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Three-Component Synthesis of 3-(Diarylmethyl)indoles Using $Fe(ClO_4)_3/SiO_2$ as Catalyst[1]

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Abstract—Three-component reaction of indole, aromatic aldehyde, and *N*,*N*-dimethyl aniline in the presence of silica-supported $Fe(ClO_4)_3$ as catalyst afforded the corresponding 3-[aryl(4-dimethylaminophenyl)methyl]-indoles in excellent yields under mild conditions. The proposed protocol offers some remarkable advantages such as the use of a solid catalyst and simple workup procedure.

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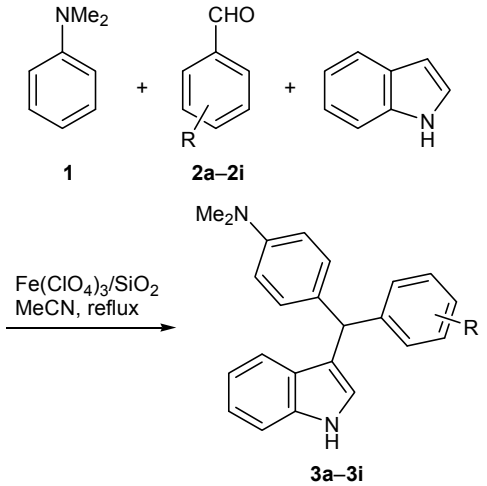
Indoles are important structural units in many natural products, and their derivatives are known to possess various biological properties [1] such as antibacterial, antioxidant, and insecticidal activities. Some indole derivatives have been used as antibiotics and pharmaceuticals [2]. Among indole derivatives, bisindolylalkanes, 3-alkylindoles, and 3-(diarylmethyl)-indoles constitute an important class of bioactive metabolites. They can be synthesized using Lewis acids as catalysis [3–8], e.g., $FeCl_3$ [11], $ZnCl_2$ [12], $CuCl_2$ [13], and Fe_3O_4–OSO_3H [14]. Although the synthesis of 3-alkylindoles has been studied extensively, more practical mild procedures for the synthesis of other unsymmetrical indole derivatives are still highly desirable.

Scheme 1.



R = H (**a**), 4-Me (**b**), 4-Cl (**c**), 2-Cl (**d**), O_2N (**e**), 3,4-$(MeO)_2$ (**f**), 3-HO (**g**), 4-HO (**h**), 4-MeO (**i**).

Following our previous research on the use of eco-friendly catalytic protocols for the synthesis of heterocyclic compounds [9–10], herein we present a new, mild, and green procedure for the preparation of 3-(diarylmethyl)indoles from *N*,*N*-dimethylaniline (**1**), aromatic aldehydes **2**, and indole in the presence of $Fe(ClO_4)_3/SiO_2$ in refluxing acetonitrile (Scheme 1).

Initially, different solvents were tried in the model reaction of benzaldehyde (**2a**) with *N*,*N*-dimethylaniline and indole. The results showed that the catalyst worked more efficiently in acetonitrile (Table 1).

We also studied the effect of the amount of $Fe(ClO_4)_3/SiO_2$ on the reaction in acetonitrile. It was found that the amount of the catalyst is crucial for achieving the desired yield. The best result was obtained using 0.2 g of $Fe(ClO_4)_3/SiO_2$ (Table 2).

Table 1. Reaction of *N*,*N*-dimethylaniline (**1**) with benzaldehyde (**2a**) and indole in the presence of $Fe(ClO_4)_3/SiO_2$ in different solvents[a]

Solvent	Temperature, °C	Yield of **3a**,[b] %
None	100	85
CH_2Cl_2	Reflux	80
$CHCl_3$	Reflux	80
MeCN	Reflux	92
H_2O	Reflux	<10<

[a] Reaction time 2 h; hereinafter, 1.0 mmol of each reactant, 0.2 g of $Fe(ClO_4)_3/SiO_2$, and 1.0 mL of the solvent were used.
[b] Hereinafter, isolated yield is given.

[1] The text was submitted by the authors in English.

To examine the scope and generality of this protocol, we used different substituted benzaldehydes. The data in Table 3 show that benzaldehydes having both electron-donating and electron-withdrawing groups afforded the desired products in high yields.

