene (**3c)** were purchased rom Aldrich. 1-Phenyladamantane[13], bis(dibenzylideneacetone)palladium(0) $[Pd(dba)_2]$[14] and 1,1'-bis(diphenylphosphino)ferrocene (dppf)[15] were prepared according to literature procedures. THF and Et_2O were refluxed over potassium and K/Na alloy respectively and distilled. MeOH, EtOH, EtOAc (EA) and petroleum ether (PE, bp 40-60 °C) were purified by distillation, $CHCl_3$ was used without purification.

Caution! 7-Methyl-2-nitrofluorene **(1a)**, 2-amino-7-methylfluorene **(2a)**, 7-trifluoromethyl-2-nitrofluorene **(1d)** and 7-trifluoromethyl-2-aminofluorene **(2d)** are highly mutagenic and must be handled with care.

In NMR assignments Ψ was used as abbreviation for pseudo.

4-(1-Adamantyl)bromobenzene (3c)

Under ice cooling Br_2 (2.46 g, 15.4 mmol) was added to a solution of 1-phenyladamantane (2.97 g, 14.0 mmol) and pyridine (0.3 mL) in CCl_4 (5 mL). After stirring for 46 h at 30–35°C with exclusion of light, excess Br_2 was removed by washing with aq dilute $NaHSO_3$ solution. The mixture was extracted with CCl_4, the organic layer was washed with brine and H_2O, dried ($MgSO_4$) and evaporated to dryness in vacuo. Chromatography (PE, 300 g silica gel) afforded **3c**; yield: 2.45 g (60%); mp 99–101°C (Lit.[16] mp 101°C). Recovered 1-phenyladamantane was reused for bromination.

^{1}H NMR ($CDCl_3$; 300 MHz): δ = 1.75 (m, 6 H, adamantyl), 1.86 (m, 6 H, adamantyl), 2.08 (m, 3 H, adamantyl), 7.21 (d, 2 H, ^3J = 8.7 Hz, H_{arom}), 7.41 (d, 2 H, ^3J = 8.7 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$; 75 MHz): δ = 28.9, 36.1, 36.7, 43.1, 119.2, 126.8, 131.1, 150.3.

MS (70 eV): *m/z* (%) = 290/292 (M^+,56), 233/235 ($M^+ - C_4H_9$, 22), 154 (234 – Br, 100).

Methyl 2-Bromo-5-nitrobenzoate (5)

A mixture of 2-bromo-5-nitrobenzoic acid (19.7 g, 80.0 mmol), anhyd MeOH (13.0 g, 407 mmol) and 98% H_2SO_4 (0.8 mL) was refluxed for 16 h. The cooled mixture was dissolved in CH_2Cl_2 and neutralized with 2 M NaOH. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated to dryness in vacuo. Recrystallization from EtOAc afforded **5**; yield: 18.7 g (90%); mp 80–81°C (Lit.[17] mp 82°C).

^{1}H NMR ($CDCl_3$; 300 MHz): δ = 3.97 (s, 3 H, OCH_3), 7.85 (d, 1 H, ^3J = 8.7 Hz, H_{arom}), 8.15 (dd, 1 H, ^3J = 8.7 Hz, ^4J = 2.7 Hz, H_{arom}), 8.63 (d, 1 H, ^3J = 2.7 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$; 75 MHz): δ = 52.9, 126.1, 126.4, 128.9, 133.1, 135.5, 146.8, 164.3.

MS (70 eV): *m/z* (%) = 259/261 (M^+, 55), 229 (100), 228 (97), 182/184 ($M^+ - OCH_3$, $- NO_2$, 40).

