A Facile Synthesis of 3-[(*N*-Alkylanilino)(aryl)methyl]indoles Using TCT[1]

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Abstract: Three component reaction of indoles, benzaldehydes, and *N*-alkylanilines in the presence of 2,4,6-trichloro-1,3,5-triazine (TCT) afforded the corresponding 3-[(*N*-alkylanilino)(aryl)methyl]indoles at room temperature in high yields (87–95%) within 1 to 2.5 hours.

Key words: 3-[(*N*-alkylanilino)(aryl)methyl]indoles, benzaldehyde, *N*-alkylanilines, TCT

Indoles possess numerous important biological properties including antioxidant, antibacterial, and insecticidal activity;[2] they act as colon cancer cell and tumor growth inhibitors;[3] and they are employed as valuable antibiotics.[2a] Some of indole derivatives occur in bioactive metabolites of terrestrial and marine organisms.[4] Among various derivatives of indoles, 3-substituted indoles have been much studied and several synthetic methods have been developed for the preparation of these compounds.[2a,5] Here we report a convenient method for the synthesis of 3-[(*N*-alkylanilino)(aryl)methyl]indoles starting from indole derivatives using 2,4,6-trichloro-1,3,5-triazine (TCT).

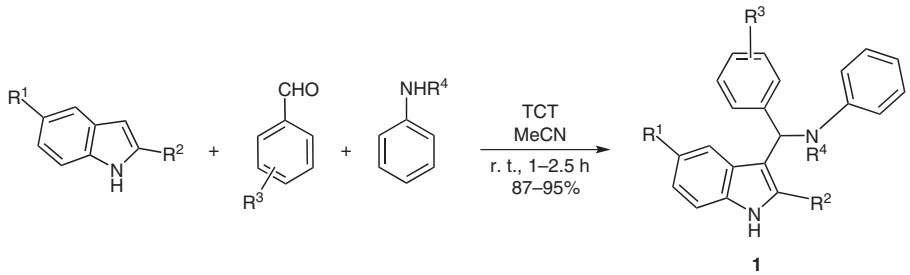
In continuation of our work[6] on the development of useful synthetic methods, we observed that the treatment of indoles with benzaldehydes and *N*-alkylanilines in acetonitrile in the presence of TCT afforded the corresponding 3-[(*N*-alkylanilino)(aryl)methyl]indoles **1** at room temperature (Scheme 1).

A series of 3-[(*N*-alkylanilino)(aryl)methyl]indoles **1a–l** were conveniently prepared using different indoles, benzaldehydes, and *N*-alkyl anilines following the above method (Table 1). The conversion was completed within 1–2.5 hours and the products were formed in high yields (87–95%). 1*H*-Indole, 5-bromo-1*H*-indole, and 2-methyl-1*H*-indole were employed as the indole derivative, benzaldehydes containing both electron-donating and electron-withdrawing groups were used, and different *N*-alkylanilines, such as *N*-methyl-, *N*-ethyl-, and *N*-propylanilines, afforded the desired products in high yields. The *N*-alkylanilines were used in excess to avoid the formation of bis(indolyl)alkanes. Various functional groups such as halogen, hydroxy, ether, and nitro groups remain intact. The structures of the products were confirmed from their

Table 1 Synthesis of 3-[(*N*-Alkylanilino)(aryl)methyl]indoles **1**[a]

Entry	R^1	R^2	R^3	R^4	Product	Time (h)	Yield[b] (%)
1	H	H	H	Me	**1a**	2.5	87
2	H	H	4-NO_2	Me	**1b**	2.0	91
3	H	H	3,4-$(OMe)_2$	Me	**1c**	1.75	90
4	H	Me	4-Cl	Me	**1d**	1.25	94
5	H	H	3,4,5-$(OMe)_3$	Me	**1e**	1.75	87
6	Br	H	3,4,5-$(OMe)_3$	Me	**1f**	1.75	89
7	Br	H	3,4-$(OMe)_2$	Me	**1g**	1.75	90
8	Br	H	4-NO_2	Me	**1h**	2.0	91
9	H	H	3,4-$(OMe)_2$	Et	**1i**	2.0	90
10	H	H	4-NO_2	Et	**1j**	1.0	95
11	H	H	3,4-$(OMe)_2$	Pr	**1k**	2.0	87
12	H	H	3-OH	Pr	**1l**	2.0	88

[a] The structures of the products were determined from their spectral (IR, ^{1}H and ^{13}C NMR, and MS) and analytical data.
[b] Yields of pure isolated products after column chromatography.



