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An efficient one-pot synthesis of 2-benzylpyrroles and 3-benzylindoles

Ratnesh Sharma, Mangilal Chouhan, Divya Sood and Vipin A. Nair*

One-pot regioselective benzylation of pyrroles and indoles using zirconium tetrachloride is discussed. This has been achieved by *in-situ* generation of di(1*H*-pyrrol-1-yl)zirconium(IV) chloride and di(1*H*-indol-1-yl)zirconium(IV) chloride. It was observed that benzylation reactions of these complexes using *n*-BuLi occurred at C-2 position for pyrrole and C-3 for indole.

Keywords: benzylation; zirconium(IV) chloride; pyrrole; indole

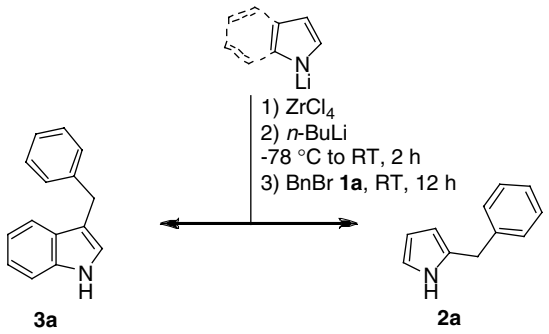
Introduction

Pyrrole and indole rings are found in many structurally diverse natural products and pharmaceutical agents, and new methods for their synthesis and functionalization continue to attract attention.[1–5] The reactions of pyrrole have always been a challenge because of its sensitivity to air and acidic condition.[1] Functional group modification of pharmacophores is one of the most popular methods employed in drug design and development. Often it has been observed that the alkylated molecules show an altered activity as compared with the lead molecule.[6,7] The methodologies available for the synthesis of alkylpyrrole have been dominated by acylation followed by reduction[8–10] since the direct alkylation using acidic condition leads to side reactions. Many alternatives have been developed like tandem alkylation-reduction of 2-acylpyrrole,[11] thermal rearrangement of *N*-alkylpyrrole,[12] pyrrolyl magnesium halide[13,14] and using ionic liquids.[15] These methods have been seriously hampered by poor regioselectivity. Recent reports indicate that ionic liquids are marine toxic[16–18] and also flammable.[19]. The synthesis of alkylindoles is mainly by Friedel Crafts alkylation,[20–22] although other approaches have also been reported.[23–25] Ionic bases such as hydroxides, hydrides and alkan-1-ides react at *N*-1 position[26] whereas the covalent metallic complexes react at C-3.[27–33] Regioselectivity is still a major concern in many of these reactions.

The regioselective alkylation of these heterocycles has thus been an obstinate problem, which defines our interest on C-alkylation of these heterocycles by zirconium complex. As part of our ongoing investigations on metal mediated functionalization reactions, we have recently reported a one-pot synthesis of 2-benzoylpyrroles using zirconium complex.[34] Based on this, an analogous strategy was employed for the C-alkylation of pyrrole and indole, which was found to be successful.

Results and Discussion

The paper discusses a new methodology for the benzylation of pyrrole using benzyl bromide (Scheme 1) in a one-pot reaction by *in-situ* generation of di(1*H*-pyrrol-1-yl)zirconium(IV) chloride. A solution of pyrrole in dry tetrahydrofuran when treated with *n*-butyllithium at −78 °C under nitrogen atmosphere yields lithium pyrrole-1-ide. The solution of lithium pyrrole-1-ide on addition to zirconium(IV) chloride in dry tetrahydrofuran maintained at the same temperature would afford di(1*H*-pyrrol-1-yl)zirconium(IV) chloride. Addition of *n*-butyllithium to this suspension generates carbanion at C-2 position. The reaction mixture was subsequently allowed to attain room temperature and reacted with benzyl bromide to afford 2-benzyl pyrrole. Various substituted benzyl bromides were tried to generalize the scope of the reaction and the yields obtained were good in all the cases (Table 1). The reaction rates were faster with electron-deficient aromatic rings as compared with electron-rich rings. Longer reaction time in the case of electron-rich substrates led to dibenzylation. The success of the strategy prompted us to extrapolate the reaction condition to indole as well. After the *NH* proton, the hydrogen at C-2 is the next most acidic proton on indole. Reactions of *N*-protected indoles with lithium bases results in lithiation exclusively at the C-2 position. Quite interestingly, the di(1*H*-indol-1-yl)zirconium(IV) chloride prepared from *N*-lithiated indole and zirconium(IV) chloride when treated with *n*-butyllithium generated carbanion at C-3 position, which on treatment with substituted



Scheme 1. Synthesis of 2-benzylpyrrole and 3-benzylindole.