Methyl 2-(4-Methylphenyl)-5-nitrobenzoate (6a); Typical Procedure

To a solution of 4-bromotoluene (2.59 g, 15.0 mmol) in Et_2O (20 mL) was added slowly *t*-BuLi (1.5 M in pentane, 21.5 mL) with a syringe under argon at –78°C to give a slightly yellow solution. After stirring for 1 h the mixture was warmed to r.t., charged with THF (20 mL) and concentrated under diminished pressure until most of pentane and Et_2O was removed. A solution of anhyd $ZnCl_2$ (2.04 g, 15.0 mmol) in THF (15 mL) was added and the mixture stirred for 1 h. The resulting colourless liquid was treated with a solution of methyl 2-bromo-5-nitrobenzoate (3.37 g, 13.0 mmol), $Pd(dba)_2$ (174 mg) and dppf (166 mg) in THF (50 mL) and stirred at r.t. for 18 h under argon. The mixture was neutralized with 1 M HCl and extracted with Et_2O. After washing with brine and H_2O, the organic layer was dried ($MgSO_4$) and evaporated to dryness in vacuo. Chromatography (PE/EA, 7:1) afforded **6a**; yield: 2.47 g (70%); mp 55–57°C.

^{1}H NMR ($CDCl_3$; 300 MHz) δ = 2.39 (s, 3 H, CH_3), 3.72 (s, 3 H, OCH_3), 7.20 (d, 2 H, ^3J=8.3 Hz, H_{arom}), 7.24 (d, 2 H, ^3J=8.3 Hz, H_{arom}), 7.53 (d, 1 H, ^3J=8.5 Hz, H_{arom}), 8.27 (dd, 1 H, ^3J=8.5 Hz, ^4J=2.5 Hz, H_{arom}), 8.58 (d, 1 H, ^4J=2.4 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 21.2, 52.5, 125.1, 125.6, 128.0, 129.2, 131.9, 132.0, 136.1, 138.6, 146.6, 148.7, 167.0.

MS (70eV): *m/z* (%) = 271 (M^+, 100) 254 ($M^+ - OH$, 4), 240 ($M^+ - OCH_3$, 90), 94 (240 – NO_2, 38), 165 (58).

HRMS (70eV): *m/z* calc. for $C_{15}H_{13}NO_4$ 271.0845, found 271.08144.

Methyl 2-(4-*tert*-Butylphenyl)-5-nitrobenzoate (6b)

Halide-metal exchange was carried out as above in Et_2O (30 mL) with 4-*tert*-butylbromobenzene (3.19 g, 15.0 mmol) and *t*-BuLi (1.5 M in pentane, 21.5 mL) followed by transmetallation with $ZnCl_2$ (2.04 g, 15.0 mmol) in THF (30 mL) and coupling with methyl 2-bromo-5-nitrobenzoate (3.37 g, 13.0 mmol), $Pd(dba)_2$ (175 mg) and dppf (160 mg) in THF (50 mL). Workup and chromatography (PE/EA, 12:1) afforded **6b**; yield: 2.97 g (73%); mp 61–63°C.

^{1}H NMR ($CDCl_3$; 300 MHz) δ = 1.34 (s, 9 H, *t*-C_4H_9), 3.71 (s, 3 H, OCH_3), 7.25 (d, 2 H, ^3J = 8.5 Hz, H_{arom}), 7.44 (d, 2 H, ^3J = 8.5 Hz, H_{arom}), 7.61 (d, 1 H, ^3J = 8.5 Hz, H_{arom}), 8.33 (dd, 1 H, ^3J = 8.5 Hz, ^4J = 2.5 Hz, H_{arom}), 8.64 (d, 1H, ^4J = 2.5 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$; 75 MHz) δ = 31.3, 34.7, 52.5, 125.1, 125.4, 125.6, 127.9, 131.9, 132.0, 136.0, 146.6, 148.6, 151.8, 167.2.

MS (70eV): *m/z* (%) = 313 (M^+, 20), 298 ($M^+ - CH_3$, 100), 268 (298 – NO, 8).[18]

HRMS (70eV): *m/z* calc. for $C_{18}H_{19}NO_4$ 313.1314, found 313.1298.

Methyl 2-(4-(1-Adamantyl)phenyl)-5-nitrobenzoate (6c)
Halide-metal exchange carried out as above in Et_2O (40 mL) with 4-(1-adamantyl)bromobenzene (3.15 g, 10.8 mmol) and *t*-BuLi (1.5 M in pentane, 16 mL) followed by transmetallation with $ZnCl_2$ (1.46 g, 10.8 mmol) in THF (30 mL) and coupling with methyl 2-bromo-5-nitrobenzoate (2.56 g, 9.8 mmol), $Pd(dba)_2$ (60 mg) and dppf (57 mg) in THF (20 mL) afforded after workup and chromatography (cyclohexane/CH_2Cl_2, 1:1) **6c**; yield: 2.45 g (64%); mp 75–77°C.