A plausible mechanism of the reaction is shown in Scheme 2. Electrophilic substitution in *N*,*N*-dimethylaniline (**1**) with $Fe(ClO_4)_3/SiO_2$-activated benzaldehyde **A** gives intermediate **B** which loses $(OH)Fe(ClO_4)_3/SiO_2$ due to "push–pull" effect of nonbonding electrons of *N*,*N*-dimethlyaniline. Cationic intermediate **C** thus formed adds to C^3 of indole, yielding 3*H*-indolium intermediate **D**, and proton abstraction from the latter leads to final 3-substituted indole **3**.

To show advantages of using $Fe(ClO_4)_3/SiO_2$ as a solid catalyst in the synthesis of 4-[(1*H*-indol-3-yl)-(phenyl)methyl]-*N*,*N*-dimethylaniline, our protocol was compared with previously reported methods (Table 4). It is evident that the proposed procedure is advantageous regarding the yield and reaction time which are very important factors for large-scale processes, especially in combination with easy separation and reusability of the catalyst.

Table 2. Effect of the catalyst amount in the synthesis of 4-[(1*H*-indol-3-yl)(phenyl)methyl]-*N*,*N*-dimethylaniline (**3a**)

$Fe(ClO_4)_3/SiO_2$, g	Reaction time, h	Yield, %
No catalyst	4.0	10
0.3	2.0	70
0.5	2.0	90
0.2	2.0	92

EXPERIMENTAL

The melting points were measured by the capillary method with an Electrothermal 9200 apparatus. The IR spectra were recorded in KBr on a Perkin Elmer FT-IR spectrometer in the range 4000–400 cm^{-1}. The ^1H and ^{13}C NMR spectra were obtained on a Bruker DRX-300 instrument (300 MHz for ^1H and 75 MHz for ^{13}C) using $CDCl_3$ as solvent; the chemical shifts were measured relative to tetramethylsilane as internal standard. The mass spectra were taken on an Agilent 5973 Network Mass Selective Detector.

Analytical TLC of all reactions was performed on silica gel 60 F-254 precoated plates (Merck). Elemental analyses of the newly synthesized compounds were

Scheme 2.