Scheme 1

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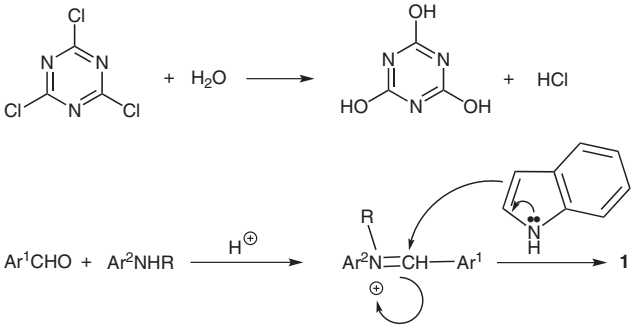
spectral (IR, ^{1}H and ^{13}C NMR, and MS) and analytical data.

TCT is an inexpensive reagent. It reacts[7] with 'incipient moisture' and releases HCl which can catalyze the present conversion. The reagent is easy to handle and is safe compared to concentrated hydrochloric acid. Initially the benzaldehyde reacts with an *N*-alkylaniline to form the corresponding aldimine, which is then attacked by the indole in the presence of HCl to form the 3-[(*N*-alkylanilino)(aryl)methyl]indole (Scheme 2). The conversion did not proceed under perfectly dry reaction conditions. Thus, the experimental procedure becomes simple. Cyanuric acid formed from TCT was washed out with water.



Scheme 2

In conclusion, we have developed a simple and efficient method for the high-yielding synthesis of 3-[(*N*-alkylanilino)(aryl)methyl]indoles by treatment of indoles, benzaldehydes, and *N*-alkylanilines in the presence of TCT at room temperature.

Infrared spectra were recorded using a Perkin-Elmer RX1 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained at 200 MHz and 50 MHz, respectively, using a Varian Gemini 200 MHz spectrometer and $CDCl_3$ as the solvent. Mass spectra (ESI-MS) were recorded using an LC-MSD Trap SL spectrometer. Elemental analyses were performed with an Elementar Vario EL instrument. Column chromatography was carried out over silica gel (BDH 100–200 mesh) and TLC was performed using silica gel GF254 (Merck) plates. The spectral and analytical data of unknown compounds **1c–l** are given. All known compounds had spectroscopic data identical to the literature values, **1a**,[5e] **1b**.[5e]

3-[(*N*-Alkylanilino)(aryl)methyl]indoles 1a–f; General Procedure

To a mixture of a benzaldehyde (1 mmol) and *N*-alkylaniline (2 mmol) in MeCN (5 mL) was added TCT (10 mol%). The mixture was stirred at r.t. for 30 min. Indole (1 mmol) was subsequently added and the mixture was allowed to stir (TLC monitoring) for the time indicated in Table 1. After completion, H_2O (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were concentrated and the residue was subjected to column chromatography (silica gel, hexane–EtOAc) to obtain pure **1**.

3-[(3,4-Dimethoxyphenyl)(*N*-methylanilino)methyl]-1*H*-indole (1c)

Violet solid; yield: 335 mg (90%).

IR (KBr): 3401, 1609, 1513, 1459 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.82 (br s, 1 H), 7.31–7.13 (m, 3 H), 7.11 (t, *J* = 8.0 Hz, 1 H), 7.01–6.84 (m, 3 H), 6.75–6.60 (m, 3 H), 6.52–6.41 (m, 3 H), 5.42 (s, 1 H), 3.82 (s, 3 H), 3.71 (s, 3 H), 2.82 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 152.9, 151.7, 148.0, 147.4, 137.9, 133.3, 130.1, 130.0, 124.2, 122.1, 121.0, 119.9, 119.2, 112.2, 111.0, 110.9, 56.0, 47.5, 29.8.

MS (ESI): *m*/*z* = 373 [M + H]$^+$.

Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.42; H, 6.45; N, 7.53. Found: C, 77.58; H, 6.38; N, 7.61.

3-[(4-Chlorophenyl)(*N*-methylanilino)methyl]-2-methyl-1*H*-indole (1d)

Violet solid; yield: 338 mg (94%).