^{1}H NMR ($CDCl_3$; 300 MHz) δ = 1.77 (m, 6 H, adamantyl), 1.93 (m, 6 H, adamantyl), 2.10 (m, 3 H, adamantyl), 3.70 (s, 3 H, OCH_3), 7.26 (d, 2 H, ^3J = 8.5 Hz, H_{arom}), 7.42 (d, 2 H, ^3J = 8.5 Hz, H_{arom}), 7.55 (d, 1 H, ^3J = 8.5 Hz, H_{arom}), 8.32 (dd, 1 H, ^3J = 8.5 Hz, ^4J = 2.5 Hz, H_{arom}), 8.58 (d, 1 H, ^4J = 2.4 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$; 100 MHz) δ = 28.9, 36.3, 36.8, 43.1, 52.5, 125.0, 125.0, 125.5, 127.9, 131.9, 132.1, 136.0,146.6, 148.6, 152.0, 167.6.

MS (70eV): *m/z* (%) = 391 (M^+, 100), 334 ($M^+ - C_4H_9$, 15), 302 (334 – CH_3OH, 75), 256 (302 – NO_2, 20).

HRMS (70eV): *m/z* calc. for $C_{24}H_{25}NO_4$ 391.1784, found 391.1792.

Methyl 5-Nitro-2-(4-trifluoromethylphenyl)benzoate (6d)
Halide-metal exchange was carried out as described above at –100°C in Et_2O (40 mL) with 4-trifluoromethylbromobenzene (11.3 mmol, 2.54 g) and *t*-BuLi (1.5 M in pentane, 16.5 mL) followed by transmetallation with $ZnCl_2$ (1.53 g, 11.3 mmol) in THF (30 mL) and coupling with methyl 2-bromo-5-nitrobenzoate (2.60 g, 10.0 mmol), $Pd(dba)_2$ (120 mg) and dppf (114 mg) in THF (20 mL). Workup and chromatography (PE/EA, 8:1 → 4:1) afforded **6d**; yield: 2.47 g (76%); mp 90–91°C.

^{1}H NMR ($CDCl_3$; 300 MHz) δ = 3.73 (s, 3 H, OCH_3), 7.41 (d, 2 H, ^3J = 8.1 Hz, H_{arom}), 7.53 (d, 2 H, ^3J = 8.5 Hz, H_{arom}), 7.69 (d, 1 H, ^3J = 8.1 Hz, H_{arom}), 8.39 (dd, 1 H, ^3J = 8.5 Hz, ^4J = 2.2 Hz, H_{arom}), 8.76 (d, 1 H, ^4J = 2.2 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$; 75 MHz) δ = 52.4, 123.9 [q, ^1J(CF) = 272.0 Hz], 125.10 [q, ^3J(CF) = 3.8 Hz], 125.3, 125.8, 130.2 [q, ^2J(CF) = 32.2 Hz], 131.6, 131.9, 142.7, 147.1 ,147.3, 165.8.

MS (70eV): *m/z* (%) = 325 (M^+, 60), 294 ($M^+ - OCH_3$, 100), 248 (294 – NO_2, 31), 228 (25).

HRMS (70eV): *m/z* calc. for $C_{15}H_{10}NO_4F_3$ 325.0562, found 325.0564.

2-(4-Methylphenyl)-5-nitrobenzyl Alcohol (7a); Typical Procedure
To a cooled (0°C) solution of **6a** (1.80 g, 6.65 mmol) in Et_2O (40 mL) under argon was injected MeOH (0.80 mL, 19.7 mmol) followed by slow dropwise addition of $LiBH_4$ (9.96 mL, 19.9 mmol, 2 M in THF) leading to gas evolution. After stirring for 1.5 h the clear solution was warmed to r.t. and stirred until TLC showed complete conversion. The reaction was quenched with H_2O and neutralized with 1 M HCl at 0°C (gas evolution). The mixture was extracted with Et_2O, the organic layer dried ($MgSO_4$) and evaporated to dryness in vacuo. Chromatography (PE/EA, 3:1) afforded **7a**; yield: 1.39 g (86%); mp 79–81°C.

