$InCl_3$/$MeSO_3H$ catalysed addition reactions of pyrrole to *N*-sulfonylimines

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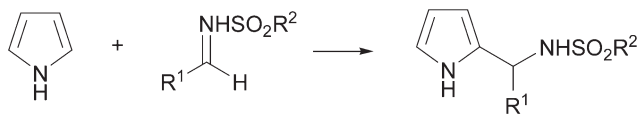
The addition reaction of pyrrole to *N*-sulfonylimines has been shown to proceed in the presence of a catalytic amount of $InCl_3$ and $MeSO_3H$, to give pyrrole sulfonamides in medium to excellent yields.

Keywords: addition reaction, pyrrole, *N*-sulfonylimines, catalysts, indium(III) chloride

Pyrroles form the starting materials and intermediates in many important natural product and drug syntheses.[1–10] As a result, their synthesis is an important industrial and synthetic goal. The common methods reported for the synthesis of aminoalkylated pyrrole derivatives involves the Mannich reaction of formaldehyde with an amine and the reactions of pyrroles with imines.[11–14] Despite significant advances, several drawbacks remain associated with such reactions, including the use stoichiometric amounts of the catalyst, byproducts, and low yields. Recently, Unaleroglu reported the use of $Cu(OTf)_2$ as a catalyst for the addition of pyrrole to *N*-tosyl imines.[15,16] Here we report that $InCl_3$–proton acid systems can serve as catalysts to promote the addition reactions of pyrrole to *N*-sulfonylimines.

Our initial explorations focused on the reaction of pyrrole (**1a**) (0.2 mmol) with *N*-benzylidene-4-methylbenzenesulfonamide (**2a**) (0.4 mmol) in the presence of a catalytic amount of $InCl_3$ (10 mol %) and methanesulfonic acid ($MeSO_3H$) (20 mol%) in THF (3 mL) at 0 °C for 8 h. This proceeded efficiently to form the addition product **3a** in 62% yield (Scheme 1, Table 1, entry 2). Investigation of the starting material stoichiometries revealed that a slight excess of *N*-sulfonyl imine (2 equiv.) was necessary to drive the reaction to full conversion (Table 1, entries 2 and 3). Only a trace of **3a** was formed at room temperature (Table 1, entry 1). Different solvents were screened, and THF was found to be the best (Table 1, entries 3–6). Decreasing the amount of $InCl_3$ or $MeSO_3H$ resulted in lower yields (entries 7 and 8). Using either $InCl_3$ or $MeSO_3H$ alone gave lower yields (entries 9 and 10). These results indicated that both $InCl_3$ and $MeSO_3H$ played a crucial role in this addition reaction. Other acid catalysts, such as trifluoromethanesulfonic acid and sulfuric acid were ineffective.

To further assess the scope of this process, we have examined the addition reaction of pyrrole to different *N*-sulfonylimines using the optimised reaction conditions as described in entry 3 of Table 1. The results are summarised in Table 2 and Scheme 1. Tosylimines with an electron-withdrawing group on the benzene ring all gave good yields (entries 2–5). In sharp contrast, where there was an electron-donating substituent on the aromatic ring, the corresponding adduct **3f** was obtained in 37% yield (entry 6). Under the same reaction conditions, the addition reaction of pyrrole to other *N*-sulfonylimines took place smoothly to afford the corresponding addition products **3g–i** with 55–67% yield (entries 7–9).



1a **2** **3a-i**

Scheme 1

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In conclusion, we have demonstrated an efficient $InCl_3$/$MeSO_3H$-catalysed addition reaction of pyrrole to *N*-sulfonylimines to produce *pyrrole derivatives* under mild conditions with perfect regioselectivity. Further efforts to expand the scope of the chemistry and studies of the detailed mechanism are currently under way in our laboratories.

Experimental

Under otherwise noted, materials were obtained from commercial suppliers and were used without further purification. *N*-sulfonylimines were prepared by the procedures in the literature. TLC was performed using silica gel 60 F254 and visualised using UV light. Column chromatography was performed with silica gel (mesh 300–400). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer in CDCl3 with Me4Si as an internal standard. Data were reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad and m = multiplet), coupling constant in (Hz) and integration. IR spectra were obtained on 370 FT-IR spectrometer; absorptions were reported in cm^{-1}. Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained from the Zhejiang University of Technology Mass Spectrometry Facility.

Synthesis of 2-substituted pyrroles **3a–i;** *general procedure*

The pyrrole (0.2 mmol) was added to a mixture of *N*-sulfonylimine (0.4 mmol), $InCl_3$ (0.02 mmol), and $MeSO_3H$ (0.04 mol) in anhydrous THF (3 mL) under N_2. The mixture was then stirred at 0 °C for 3–6 h. The mixture was quenched with saturated solution of $NaHCO_3$ and then extracted with dichloromethane (20 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel) to yield the product in an analytically pure form.