IR (KBr): 3401, 1685, 1613, 1519, 1487 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.69 (br s, 1 H), 7.21–6.80 (m, 11 H), 6.48 (d, *J* = 8.0 Hz, 2 H), 5.56 (s, 1 H), 2.81 (s, 3 H), 2.03 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 147.5, 144.2, 135.4, 132.2, 132.0, 130.1, 130.0, 129.5, 126.6, 121.0, 120.0, 119.9, 113.4, 111.1, 46.5, 30.8, 29.5.

MS (ESI): *m*/*z* = 361, 363 [M + H]$^+$.

Anal. Calcd for $C_{23}H_{21}ClN_2$: C, 76.56; H, 5.83; N, 7.77. Found: C, 76.68; H, 5.74; N, 7.82.

3-[(*N*-Methylanilino)(3,4,5-trimethoxyphenyl)methyl]-1*H*-indole (1e)

Light red solid; yield: 350 mg (87%).

IR (KBr): 3407, 1591, 1509, 1457, 1420 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.87 (br s, 1 H), 7.30–7.09 (m, 4 H), 7.01–6.90 (m, 3 H), 6.51 (br s, 1 H), 6.48 (d, *J* = 8.0 Hz, 2 H), 6.39 (s, 2 H), 5.44 (s, 1 H), 3.80 (s, 3 H), 3.68 (s, 6 H), 2.81 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 152.8, 148.7, 140.2, 132.1, 129.9, 126.7, 124.3, 121.8, 119.9, 119.8, 119.1, 112.7, 111.1, 106.0, 61.1, 56.0, 48.5, 29.6.

MS (ESI): *m*/*z* = 403 [M + H]$^+$.

Anal. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.63; H, 6.47; N, 6.97. Found: C, 74.52; H, 6.51; N, 6.94.

5-Bromo-3-[(*N*-methylanilino)(3,4,5-trimethoxyphenyl)methyl]-1*H*-indole (1f)

Violet solid; yield: 428 mg (89%).

IR (KBr): 3415, 1590, 1513, 1457, 1221 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.81 (br s, 1 H), 7.37–7.12 (m, 4 H), 6.92 (d, *J* = 8.0 Hz, 2 H), 6.58 (br s, 1 H), 6.51 (d, *J* = 8.0 Hz, 2 H), 6.37 (s, 2 H), 5.39 (s, 1 H), 3.81 (s, 3 H), 3.70 (s, 6 H), 2.81 (s, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.1, 149.2, 140.0, 136.9, 129.9, 127.0, 125.2, 125.0, 122.6, 120.4, 120.0, 112.5, 110.0, 105.9, 61.0, 56.3, 48.1, 29.8.

MS (ESI): *m*/*z* = 481, 483 [M + H]$^+$.

Anal. Calcd for $C_{25}H_{25}BrN_2O_3$: C, 62.37; H, 5.20; N, 5.82. Found: C, 62.45; H, 5.26; N, 5.74.

5-Bromo-3-[(3,4-dimethoxyphenyl)(*N*-methylanilino)methyl]-1*H*-indole (1g)

Light red solid; yield: 406 mg (90%).

IR (KBr): 3410, 1607, 1514, 1434 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.82 (br s, 1 H), 7.32 (s, 1 H), 7.18–7.11 (m, 3 H), 6.95 (d, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 8.0 Hz, 1

H), 6.64 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.57–6.42 (m, 4 H), 5.82 (s, 1 H), 3.69 (s, 3 H), 3.61 (s, 3 H), 2.81 (s, 3 H).

MS (ESI): *m*/*z* = 453, 451 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{23}BrN_2O_2$: C, 63.86; H, 5.10; N, 6.21. Found: C, 63.72; H, 5.15; N, 6.28.

5-Bromo-3-[(*N*-methylanilino)(4-nitrophenyl)methyl]-1*H*-indole (1h)
Light green solid; yield: 397 mg (91%).

IR (KBr): 3410, 1609, 1517, 1442 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.52 (br s, 1 H), 8.13 (d, *J* = 8.0 Hz, 2 H), 7.32–7.15 (m, 6 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 6.51–6.42 (m, 3 H), 5.53 (s, 1 H), 2.82 (s, 3 H).

MS (ESI): *m*/*z* = 438, 436 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{18}BrN_3O_2$: C, 60.55; H, 4.13; N, 9.63. Found: C, 60.68; H, 4.08; N, 9.76.