^{1}H NMR ($CDCl_3$; 300 MHz) δ = 2.08 (t, 1 H, ^3J = 5.5 Hz, OH), 2.40 (s, 3 H, CH_3), 4.61 (d, 2 H, ^3J = 5.4 Hz, CH_2), 7.20 (d, 2 H, ^3J = 8.1 Hz, H_{arom}), 7.25 (d, 2 H, ^3J = 8.1 Hz, H_{arom}), 7.38 (d, 1H, ^3J = 8.4 Hz, H_{arom}), 8.13 (dd, 1 H, ^3J = 8.4 Hz, ^4J = 2.4 Hz, H_{arom}), 8.45 (d, 1 H, ^4J = 2.4 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 21.2, 62.3, 122.2, 122.9, 128.5, 129.3, 130.9, 135.6, 138.4, 140.1, 147.4[20].

MS (70eV): *m/z* (%) = 243 (M^+, 100), 225 ($M^+ - H_2O$, 26), 179 (225 – NO_2, 60).

HRMS (70eV): *m/z* calc. for $C_{14}H_{13}NO_3$ 243.0895, found 243.0897.

2-(4-*t*Butylphenyl)-5-nitrobenzyl alcohol (7b)
The reduction of **6b** (1.35 g, 4.30 mmol) was carried out in Et_2O (60 mL) with MeOH (0.26 mL) and $LiBH_4$ (3.23, 6.45 mmol). Workup afforded **7b** (one spot in TLC); yield: 1.21 g (99%); mp 97–98°C.

^{1}H NMR ($CDCl_3$; 300 MHz) δ = 1.38 (s, 9 H, *t*-C_4H_9), 1.86 (br s, 1 H, OH), 4.64 (s, 2 H, CH_2), 7.25 (d, 2 H, ^3J = 8.7 Hz, H_{arom}), 7.40 (d, 2 H, ^3J = 8.5 Hz, H_{arom}), 7.46 (d, 1 H, ^3J = 8.5 Hz, H_{arom}), 8.15 (dd, 1 H, ^3J = 8.4 Hz, ^4J = 2.4 Hz, H_{arom}), 8.47 (d, 1 H, ^4J = 2.4 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 31.3, 34.7, 62.4, 122.3, 123.0, 125.6, 128.4, 131.0, 135.6, 140.1, 147.4,[20] 151.6.

MS (70eV): *m/z* (%) = 285 (M^+, 27), 270 ($M^+ - CH_3$, 100), 268 (M^+ – OH, 39), 254 (11), 224 (270 – NO_2, 16).

HRMS (70eV): *m/z* calc. for $C_{17}H_{19}NO_3$ 285.1365, found 285.1362.

2-(4-(1-Adamantyl)phenyl)-5-nitrobenzyl alcohol (7c)
The reduction of **6c** (1.44 g, 3.68 mmol) was carried out in a mixture of Et_2O (60 mL) and THF (10 mL) with MeOH (0.44 mL, 5.79 mmol) and $LiBH_4$ (2.8 mL, 5.79 mmol). Workup afforded **7c** (one spot in TLC); yield: 1.21 g (90%); mp 139–140°C.

^{1}H NMR (CD_2Cl_2; 200 MHz) δ = 1.81 (m, 6 H, adamantyl), 1.97 (m, 6 H, adamantyl), 2.00 (br s, 1 H, OH), 2.12 (m, 3 H, adamantyl), 4.69 (s, 2 H, CH_2), 7.29 (d, 2 H, ^3J = 8.1 Hz, H_{arom}), 7.43 (d, 1 H, ^3J = 8.1 Hz, H_{arom}), 7.47 (d, 2 H, ^3J = 8.4 Hz, H_{arom}), 8.15 (dd, 1 H, ^3J = 8.4 Hz, ^4J = 2.4 Hz, H_{arom}), 8.45 (d, 1 H, ^4J = 2.4 Hz, H_{arom}).