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Table 1. Synthesis of 2-benzylpyrroles

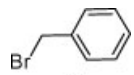
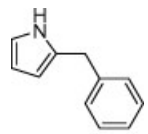
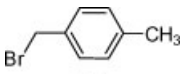
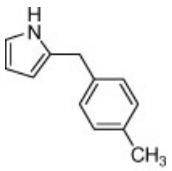
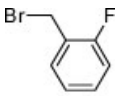
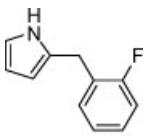
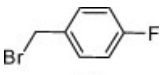
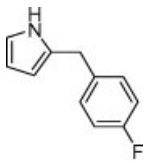
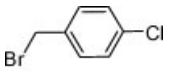
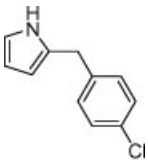
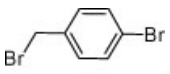
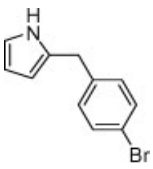
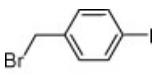
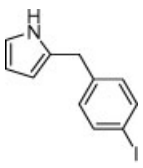
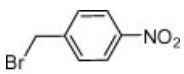
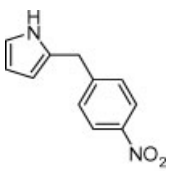
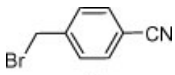
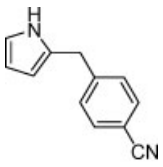
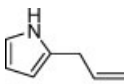
Sample no.	Starting material	Product	Yield (%)
1	 **1a**	 **2a**	79[8]
2	 **1b**	 **2b**	87[8]
3	 **1c**	 **2c**	82
4	 **1d**	 **2d**	64[14]
5	 **1e**	 **2e**	86[8]
6	 **1f**	 **2f**	95
7	 **1g**	 **2g**	90
8	 **1h**	 **2h**	67
9	 **1i**	 **2i**	90

Table 1. (*Continued*)

Sample no.	Starting material	Product	Yield (%)
10	 **1j**	 **2j**	72[32]

benzyl bromides afforded 3-benzylindoles (Table 2). A kinetic study of the reaction suggests that reaction follows a first-order rate equation. The initial phase of the reaction demonstrated an exponential increase in product formation, followed by a gradual increase in yield with time. Since concentration of benzyl bromide did not affect the rate of reaction, the rate-determining step would be the generation of carbanion.

Conclusion

The above strategy afforded 2-benzylpyrroles and 3-benzylindoles with reasonably good yields in a one-pot reaction which had previously been synthesized in 2–3 steps or by using expensive and toxic chemicals.

Experimental

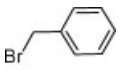
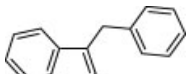
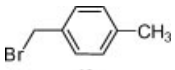
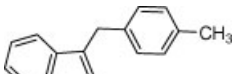
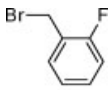
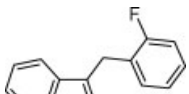
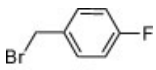
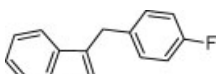
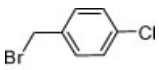
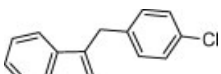
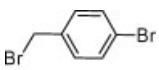
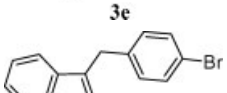
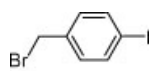
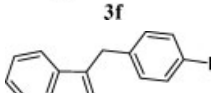
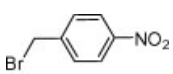
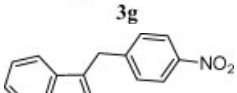
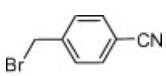
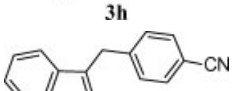
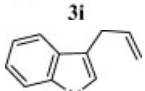
General Procedure for 2-Benzylpyrroles