4-Methyl-N-(phenyl(1H-pyrrol-2-yl)methyl)benzenesulfonamide (**3a**): M.p. 130–131 °C (lit.[15] 132–133 °C); ^1H NMR (500 MHz, $CDCl_3$): δ 8.59 (br, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.21–7.19 (m, 3H), 7.15–7.09 (m, 4H), 6.701–6.70 (m, 1H), 6.02–6.01 (m, 1H), 5.60–5.59 (m, 1H), 5.54 (d, *J* = 8.1 Hz, 1H), 5.37 (d, *J* = 8.1 Hz, 1H), 2.36 (s, 3H).

N-((4-Fluorophenyl)(1H-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (**3b**):[15] ^1H NMR (500 MHz, $CDCl_3$): δ 8.59 (br, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.10–7.06 (m, 2H), 6.91–6.85 (m, 2H), 6.72–6.70 (m, 1H), 6.02 (dd, *J* = 6.0, 2.8 Hz, 1H), 5.58–5.56 (m, 1H), 5.54 (d, *J* = 8.1 Hz, 1H), 5.40 (d, *J* = 8.1 Hz, 1H), 2.38 (s, 3H).

N-((4-Chlorophenyl)(1H-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (**3c**): M.p. 114–115 °C (lit.[16] 115–116 °C); ^1H NMR (500 MHz, $CDCl_3$): δ 8.58 (br, 1H), 7.4 (d, *J* = 8.5 Hz, 2H), 7.17–7.15 (m, 4H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.72–6.70 (m, 1H), 6.03–6.02 (m, 1H), 5.57–5.54 (m, 1H), 5.53 (d, *J* = 8.1 Hz, 1H), 5.37 (d, *J* = 8.1 Hz, 1H), 2.39 (s, 3H).

N-((4-Bromophenyl)(1H-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (**3d**): M.p. 118–119 °C (lit.[16] 116–117 °C); ^1H NMR (500 MHz, $CDCl_3$): δ 8.55 (br, 1H), 7.53 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 9.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 6.73–6.71 (m, 1H), 6.02 (dd, *J* = 6.0, 2.8 Hz, 1H), 5.58–5.56 (m, 1H), 5.52 (d, *J* = 8.1 Hz, 1H), 5.31 (d, *J* = 8.1 Hz, 1H), 2.03 (s, 3H).

4-Methyl-N-((4-nitrophenyl)(1H-pyrrol-2-yl)methyl)benzenesulfonamide (**3e**): M.p. 150–151 °C (lit.[15] 153–154 °C); ^1H NMR (500 MHz, $CDCl_3$): δ 8.52 (br, 1H), 8.07 (d, *J* = 9.0 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 9.0 Hz, 2H), 6.76–6.75 (m, 1H), 6.04 (dd, *J* = 6.0, 2.8 Hz, 1H), 5.68 (d, *J* = 7.9 Hz, 1H), 5.55–5.54 (m, 1H), 5.36–5.34 (d, *J* = 7.9 Hz, 1H), 2.38 (s, 3H).

Table 1 The reaction of pyrrole (**1a**) with **2a** with $InCl_3$[a]

Entry	$InCl_3$ /mol%	$MeSO_3H$ /mol%	Ratio (**1a**:**2a**)	Solvent	Temp./°C	Yield of **3a** /%[b]
1	10	20	1:1	THF	rt	Trace
2	10	20	1:1	THF	0	28
3	10	20	1:2	THF	0	62
4	10	20	1:2	Toluene	0	0
5	10	20	1:2	CH_2Cl_2	0	0
6	10	20	1:2	Dioxane	0	Trace
7	5	20	1:2	THF	0	48
8	10	10	1:2	THF	0	54
9	10	–	1:2	THF	0	25
10	–	20	1:2	THF	0	8

[a] The reactions were performed with **1a** (0.2 mmol), **2a** (0.2–0.4 mmol), $InCl_3$ (0–10 mol%), and $MeSO_3H$ (0–20 mol%) in solvent (3 mL) for 8 h.
[b] Isolated yield.