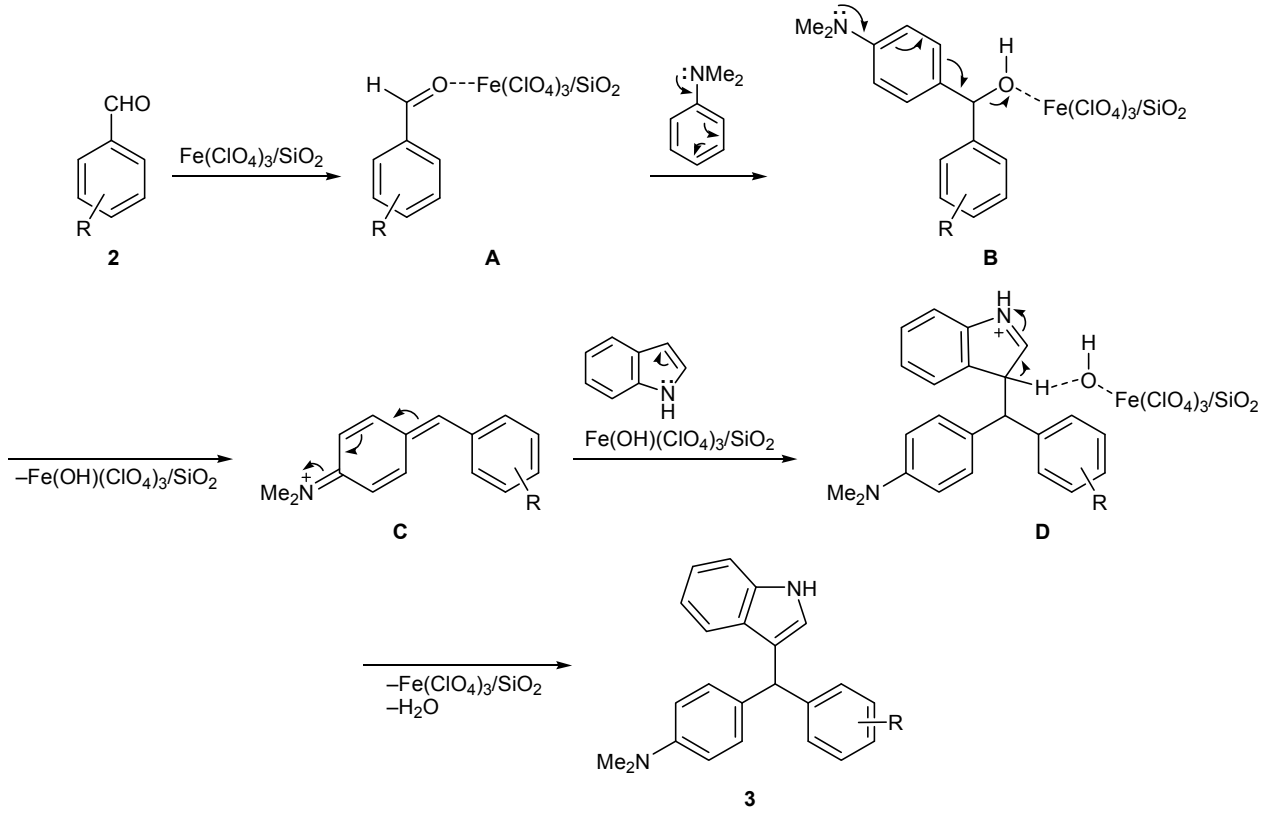


Table 3. Synthesis of 3-(diarylmethyl)indoles **3a**–**3i** in the presence of $Fe(ClO_4)_3/SiO_2$

Aldehyde no.	R	Product no.	Reaction time, h	Yield, %	mp, °C	
					found	reported [4]
2a	H	**3a**	2.0	92	158–160	161–162
2b	4-Me	**3b**	2.0	90	160–163	164–165
2c	4-Cl	**3c**	2.0	95	129–130	130–132
2d	2-Cl	**3d**	2.0	95	150–152	152–153
2e	$3\text{-}O_2N$	**3e**	3.0	90	130–132	–
2f	$3,4\text{-}(MeO)_2$	**3f**	2.0	95	138–140	–
2g	3-HO	**3g**	2.0	90	150–152	–
2h	4-HO	**3h**	2.0	90	142–144	–
2i	4-MeO	**3i**	3.0	90	145–150	–

Table 4. Synthesis of 4-[(1*H*-indol-3-yl)(phenyl)methyl]-*N,N*-dimethylaniline (**3a**) in the presence of different catalysts

Catalyst, mol % (g)	Solvent	Temperature, °C	Reaction time, h	Yield, %	Reference
$FeCl_3$, 10	1,2-Dichloroethane	100	24	65	[11]
$Fe(NO_3)_3 \cdot 9H_2O$, 10	1,2-Dichloroethane	100	24	15	[11]
$Fe(SO_4)_3 \cdot 7H_2O$, 10	1,2-Dichloroethane	100	24	18	[11]
$Fe_2(SO_4)_4$, 10	1,2-Dichloroethane	100	24	31	[11]
$Fe(acac)_3$, 10	1,2-Dichloroethane	100	24	26	[11]
$FeCl_2$, 10	1,2-Dichloroethane	100	24	38	[11]
$ZnCl_2$, 100	Toluene	100	0.05.0	76	[12]
PMA-SiO_2, 15	PEG-400	110	11	65	[15]
$Fe(ClO_4)_3/SiO_2$ (0.2)	MeCN	Reflux	2.0	95	This work

obtained using a Vario EL III analyzer and were in a good agreement with the calculated values. All starting materials were purchased from Merck and Acros Organics.

Silica-supported iron(III) perchlorate. A solution of 1.0 g of $Fe(ClO_4)_3$ in 10 ml of ethanol was added to a suspension of 10 g of silica gel (Kieselgel 40, 70–230 mesh; Merck) in 30 ml of ethanol. The mixture was stirred for 30 min, and the solvent was evaporated under reduced pressure. The resulting brown powder was further dried in a vacuum drying cabinet at 60°C under reduced pressure (20 mm) [16].

General procedure for the synthesis of 3-(diarylmethyl)indoles 3a–3i. To a mixture of aromatic aldehyde (1.0 mmol), *N*,*N*-dimethylaniline (1.0 mmol), and indole (1.0 mmol) in acetonitrile (1.0 ml) 0.2 g of $Fe(ClO_4)_3/SiO_2$ was added, and the reaction mixture was refluxed with stirring for appropriate time. After completion of the reaction (TLC), the mixture was cooled, 25 ml of CH_2Cl_2 was added, and the catalyst was separated by filtration. The filtrate was evaporated under reduced pressure, and the crude product was purified by recrystallization from ethanol. The catalyst is reusable and could be recycled for five runs without appreciable decrease in catalytic activity. The yields and melting points of **3a–3i** are given in Table 3.