To a solution of pyrrole (0.5 g, 7.5 mmol) in dry tetrahydrofuran (10 ml), *n*-butyllithium (1.6 M in hexane, 4.7 ml, 7.5 mmol) was added at −78 °C and stirred for 20 min under nitrogen atmosphere. The solution of lithium pyrrole-1-ide was then added to a solution of zirconium(IV) chloride (0.87 g, 3.75 mmol) in dry tetrahydrofuran (10 ml) at −78 °C. It was stirred for additional 20 min and to this suspension *n*-butyllithium (4.7 ml, 7.5 mmol) was added drop-wise and stirred for 10 min. It was allowed to reach RT and stirred for 2 h, followed by the addition of benzyl bromide (3.75 mmol) and stirred for another 12 h at RT. Progress of the reaction was monitored by GCMS. Reaction mixture was quenched with aqueous NH_4Cl solution, filtered through celite, extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to get the crude mixture. The product was isolated from the crude mixture by column chromatography on silica gel (100–200 mesh) using ethyl acetate–hexane mixture as eluent. The product was characterized by spectroscopic methods. The spectral data of compounds **2a, 2b, 2d, 2e** and **2j** have been compared with literature reports.[8,14,32]

2-(2-Fluorobenzyl)-1*H*-pyrrole, 2c

Liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (bs, 1H, Pyrrole–N*H*), 7.21–7.13 (m, 2H, Ar–*H*), 7.06–6.97 (m, 2H, Ar–*H*), 6.65 (d, J = 1.3 Hz, 1H, Pyrrole–*H*), 6.11 (q, J = 2.8 Hz, 1H, Pyrrole–*H*), 6.00–5.97 (m, 1H, Pyrrole–*H*), 3.96 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6 (Ar–*C*), 130.8 (Ar–*C*), 129.4 (pyrrole–*C*), 128.2 (Ar–*C*), 126.9 (Ar–*C*), 124.3 (Ar–*C*), 117.1 (pyrrole–*C*), 115.4 (Ar–*C*), 108.4 (pyrrole–*C*), 106.5 (pyrrole–*C*), 27.3 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{11}H_{10}FN$: 175.08; found: 175.04 [M^+]. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{10}FN$: 176.0876; found: 176.0870.

Table 2. Synthesis of 3-benzylindoles

Sample no.	Starting material	Product	Yield (%)
1	 **1a**	 **3a**	85[23]
2	 **1b**	 **3b**	74
3	 **1c**	 **3c**	76
4	 **1d**	 **3d**	79
5	 **1e**	 **3e**	92[23]
6	 **1f**	 **3f**	93
7	 **1g**	 **3g**	85
8	 **1h**	 **3h**	89
9	 **1i**	 **3i**	90
10	 **1j**	 **3j**	86[32]

2-(4-Bromobenzyl)-1*H*-pyrrole, 2f

Liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (bs, 1H, Pyrrole–N*H*), 7.44 (d, J = 8.4 Hz, 2H, Ar–*H*), 7.09 (d, J = 8.5 Hz, 2H, Ar–*H*), 6.71–6.69 (m, 1H, Pyrrole–*H*), 6.17 (q, J = 2.92 Hz, 1H, Pyrrole–*H*), 6.00–5.99 (m, 1H, Pyrrole–*H*), 3.94 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5 (Ar–*C*), 131.6 (Ar–*C*), 131.2 (Ar–*C*), 130.4 (pyrrole–*C*), 120.2 (pyrrole–*C*), 117.2 (Ar–*C*), 108.5 (pyrrole–*C*), 106.7 (pyrrole–*C*), 33.5 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{11}H_{10}BrN$: 235.00; found: 235.36 [M^+], 237.36 [M^{+2}]. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_{10}BrN$: 236.0075; found: 236.0077.