Table 2 $InCl_3$ / $MeSO_3H$ catalysed reaction of pyrrole with *N*-sulfonyl imines[a]

Entry	R^1	R^2	Time/h	Imine	Yield/%[b]
1	C_6H_5	4-CH_3-C_6H_4	8	**3a**	62
2	4-F-C_6H_4	4-CH_3-C_6H_4	8	**3b**	76
3	4-Cl-C_6H_4	4-CH_3-C_6H_4	6	**3c**	59
4	4-Br-C_6H_4	4-CH_3-C_6H_4	6	**3d**	71
5	4-NO_2-C_6H_4	4-CH_3-C_6H_4	4	**3e**	82
6	4-^{t}Bu-C_6H_4	4-CH_3-C_6H_4	4	**3f**	37
7	C_6H_5	C_6H_5	4	**3g**	55
8	4-Cl-C_6H_4	C_6H_5	4	**3h**	67
9	4-Br-C_6H_4	C_6H_5	4	**3i**	62

[a] The reactions were performed with **1a** (0.2 mmol), **2** (0.4 mmol), $InCl_3$ (10 mol%), and $MeSO_3H$ (20 mol%) at 0 °C in THF (3 mL).
[b] Isolated yield.

N-((4-Tert-butylphenyl)(1H-pyrrol-2-yl)methyl)-4-methylbenzenesulfonamide (**3f**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (br, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.81–6.66 (m, 1H), 6.01 (dd, *J* = 5.9, 2.8 Hz, 1H), 5.65–5.63 (m, 1H), 5.54 (d, *J* = 8.0 Hz, 1H), 5.41 (d, *J* = 8.0 Hz, 1H), 2.34 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.9, 143.1, 137.2, 135.5, 130.8, 129.4, 127.2, 127.0, 125.3, 118.5, 108.2, 107.9, 55.7, 34.5, 31.3, 21.5; IR (KBr, cm^{-1}): 3414.4, 2963.3, 1793.6, 1560.3, 1508.3, 1458.4, 1384.3, 1326.1, 1266.2, 1159.7, 1092.5, 1027.8, 924.5, 845.6, 812.6, 747.3, 704.2, 665.3, 579.5 cm^{-1}; Mass spectrum (ESI) *m/z* (rel, int,%) 405.1 (M^+ Na, 100), 212.1 (5.7), 308.1 (34.4), 615.1 (22.3), 787.3(10.8). HRMS (ESI) for $C_{22}H_{26}N_2NaO_2S$: Calcd: 405.1620; found 405.1613.

N-(Phenyl(1H-pyrrol-2-yl)methyl)benzenesulfonamide (**3g**): M.p. 128–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (br, 1H), 7.65(d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.22–7.16 (m, 3H), 7.08 (dd, *J* = 8.0, 2 Hz, 2H), 6.70–6.68 (m, 1H), 6.01 (dd, *J* = 6.0, 2.8 Hz, 1H), 5.81–5.79 (m, 2H), 5.55 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.0, 138.4, 132.6, 130.5, 128.9, 128.6, 128.0, 127.3, 127.1, 118.7, 108.3, 108.2, 55.9; IR (KBr, cm^{-1}): 3453.0, 1636.8, 1384.1, 1158.8, 1091.7, 913.1, 743.2, 554.4 cm^{-1}; Mass spectrum (ESI) *m/z* (rel, int,%) 313.1 (M^+ H, 2.2), 335.1 (M^+ Na, 1.1), 83.1 (12), 130.2 (0.7), 139.1 (100), 156.1 (4.1), 246.1(1.1). HRMS (ESI) for $C_{17}H_{16}N_2NaO_2S$: Calcd: 335.0831; found 335.0830.

N-((4-Chlorophenyl)(1H-pyrrol-2-yl)methyl)benzenesulfonamide (**3h**):[16] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (br, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.69–6.68 (m, 1H), 6.00 (dd, *J* = 6.0, 2.8 Hz, 1H), 5.75–5.73 (m, 1H), 5.58–5.56 (m, 2H).

N-((4-Bromophenyl)(1H-pyrrol-2-yl)methyl)benzenesulfonamide (**3i**): M.p. 123–124 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (br, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 7.5 Hz, 2H), 6.67–6.66 (m, 1H), 6.00–5.96 (m, 1H), 5.80–5.79 (d, *J* = 8.5 Hz, 1H), 5.55 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.9, 139.5, 132.7, 131.6, 129.8, 129.1, 129.0, 127.0, 122.0, 119.0, 108.4, 108.3, 55.4; IR (KBr, cm^{-1}): 3418.3, 1636.6, 1384.2, 1324.1, 1159.6, 750.0, 723.3, 686.7, 589.8, 556.2 cm^{-1}; Mass spectrum (ESI) *m/z* (rel, int,%) 413 (M^+ Na, 95), 391 (21), 393 (18), 414 (15.5), 415 (100), 416 (16.4). HRMS (ESI): *m/z* Calcd for $C_{17}H_{15}BrN_2NaO_2S$: 412.9936; found: 412.9935.

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