4-[(1*H*-Indol-3-yl)(phenyl)methyl]-*N*,*N*-dimethylaniline (3a). IR spectrum, ν, cm^{-1}: 3400 (NH), 1676 (C=N), 1614, 1518, 1492, 1455, 1417 (C=C), 1223, 1124 (C–N). ^1H NMR spectrum (300 MHz, δ, ppm: 2.93 s (6H, NCH_3), 5.59 s (1H, CH), 6.80 s (1H, 2-H), 7.30–6.80 m (12H, H_{arom}), 7.92 s (1H, H_{arom}), 9.88 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.67 (NCH_3), 54.66 (CH), 111.05, 114.32, 116.22, 118.84, 122.09, 127.33, 130.45, 132.12, 134.30, 144.08, 148.11. Mass spectrum: *m*/*z* 326.43 $[M]^+$.

4-[(1*H*-Indol-3-yl)(4-methylphenyl)methyl]-*N*,*N*-dimethylaniline (3b). IR spectrum, ν, cm^{-1}: 3411

(NH), 1658 (C=N), 1610, 1510, 1483, 1456, 1416 (C=C), 1217, 1092 (C–N). ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, CH_3), 2.92 s (6H, NCH_3), 5.56 s (1H, CH), 6.64 s (1H, 2-H), 7.24–6.8 m (11H, H_{arom}), 7.90 s (1H, H_{arom}), 9.87 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 25 (CH_3), 40.45 (NCH_3), 54.45 (CH), 111.31, 114.02, 116.31, 118.11, 122.80, 127.14, 130.33, 132.20, 135.28, 140.12, 147.09. Mass spectrum: *m*/*z* 340.46 $[M]^+$.

4-[(4-Chlorophenyl)(1*H*-indol-3-yl)methyl]-*N*,*N*-dimethylaniline (3c). IR spectrum, ν, cm^{-1}: 3410 (NH), 1698 (C=N), 1611, 1575, 1518, 1487, 1456, 1417 (C=C), 1219, 1123 (C–N). ^{1}H NMR spectrum, δ, ppm: 2.90 s (6H, NCH_3), 5.53 s (1H, CH), 6.50 s (1H, 2-H), 7.29–6.66 m (11H, H_{arom}), 7.87 s (1H, H_{arom}), 9.83 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.52 (NCH_3), 54.48 (CH), 111.08, 114.12, 116.28, 120.11, 122.21, 127.71, 130.40, 132.06, 136.03, 140.13, 147.31. Mass spectrum: *m*/*z* 360.14/362.14 $[M]^+$.

4-[(2-Chlorophenyl)(1*H*-indol-3-yl)methyl]-*N*,*N*-dimethylaniline (3d). IR spectrum, ν, cm^{-1}: 3410 (NH), 1694 (C=N), 1611, 1518, 1456, 1442 (C=C), 1093, 1036 (C–N). ^{1}H NMR spectrum, δ, ppm: 2.92 s (6H, NCH_3), 6.00 s (1H, CH), 6.54 s (1H, 2-H), 7.37–6.72 m (11H, H_{arom}), 7.92 s (1H, H_{arom}), 9.85 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.38 (NCH_3), 50.65 (CH), 111.11, 114.07, 116.31, 120.22, 122.00, 127.13, 130.31, 133.03, 136.44, 143.01, 147.04. Mass spectrum: *m*/*z* 360.14/362.14 $[M]^+$.

4-[(1*H*-Indol-3-yl)(3-nitrophenyl)methyl]-*N*,*N*-dimethylaniline (3e). IR spectrum, ν, cm^{-1}: 3411 (NH), 1702 (C=N), 1614 (C=C), 1521 (NO_2, asym.), 1349 (NO_2, sym.), 1219, 1125 (C–N). ^{1}H NMR spectrum, δ, ppm: 2.94 s (6H, NCH_3), 5.68 s (1H, CH), 6.60 s (1H, 2-H), 8.00–6.68 m (11H, H_{arom}), 8.12 s (1H, H_{arom}), 9.85 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.50 (NCH_3), 54.61 (CH), 111.07, 114.12, 116.01, 118.45, 122.03, 127.34, 130.26, 132.14, 134.71, 144.30, 148.10. Mass spectrum: *m*/*z* 371.16 $[M]^+$.