2-(4-Iodobenzyl)-1*H*-pyrrole, 2g

Liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (bs, 1H, Pyrrole–N*H*), 7.63 (d, J = 8.4 Hz, 2H, Ar–*H*), 6.97 (d, J = 8.4 Hz, 2H, Ar–*H*), 6.67–6.66 (m, 1H, Pyrrole–*H*), 6.15–6.12 (q, J = 2.9 Hz, 1H, Pyrrole–*H*), 5.97–5.96 (m, 1H, Pyrrole–*H*), 3.92 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2 (Ar–*C*), 137.6 (Ar–*C*), 130.7 (Ar–*C*), 129.8 (pyrrole–*C*), 117.2 (pyrrole–*C*), 108.5 (pyrrole–*C*), 106.8 (pyrrole–*C*), 91.5 (Ar–*C*) 33.6 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{11}H_{10}IN$: 282.99; found: 282.94 [M^+]. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_{10}IN$: 283.9936; found: 283.9928.

2-(4-Nitrobenzyl)-1*H*-pyrrole, 2h

Liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.7 Hz, 2H, Ar–*H*), 8.00 (bs, 1H, Pyrrole–N*H*), 7.36 (d, J = 8.7 Hz, 2H, Ar–*H*), 6.75–6.73 (m, 1H, Pyrrole–*H*), 6.19 (q, J = 2.8 Hz, 1H, Pyrrole–*H*), 6.02–6.01 (m, 1H, Pyrrole–*H*), 4.08 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5 (Ar–*C*), 146.6 (Ar–*C*), 129.3 (Ar–*C*), 128.5 (pyrrole–*C*), 123.7 (Ar–*C*), 117.7 (pyrrole–*C*), 108.7 (pyrrole–*C*), 107.4 (pyrrole–*C*), 33.9 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{11}H_{10}N_2O_2$: 202.07; found 202.00 [M^+]. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{11}H_{10}N_2O_2$: 225.0640; found: 225.0631.

4-[(1*H*-Pyrrol-2-yl)methyl]benzonitrile, 2i

Liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (bs, 1H, Pyrrole–N*H*), 7.56 (d, J = 8.0 Hz, 2H, Ar–*H*), 7.29 (d, J = 8.1 Hz, 2H, Ar–*H*), 6.72–6.70 (m, 1H, Pyrrole–*H*), 6.16 (q, J = 2.8 Hz, 1H, Pyrrole–*H*), 5.99–5.96 (m, 1H, Pyrrole–*H*), 4.04 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4 (Ar–*C*), 132.3 (Ar–*C*), 129.3 (Ar–*C*), 128.7 (pyrrole–*C*), 118.9 (Ar–*C*≡N), 117.6 (pyrrole–*C*), 110.2 (Ar–*C*), 108.6 (pyrrole–*C*), 107.3 (pyrrole–*C*), 34.1 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{12}H_{10}N_2$: 182.08; found 182.03 [M^+]. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{10}N_2$: 205.0742; found: 205.0738.

General Procedure for 3-Benzylindoles

To a solution of indole (0.38 g, 3.2 mmol) in dry tetrahydrofuran (5 ml), *n*-butyllithium (1.6 M in hexane, 2 ml, 3.2 mmol) was added at −78 °C and stirred for 20 min under nitrogen atmosphere. The solution of lithium indole-1-ide was then added to a solution of zirconium(IV) chloride (0.37 g, 1.6 mmol) in dry tetrahydrofuran (5 ml) at −78 °C. It was stirred for additional 20 min and to this suspension *n*-butyllithium (2 ml, 3.2 mmol) was added drop-wise and stirred for 10 min. It was allowed to reach RT and stirred for 2 h followed by the addition of benzyl bromide (1.6 mmol). It was allowed to stir for 12 h at RT. Progress of the reaction was monitored by GCMS. The reaction mixture was quenched with aqueous NH_4Cl solution, filtered through celite, extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to get the crude mixture. The product was isolated from the crude mixture by column chromatography on silica gel (100–200 mesh) using ethyl acetate–hexane mixture as eluent. The product was characterized by spectroscopic methods. The spectral data of compounds **3a, 3e** and **3j** have been compared with literature reports.[23,32]