3-[(3,4-Dimethoxyphenyl)(*N*-ethylanilino)methyl]-1*H*-indole (1i)
Violet solid; yield: 347 mg (90%).

IR (KBr): 3412, 1606, 1512, 1342 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.90 (br s, 1 H), 7.32–7.22 (m, 3 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 7.08–6.92 (m, 3 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 6.71–6.50 (m, 5 H), 5.94 (s, 1 H), 3.71 (s, 3 H), 3.61 (s, 3 H), 3.11 (q, *J* = 7.0 Hz, 2 H), 1.2 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.0, 151.6, 146.5, 137.1, 135.2, 132.8, 129.9, 127.1, 124.2, 121.4, 120.1, 120.0, 119.1, 117.0, 112.5, 111.8, 111.0, 110.9, 56.3, 55.9, 40.8, 38.9, 15.2.

MS (ESI): *m*/*z* = 387 $[M + H]^+$.

Anal. Calcd for $C_{25}H_{26}N_2O_2$: C, 77.72; H, 6.74; N, 7.25. Found: C, 77.68; H, 6.82; N, 7.21.

3-[(*N*-Ethylanilino)(4-nitrophenyl)methyl]-1*H*-indole (1j)
Light yellow solid; yield: 352 mg (95%).

IR (KBr): 3411, 1606, 1516, 1343 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 8.0 Hz, 2 H), 8.04 (br s, 1 H), 7.42–7.33 (m, 4 H), 7.20–7.13 (m, 2 H), 7.03–6.95 (m, 3 H), 6.61–6.52 (m, 3 H), 5.62 (s, 1 H), 3.11 (q, *J* = 7.0 Hz, 2 H), 1.22 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 152.1, 147.3, 140.1, 136.4, 130.8, 130.0, 129.1, 126.4, 124.6, 124.5, 123.7, 122.2, 119.5, 112.4, 111.0, 47.5, 38.3, 14.6.

MS (ESI): *m*/*z* = 372 $[M + H]^+$.

Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.39; H, 5.66; N, 11.32. Found: C, 74.46; H, 5.72; N, 11.38.

3-[(3,4-Dimethoxyphenyl)(*N*-propylanilino)methyl]-1*H*-indole (1k)
Violet solid; yield: 348 mg (87%).

IR (KBr): 3408, 1606, 1512, 1422 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.89 (br s, 1 H), 7.32–7.23 (m, 3 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 7.06–6.91 (m, 3 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 6.71–6.50 (m, 5 H), 5.92 (s, 1 H), 3.72 (s, 3 H), 3.61 (s, 3 H), 3.02 (t, *J* = 7.0 Hz, 2 H), 1.65–1.57 (m, 2 H), 0.99 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.8, 152.2, 148.3, 146.2, 138.4, 134.6, 132.2, 129.5, 124.0, 122.0, 119.9, 119.1, 117.2, 112.5, 111.4, 110.1, 110.0, 56.5, 55.2, 46.2, 40.5, 22.2, 11.1.

MS (ESI): *m*/*z* = 401 $[M + H]^+$.

Anal. Calcd For $C_{26}H_{28}N_2O_2$: C, 78.00; H, 7.00; N, 7.00. Found: C, 78.18; H, 7.08; N, 7.10.

3-[(4-Hydroxyphenyl)(*N*-propylanilino)methyl]-1*H*-indole (1l)
Violet solid; yield: 313 mg (88%).

IR (KBr): 3414, 1607, 1513, 1457 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 7.90 (br s, 1 H), 7.34–7.20 (m, 4 H), 7.19–7.04 (m, 2 H), 7.01–6.94 (m, 3 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.62 (d, *J* = 8.0 Hz, 1 H), 6.60 (br s, 1 H), 6.57–6.46 (m, 3 H), 5.46 (s, 1 H), 3.01 (t, *J* = 7.0 Hz, 2 H), 1.62–1.50 (m, 2 H), 0.98 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.6, 146.8, 146.0, 136.5, 132.8, 129.7, 129.0, 128.1, 126.4, 124.1, 121.9, 121.3, 119.8, 119.6, 119.1, 115.2, 115.1, 110.4, 48.3, 46.1, 22.5, 11.2.

MS (ESI): *m*/*z* = 357 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.90; H, 6.74; N, 7.87. Found: C, 80.82; H, 6.70; N, 7.93.

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