^{13}C NMR (CD_2Cl_2; 75 MHz) δ = 29.2, 36.3, 36.8, 43.2, 62.3, 122.2, 122.8, 125.2,[20] 128.6,[20] 131.0, 135.8, 140.5, 147.5,[20] 151.9.

MS (70eV): *m/z* (%) = 363 (M^+,56), 306 ($M^+ - C_4H_9$, 11), 288 (306 – H_2O,4), 242 (288 – NO_2, 44).

HRMS (70eV): *m/z* calc. for $C_{23}H_{25}NO_3$ 363.1834, found 363.1839.

5-Nitro-2-(4-trifluoromethylphenyl)benzyl alcohol (7d)
The reduction of **6d** (1.56 g, 4.79 mmol) was carried out in Et_2O (25 mL) with MeOH (0.29 mL) and $LiBH_4$ (3.6 mL, 7.19 mmol). Workup and chromatography (PE/EA, 3:1) afforded **7d**; yield: 1.31 g (92%); mp 85–86°C.

^{1}H NMR ($CDCl_3$; 300 MHz) δ = 2.03 (br s, 1 H, OH), 4.64 (s, 2 H, CH_2), 7.41 (d, 1 H, ^3J = 8.4 Hz, H_{arom}), 7.47 (d, 2 H, ^3J = 8.1 Hz, H_{arom}), 7.72 (d, 2 H, ^3J = 8.1 Hz, H_{arom}), 8.19 (dd, 1 H, ^3J = 8.4 Hz, ^4J = 2.5 Hz, H_{arom}), 8.49 (d, 1 H,^4J = 2.5 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$; 100 MHz) δ = 62.1, 122.5, 123.3, 123.9 [q, ^1J(CF) = 272.0 Hz], 125.7 [q, ^3J(CF) = 3.8 Hz], 129.2, 130.7 [q, ^2J(CF) = 32.5 Hz], 130.8, 140.1, 142.2, 145.9, 148.0.

MS (70eV): *m/z* (%) = 297 (M^+, 100), 279 ($M^+ - H_2O$, 39), 251 (M^+ – NO_2, 25), 233 (279 – NO_2, 78).

HRMS (70eV): *m/z* calc. for $C_{14}H_{10}NO_3F_3$ 297.0613, found 297.0603.

7-Methyl-2-nitrofluorene (1a); Typical Procedure
To a mixture of PPA (5.5 g) in $MeSO_3H$ (19 mL) was added **7a** (0.850 g, 3.49 mmol) in $CHCl_3$ (40 mL). The homogeneous mixture was refluxed with stirring until TLC showed complete conversion. After addition of $CHCl_3$ (100 mL) the mixture was neutralized with NaOH while cooling in ice. The organic layer was washed several times with H_2O, dried ($MgSO_4$) and evaporated to dryness in vacuo.

Chromatography (cyclohexane/CH_2Cl_2, 2:1) afforded **1a**; yield: 0.597 g (76%); mp 180–182°C (Lit.[6] mp 180–181°C)

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.45 (s, 3 H, CH_3), 3.93 (s, 2 H, CH_2), 7.27 (d, 1 H, ^3J = 7.8 Hz, H_{arom}), 7.41 (Ψs, 1 H, H_{arom}), 7.73 (d, 1 H, ^3J = 7.8 Hz, H_{arom}), 7.79 (d, 1 H, ^3J = 8.4 Hz, H_{arom}), 8.26 (dd, 1 H, ^3J = 8.4 Hz, ^4J = 2.1 Hz, H_{arom}), 8.35 (Ψs, 1 H, H_{arom}).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 21.8, 36.8, 119.4, 120.4, 121.1, 123.1, 126.1, 128.4, 136.9, 139.2, 143.7, 145.2, 146.4, 148.2.

MS (70eV): *m/z* (%) = 225 (M^+, 95), 179 ($M^+ - NO_2$, 98) 178 (179 – H, 100).

HRMS (70eV): *m/z* calc. for $C_{14}H_{11}NO_2$ 225.0790, found 225.0796.