3-(4-Methylbenzyl)-1*H*-indole, 3b

Pink solid. M.p. 78–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (bs, 1H, Indole–N*H*), 7.52 (d, J = 7.8 Hz, 1H, Indole–*H*), 7.33 (d, J = 8.1 Hz, 1H, Indole–*H*), 7.19–7.16 (m, 3H, Ar–*H*, Indole–*H*), 7.09–7.05 (m, 3H, Ar–*H*, Indole–*H*), 6.89 (m, 1H, Indole–*H*), 4.07 (s, 2H, Ar–CH_2), 2.30 (s, 3H, Ar–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1 (Indole–*C*), 136.4 (Ar–*C*), 135.2 (Ar–*C*), 129.0 (Ar–*C*), 128.5 (Ar–*C*), 127.4 (Indole–*C*), 122.2 (Indole–*C*), 122.0 (Indole–*C*), 119.3 (Indole–*C*), 119.1 (Indole–*C*), 116.1 (Indole–*C*), 111.0 (Indole–*C*), 31.1 (Ar–CH_2), 21.0 (Ar–CH_3). MS (EI): *m/z* calcd for $C_{16}H_{15}N$: 221.12; found: 221.15 [M^+]. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{15}N$: 244.1102; found: 244.1089.

3-(2-Fluorobenzyl)-1*H*-indole, 3c

Pink solid. M.p. 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (bs, 1H, Indole–N*H*), 7.56 (d, J = 7.9 Hz, 1H, Indole–*H*), 7.34 (d, J = 8.1 Hz, 1H, Indole–*H*), 7.20–6.94 (m, 7H, Ar–*H*, Indole–*H*), 4.13 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (Ar–*C*), 136.3 (Indole–*C*), 130.8 (Ar–*C*), 130.7 (Ar–*C*), 128.2 (Ar–*C*), 128.0 (Ar–*C*), 127.6 (Indole–*C*), 127.3 (Ar–*C*), 123.9 (Ar–*C*), 122.4 (Indole–*C*), 122.1 (Indole–*C*), 119.4 (Indole–*C*), 119.1 (Indole–*C*), 115.0 (Ar–*C*), 114.2 (Indole–*C*), 111.1 (Indole–*C*), 24.3 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{15}H_{12}FN$: 225.10; found: 225.14 [M^+]. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{12}FN$: 248.0852; found: 248.0880.

3-(4-Fluorobenzyl)-1*H*-indole, 3d

Pink solid. M.p. 103–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (bs, 1H, Indole–N*H*), 7.47 (dd, J = 0.6 Hz, J = 8.1 Hz, 1H, Indole–*H*), 7.36 (dd, J = 0.7 Hz, J = 8.1 Hz, 1H, Indole–*H*), 7.24–7.16 (m, 3H, Ar–*H*, Indole–*H*), 7.07 (m, 1H, Indole–*H*), 6.97–6.90 (m, 3H, Ar–*H*, Indole–*H*), 4.08 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1 (Ar–*C*), 136.7 (Indole–*C*), 136.4 (Ar–*C*), 130.0 (Ar–*C*), 129.9 (Ar–*C*), 127.2 (Indole–*C*), 122.2 (Indole–*C*), 122.1 (Indole–*C*), 119.4 (Indole–*C*), 119.0 (Indole–*C*), 115.7 (Indole–*C*), 115.1 (Ar–*C*), 114.9 (Ar–*C*), 111.1 (Indole–*C*), 30.8 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{15}H_{12}FN$: 225.10; found: 225.08 [M^+], 130.13. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{12}FN$: 226.1032; found: 226.1028.

3-(4-Bromobenzyl)-1*H*-indole, 3f

Pink solid. M.p. 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (bs, 1H, Indole–N*H*), 7.47–7.44 (m, 1H, Indole–*H*) 7.39–7.34 (m, 3H, Ar–*H*), 7.21–7.05 (m, 4H, Indole–*H*, Ar–*H*), 6.92–6.91 (m, 1H, Indole–*H*), 4.08 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1 (Indole–*C*), 136.4 (Ar–*C*), 131.3 (Ar–*C*), 130.4 (Ar–*C*), 127.2 (Indole–*C*), 122.3 (Indole–*C*), 122.1 (Indole–*C*), 119.6 (Ar–*C*), 119.4 (Indole–*C*), 119.0 (Indole–*C*), 115.1 (Indole–*C*), 111.1 (Indole–*C*), 31.0 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{15}H_{12}BrN$: 285.02; found: 285.06 [M^+]. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{12}BrN$: 286.0231; found: 286.0225.