4-[(3,4-Dimethoxyphenyl)(1*H*-indol-3-yl)-methyl]-*N*,*N*-dimethylaniline (3f). IR spectrum, ν, cm^{-1}: 3403 (NH), 1671 (C=N), 1599, 1509, 1456 (C=C), 1216, 1156 (C–N). ^{1}H NMR spectrum, δ, ppm: 2.92 s (6H, NCH_3), 3.76 s (3H, OCH_3), 3.85 s (3H, OCH_3), 5.54 s (1H, CH), 6.56 s (1H, 2-H), 7.33–6.67 m (10H, H_{arom}), 8.00 s (1H, H_{arom}), 9.87 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.42 (NCH_3), 56.63 (CH, OCH_3), 111.07, 114.32, 116.43, 119.87, 122.31, 127.45, 129.00, 132.10, 136.21, 147.08, 150.02. Mass spectrum, *m*/*z* (I_{rel}, %): 386.20 (27.9) $[M]^+$, 116 (100). Found, %: C 77.56; H 6.58; N 7.11. $C_{25}H_{26}N_2O_2$. Calculated, %: C 77.69; H 6.78; N 7.25.

4-[(3-Hydroxyphenyl)(1*H*-indol-3-yl)methyl]-*N*,*N*-dimethylaniline (3g). IR spectrum, ν, cm^{-1}: 3380 (NH, OH), 1679 (C=N), 1587, 1512, 1456, 1422 (C=C), 1268, 1136 (C–N). ^{1}H NMR spectrum, δ, ppm: 2.88 s (6H, NCH_3), 5.52 s (1H, CH), 6.56 s (1H, 2-H), 7.33–6.67 m (12H, H_{arom}), 7.92 s (1H, OH), 9.80 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.64 (NCH_3), 55.32 (CH), 114.00, 111.31, 116.11, 119.41, 122.17, 127.04, 129.02, 132.31, 136.43, 147.08, 156.10. Mass spectrum, *m*/*z* (I_{rel}, %): 342.17 (25.5) $[M]^+$, 116 (100). Found, %: C 80.55; H 6.45; N 8.11. $C_{23}H_{22}N_2O$. Calculated, %: C 80.67; H 6.48; N 8.18.

4-[(4-Hydroxyphenyl)(1*H*-indol-3-yl)methyl]-*N*,*N*-dimethylaniline (3h). IR spectrum, ν, cm^{-1}: 3408 (NH, OH), 3044, 1681 (C=N), 1586, 1516, 1481, 1450 (C=C), 1220 (C–O), 1142 (C–N). ^{1}H NMR spectrum, δ, ppm: 2.92 s (6H, NCH_3), 5.54 s (1H, CH), 6.56 s (1H, 2-H), 7.33–6.67 m (12H, H_{arom}), 7.92 s (1H, OH), 9.80 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.45 (NCH_3), 55.34 (CH), 111.13, 114.00, 116.15, 119.05, 122.78, 127.07, 129.64, 132.06, 136.31, 147.46, 156.64. Mass spectrum, *m*/*z* (I_{rel}, %): 342.17 (25.7) $[M]^+$, 116 (100). Found, %: C 80.58; H 6.37; N 8.10. $C_{23}H_{22}N_2O$. Calculated, %: C 80.67; H 6.48; N 8.18.

4-[(1*H*-Indol-3-yl)(4-methoxyphenyl)methyl]-*N*,*N*-dimethylaniline (3i). IR spectrum, ν, cm^{-1}: 3408 (NH), 1673 (C=N), 1600, 1510, 1456 (C=C), 1216, 1156 (C–N). ^{1}H NMR spectrum, δ, ppm: 2.93 s (6H, NCH_3), 5.53 s (1H, CH), 6.56 s (1H, 2-H), 7.33–6.77 m (11H, H_{arom}), 7.92 s (1H, H_{arom}), 9.86 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 40.46 (NCH_3), 55.60 (CH, OCH_3), 111.08, 114.71, 116.00, 119.07, 122.02, 127.70, 129.99, 132.06, 135.25, 147.01, 158.50. Mass spectrum, *m*/*z* (I_{rel}, %): 356.19 (27.8) $[M]^+$, 116 (100). Found, %: C 80.67; H 6.66; N 7.75. $C_{24}H_{24}N_2O$. Calculated, %: C 80.87; H 6.79; N 7.86.

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