7-*tert*-Butyl-2-nitrofluorene (1b)

Reaction of **7b** (0.623 g, 2.18 mmol) with PPA (3.7 g) in $MeSO_3H$ (12 mL) and $CHCl_3$ (40 mL) gave after workup and chromatography (cyclohexane/CH_2Cl_2, 2:1) **1b**; yield: 0.420 g (72%); mp 189–191°C (subl.).

^{1}H NMR ($CDCl_3$; 300 MHz) δ = 1.37 (s, 9 H, *t*-C_4H_9), 3.96 (s, 2 H, CH_2), 7.49 (dd, 1 H, ^3J = 8.1 Hz, ^4J = 1.7 Hz, H_{arom}), 7.64 (Ψs, 1 H, H_{arom}), 7.77 (d, 1 H, ^3J = 8.1 Hz, H_{arom}), 7.81 (d, 1 H, ^3J = 8.4 Hz, H_{arom}), 8.26 (dd, 1 H, ^3J = 8.4 Hz, ^4J = 2.2 Hz, H_{arom}), 8.36 (Ψs, 1 H, H_{arom}).

^{13}C NMR ($CDCl_3$; 75 MHz) δ = 31.5, 35.1, 37.0, 119.5, 120.4, 120.9, 122.3, 123.1, 124.8, 136.9, 144.0, 144.9, 146.5, 148.2, 152.6.

MS (70eV): *m/z* (%) = 267 (M^+, 28), 252 ($M^+ - CH_3$, 100), 206 (252 – NO_2, 15).

HRMS (70eV): *m/z* calc. for $C_{16}H_{17}NO_2$ 267.1259, found 267.1258.

7-(1-Adamantyl)-2-nitrofluorene (1c)

Compound **7c** (0.974 g, 2.68 mmol) was reacted with PPA (4.6 g) in $MeSO_3H$ (14 mL) and $CHCl_3$ (40 mL). Workup and chromatography (cyclohexane/CH_2Cl_2, 2:1) afforded **1c**; yield: 0.638 g (69%); mp >230°C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.79 (m, 6 H, adamantyl), 1.96 (m, 6 H, adamantyl), 2.12 (m, 3 H, adamantyl), 3.96 (s, 2 H, CH_2), 7.46 (Ψd, 1 H, ^3J = 8.6 Hz, H_{arom}), 7.61 (Ψs, 1 H, H_{arom}), 7.79 (d, 1 H, ^3J = 8.2 Hz, H_{arom}), 7.80 (d, 1 H, ^3J = 8.4 Hz, H_{arom}), 8.26 (dd, 1 H, ^3J = 8.4 Hz, ^4J = 2.1 Hz, H_{arom}), 8.36 (Ψs, 1 H, H_{arom}).

^{13}C NMR ($CDCl_3$; 100 MHz) δ = 26.9, 28.9, 36.7, 37.0, 43.3, 119.5, 120.4, 120.9, 121.9, 123.2, 124.4, 137.0, 144.0, 145.0, 146.4, 148.3, 152.9.

MS (70eV): *m/z* (%) = 345 (M^+, 100), 288 ($M^+ - C_4H_9$, 38) 251 (21), 242 (288 – NO_2, 48) 135 (33).

HRMS (70eV): *m/z* calc. for $C_{23}H_{23}NO_2$ 345.1729, found 345.1728.

2-Nitro-7-trifluoromethylfluorene (1d)

Compound **7d** (1.00 g, 3.36 mmol) was dissolved in $CHCl_3$ (5 mL) and PPA (11.0 g) was added. The mixture was heated to 80°C under argon for 16 h. Workup and chromatography (cyclohexane/CH_2Cl_2, 3:1) afforded **1d**; yield: 0.431g (46%); mp 180–182°C (subl.).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.1 (s, 2 H, CH_2), 7.71 (Ψd, 1 H, ^3J = 8.6 Hz, H_{arom}), 7.86 (Ψs, 1 H, H_{arom}), 7.92 (d, 1 H, ^3J = 8.8 Hz, H_{arom}), 7.95 (d, 1 H, ^3J = 8.8 Hz, H_{arom}), 8.32 (dd, 1 H, ^3J = 8.8 Hz, ^4J = 1.8 Hz, H_{arom}), 8.43 (Ψs, 1 H, H_{arom}).