3-(4-Iodobenzyl)-1*H*-indole, 3g

Off-white solid. M.p. 125–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (bs, 1H, Indole–N*H*), 7.57 (d, J = 8.3 Hz, 2H, Ar–*H*), 7.46 (d, J = 7.8 Hz, 1H, Indole–*H*), 7.36 (d, J = 8.1 Hz, 1H, Indole–*H*), 7.21–7.17 (m, 1H, Indole–*H*), 7.09–7.05 (m, 1H, Indole–*H*), 7.02 (d, J = 8.3 Hz, 2H, Ar–*H*) 6.92–6.91 (m, 1H, Indole–*H*), 4.05 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8 (Indole–*C*), 137.3 (Ar–*C*), 136.4 (Ar–*C*), 130.7 (Ar–*C*), 127.2 (Indole–*C*), 122.3 (Indole–*C*), 122.1 (Indole–*C*), 119.4 (Indole–*C*), 119.0 (Indole–*C*), 115.0 (Indole–*C*), 111.1 (Indole–*C*), 90.9 (Ar–*C*), 31.1 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{15}H_{12}IN$: 333.00; found: 333.05 [M^+]. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{12}IN$: 334.0092; found: 334.0083.

3-(4-Nitrobenzyl)-1*H*-indole, 3h

Dark-brown solid. M.p. 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 11.0 Hz, 2H, Ar–*H*), 8.05 (bs, 1H, Indole–N*H*), 7.42–7.36 (m, 4H, Indole–*H*, Ar–*H*), 7.22–7.18 (m, 1H, Indole–*H*), 7.10–7.06 (m, 1H, Indole–*H*), 6.98–6.97 (m, 1H, Indole–*H*), 4.20 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1 (Ar–*C*), 146.4 (Ar–*C*), 136.4 (Indole–*C*), 129.3 (Ar–*C*), 127.0 (Indole–*C*), 123.6 (Ar–*C*), 122.6 (Indole–*C*), 122.4 (Indole–*C*), 119.7 (Indole–*C*), 118.8 (Indole–*C*), 113.8 (Indole–*C*), 111.3 (Indole–*C*), 31.5 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{15}H_{12}N_2O_2$: 252.09; found: 252.08 [M^+]. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{15}H_{12}N_2O_2$: 275.0797; found: 275.0791.

4-[(1*H*-indol-3-yl)methyl]benzonitrile, 3i

Off-white solid. M.p. 139–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (bs, 1H, Indole–N*H*), 7.54 (d, J = 8.3 Hz, 2H, Ar–*H*), 7.42–7.35 (m, 4H, Ar–*H*, Indole–*H*), 7.22–7.18 (m, 1H, Indole–*H*), 7.10–7.06 (m, 1H, Indole–*H*), 6.97–6.96 (m, 1H Indole–*H*), 4.17 (s, 2H, Ar–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9 (Ar–*C*), 136.4 (Indole–*C*), 132.1 (Ar–*C*), 129.3 (Ar–*C*), 127.0 (Indole–*C*), 122.5 (Indole–*C*), 122.3 (Indole–*C*), 119.6 (Indole–*C*), 119.1 (Indole–*C*), 118.8 (Ar–*C*≡N), 113.9 (Indole–*C*), 111.2 (Indole–*C*), 109.7 (Ar–*C*), 31.7 (Ar–CH_2). MS (EI): *m/z* calcd for $C_{16}H_{12}N_2$: 232.10; found: 232.06 [M^+]. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{12}N_2$: 255.0898; found: 255.0890.