^{13}C NMR ($CDCl_3$; 100 MHz) δ = 37.0, 120.6, 120.8, 121.5, 122.3, 123.3 [q ^3J(CF) = 3.8 Hz], 124.2 [q ^1J(CF) = 272.4 Hz], 124.7 [q ^3J(CF) = 3.7 Hz], 130.6 [q ^2J(CF) = 32.3 Hz], 142.7, 144.5, 144.9, 146.3, 147.6.

MS (70eV): *m/z* (%) = 279 (M^+, 92), 262 (M^+, 42), 249 (M^+ – NO, 18), 233 ($M^+ - NO_2$, 100).

HRMS (70eV): *m/z* calc. for $C_{14}H_8NO_2F_3$ 279.0508, found 279.0503.

2-Amino-7-methylfluorene (2a); Typical Procedure

A mixture of **1a** (0.420 g, 1.86 mmol) and $SnCl_2 \cdot 2H_2O$ (2.10 g, 9.32 mmol) in EtOH (15 mL) and EtOAc (15 mL) was heated to 70°C under argon until the starting material had disappeared according to TLC (up to 10 h). The cooled solution was poured onto ice and the pH was made slightly basic by addition of $NaHCO_3$ solution to form SnO_2 (aq). After extraction with EtOAc the organic layer was thoroughly washed with H_2O and brine,[19] dried ($MgSO_4$) and evaporated to dryness in vacuo. Chromatography (PE/EA, 2:1) afforded **2a**; yield: 0.348 g (96%); mp 106–107°C (Lit.[6] 105–106°C).

^{1}H NMR (CD_2Cl_2; 300 MHz) δ = 2.40 (s, 3 H, CH_3), 3.75 (s, 2 H, CH_2), 3.71–3.79 (br s, 2 H, NH_2), 6.67 (dd, 1 H, ^3J = 8.1 Hz, ^4J = 2.1 Hz, H_{arom}), 6.84 (Ψs, 1 H, H_{arom}), 7.13 (Ψd, 1 H, ^3J = 7.7 Hz, H_{arom}), 7.30 (Ψs, 1 H, H_{arom}), 7.51 (d, 1 H, ^3J = 8.1 Hz, H_{arom}), 7.52 (d, 1 H, ^3J = 7.7 Hz, H_{arom}).

^{13}C NMR (CD_2Cl_2; 75 MHz) δ = 21.7, 37.1, 112.1, 114.1, 118.6, 120.6, 126.0, 127.8, 133.2, 135.3, 140.0, 143.1, 145.6, 146.4.

MS (70eV): *m/z* (%) = 195 (M^+, 100), 180 ($M^+ - CH_3$, 47), 165 (M^+ – NH, 12), 152 (13).

HRMS (70eV): *m/z* calc. for $C_{14}H_{13}N$ 315.1048, found 195.1042.

2-Amino-7-*tert*-butylfluorene (2b)

Compound **1b** (0.400 g, 1.50 mmol) was reduced with $SnCl_2 \cdot 2H_2O$ (1.70 g, 7.19 mmol) in EtOH (20 mL) and EtOAc (20 mL). Workup and chromatography ($CHCl_3$) afforded **2b**; yield: 0.327 g (92%); mp 155–157°C (subl.).

^{1}H NMR ($CDCl_3$; 300 MHz) δ = 1.35 (s, 9 H, *t*-C_4H_9), 3.40–3.90 (br s, 2 H, NH_2), 3.78 (s, 2 H, CH_2), 6.67 (dd, 1 H, ^3J = 8.1 Hz, ^4J = 2.2 Hz, H_{arom}), 6.85 (Ψs, 1 H, H_{arom}), 7.34 (Ψd, 1 H, ^3J = 8.1 Hz, H_{arom}), 7.50 (Ψs, 1 H, H_{arom}), 7.51 (d, 1 H, ^3J = 8.1 Hz, H_{arom}), 7.55 (d, 1 H, ^3J = 8.1 Hz, H_{arom})

^{13}C NMR ($CDCl_3$; 75 MHz) δ = 31.6, 34.7, 36.9, 111.9, 113.9, 118.1, 120.3, 121.7, 123.7, 133.1, 139.5, 142.2, 145.2, 145.3, 148.3.

MS (70eV): *m/z* (%) = 237 (M^+, 89), 222 ($M^+ - CH_3$, 100), 193 ($M^+ - C_2H_5$, 22), 180 ($M^+ - C_4H_9$, 33).

HRMS (70eV): *m/z* calc. for $C_{17}H_{19}N$ 237.1517, found 237.1515.

7-(1-Adamantyl)- 2-aminofluorene (2c)

Compound **1c** (0.300 g, 0.868 mmol) was reduced with $SnCl_2 \cdot 2H_2O$ (0.980 g, 4.32 mmol) in EtOH (30 mL) and EtOAc (30 mL). Workup and chromatography (PE/EA, 5:2) afforded **2c**; yield: 0.246 g (90%); mp 228–230°C.

^{1}H NMR ($CDCl_3$; 300 MHz) δ = 1.77 (m, 6 H, adamantyl), 1.95 (m, 6 H, adamantyl), 2.09 (m, 3 H, adamantyl), 3.77 (s, 2 H, CH_2), 3.70–3.79 (br s, 2 H, NH_2), 6.67 (dd, 1 H, ^3J = 8.1 Hz, ^4J = 2.1 Hz, H_{arom}), 6.85 (Ψs, 1 H, H_{arom}), 7.31 (Ψd, 1 H, ^3J = 8.0 Hz, H_{arom}), 7.47 (Ψs, 1 H, H_{arom}), 7.50 (d, 1 H, ^3J = 8.1 Hz, H_{arom}), 7.55 (d, 1 H, ^3J = 8.0 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$; 75 MHz) δ = 29.2, 36.4, 37.0[20], 43.6, 112.0, 114.0, 118.2, 120.5, 121.4, 123.4, 136.6, 139.7, 142.3, 145.4[20], 148.8.

MS (70eV): *m/z* (%) = 315 (M^+, 100), 262 (13), 258 ($M^+ - C_4H_9$, 29).

HRMS (70eV) *m/z* calc. for $C_{23}H_{25}N$ 315.1987, found 315.1992.

2-Amino-7-trifluoromethylfluorene (2d)
Reduction of **1d** (0.220 g, 0.789 mmol) with $SnCl_2 \cdot 2H_2O$ (0.887 g, 3.93 mmol) in EtOH (10 mL) and EtOAc (10 mL) gave after work-up and chromatography ($CHCl_3$) **2d**; yield: 0.186 g (95%); mp 165–167°C.

^{1}H NMR ($CDCl_3$; 400 MHz) δ = 3.7–3.9 (br s, 2 H, NH_2), 3.81 (s, 2 H, CH_2), 6.71 (dd, 1 H, ^3J = 8.1 Hz, ^4J = 2.2 Hz, H_{arom}), 6.86 (Ψs, 1 H, H_{arom}), 7.54–759 (m, 2 H, H_{arom}), 7.62–7.68 (m, 2 H, H_{arom}).

^{13}C NMR ($CDCl_3$; 100 MHz) δ = 36.7, 111.5, 114.2, 118.3, 121.55 [q, ^3J(CF) = 3.9 Hz), 121.5, 124.03 [q, ^3J(CF) = 3.9 Hz], 124.9 [q ,^1J(CF) = 271.6 Hz], 126.8 [q, ^2J(CF) = 31.9 Hz], 131.4, 142.4, 145.6, 145.9, 146.8.

MS (70eV): *m*/*z* (%) = 249 (M^+, 100), 180 ($M^+ - CF_3$, 56), 152 (21).

HRMS (70eV): *m*/*z* calc. for $C_{14}H_{10}NF_3$ 249.0766, found 249.0769.

Acknowledgement

We thank BASF AG for financial support for the Ames-Tests and M. Wrackmeyer and B. Stegemann for synthetic assistance.

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Article Identifier:
1437-210X,E;1999,0,07,1246,1250,ftx,en;Z09698SS.pdf