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References

[1] G. P. Bean, *Pyrroles*, ed. Jones R. A., Wiley: New York, **1990**, p. 105.
[2] R. J. Sundberg, *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Elsevier: Oxford, **1996**, Vol. 2, p. 119.
[3] G. W. Gribble, *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Elsevier: Oxford, **1996**, Vol. 2, p. 207.
[4] G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875.
[5] T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491.
[6] D. A. Williams, *Foye's Principles of Medicinal Chemistry* (Eds.: T. L. Lemke, D. A. Williams, V. F. Roche, S. W. Zito), Lippincott Williams & Wilkins: Philadelphia, PA, **2008**, *6*, 253.
[7] R. B. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, 2nd edn. Elsevier: Oxford, **2004**, Vol. 2, p. 7.
[8] G. McGillivray, E. Smal, *J. Chem. Soc., Perkin Trans. 1* **1983**, 633.
[9] H.-P. Kaiser, J. M. Muchowski, *J. Org. Chem.* **1984**, *49*, 4203.
[10] R. Greenhouse, C. Ramirez, J. M. Muchowski, *J. Org. Chem.* **1985**, *50*, 2961.
[11] D. P. Schumacher, S. S. Hall, *J. Org. Chem.* **1981**, *46*, 5060.
[12] J. M. Patterson, S. Soedigdo, *J. Org. Chem.* **1968**, *33*, 2057.
[13] F. Knefeli, K. K. Mayer, T. Poettinger, G. Stoeber, W. Wiegrebe, *Arch. Pharm.* **1983**, *316*, 773.
[14] Merck and Tularik, US Patent 6306891, **2001**.
[15] Y. R. Jorapur, C.-H. Lee, D. Y. Chi, *Org. Lett.*, **2005**, *7*, 1231.
[16] C. Pretti, C. Chiappe, D. Pieraccini, M. Gregori, F. Abramo, G. Monni, L. Intorre, *Green Chem.* **2006**, *8*, 238.
[17] D. Zhao, Y. Liao and Z. Zhang, *Clean: Soil, Air, Water* **2007**, *35*, 42.

[18] J. Ranke, S. Stolte, R. Störmann, J. Arning, B. Jastorff, *Chem. Rev.* **2007**, *107*, 2183.
[19] M. Smiglak, W. M. Reichert, J. D. Holbrey, J. S. Wilkes, L. Sun, J. S. Thrasher, K. Kirichenko, S. Singh, A. R. Katritzky, R. D. Rogers, *Chem. Commun.* **2006**, *24*, 2554.
[20] M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199.
[21] M. Zeng, S.-L. You, *Synlett* **2010**, *9*, 1289.
[22] M. Bandini, A. Eichholzer, *Angew. Chem., Int. Ed.* **2009**, *48*, 9608.
[23] S. Whitney, R. Grigg, A. Derrick, A. Keep, *Org. Lett.* **2007**, *9*, 3299.
[24] J. H. Wynne, W. M. Stalick, *J. Org. Chem.* **2002**, *67*, 5850.
[25] P. Wiedenau, S. Blechert, *Synth. Commun.* **1997**, *27*, 2033.
[26] H. Heaney, S. V. Ley, *Org. Synth.* **1974**, *54*, 58.
[27] X. Zhu, A. Ganesan, *J. Org. Chem.* **2002**, *67*, 2705.
[28] S. Kasparek, R. A. Heacock, *Can. J. Chem.* **1967**, *45*, 771.
[29] L. Perez-Serrano, L. Casarrubios, G. Dominguez, G. Freire, J. Perez-Castells, *Tetrahedron* **2002**, *58*, 5407.
[30] J. Bergman, L. Venemalm, *Tetrahedron* **1990**, *46*, 6061.
[31] R. A. Heacock, S. Kasparek, *Adv. Heterocyl. Chem.* **1969**, *10*, 43.
[32] J. S. Yadav, B. V. S. Reddy, P. M. Reddy, C. Srinivas, *Tetrahedron Lett.* **2002**, *43*, 5185.
[33] G. Adam, J. Andrieux, M. Plat, *Tetrahedron* **1985**, *41*, 399.
[34] R. Sharma, M. Chouhan, V. A. Nair, *Tetrahedron Lett.* **2010**, *51*, 2039.

