Scandium triflate-catalysed synthesis of *N*-substituted pyrroles from amine and 2,5-dimethoxytetrahydrofuran

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The Clauson–Kass pyrrole synthesis catalysed by scandium triflate afforded *N*-substituted 2- and 3-unsubstituted pyrroles with yields ranged from good to excellent. Aromatic amines, heteroaomatic amines, 4-methylbenzenesulfonamide and 2-chlorobenzamide are good substrates in this transformation.

Keywords: *N*-substitued pyrroles, 2,5-dimethoxytetrahydrofuran, scandium triflate, Clauson–Kaas

The pyrrole skeleton is prevalent in a wide range of natural and pharmacologically active compounds.[1-3] In recent years, great interest has been paid to the synthesis of pyrrole derivatives. Among the existing methods, the most commonly used methods are the Knorr pyrrole synthesis, the Hantzch pyrrole synthesis, the Paal–Knorr synthesis and the Clauson–Kass synthesis.[4-7] The Clauson–Kass pyrrole synthesis involves the condensation reaction of the amine with 2,5-dimethoxytetrahydrofuran for the synthesis of the *N*-substituted, 2- and 3-unsubstituted pyrroles, where the 2- and 3-positions can be reacted for further functionalisation. By far, a number of synthetic strategies have been developed for the condensation of Clauson–Kass pyrrole synthesis. Various acidic materials, such as glacial acetic acid,[8] TfOH,[9] P_2O_5,[10] montmorillonite K-10,[11] 4-chloropyridine hydrochloride,[12] as well as the microwave technology[11] have been used to promote these condensations. However, some of these methods often suffer from certain drawbacks such as strong acidic reaction conditions,[9] long reaction time,[11] high reaction temperature,[13] strictly anhydrous condition,[10] tedious workup[11] and large amounts of solid catalysts.[11] Hence, an efficient and mild Clauson–Kass condensation is needed for contemporary chemical synthesis.

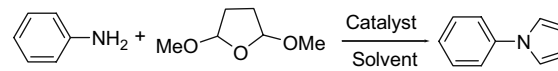
The application of new types of Lewis acid catalysts to replace traditional, harmful, and corrosive mineral acids is a rapidly growing area in organic synthesis. Among the new various kinds of Lewis acid, rare-earth metal triflates enjoy great prestige and are frequently used as potent environmentally-benign Lewis acids and have the advantages of low toxicity, high stability, easy handling and recovery from water, and high reactivity in green media such as water, ionic liquids, super critical CO_2, solvent-free conditions as well as solid supported synthesis.[14-16]

Recently, we have also successfully applied metal triflates in several organic synthesis reactions.[18-23] To deepen our interest in Lewis acid-catalysed organic reactions, we herein reported a practical method for the synthesis of the *N*-substituted, 2- and 3-unsubstituted pyrroles.

Initially, we investigated the effect of catalysts for the formation of pyrrole from aniline (Scheme 1), and the results are listed in Table 1. Among all metal triflates examined, scandium triflate is shown to be the most effective. In contrast, Lewis acids such as $FeCl_3$, $CuCl_2$ and $InCl_3$ gave much lower yields. Nevertheless, no product was obtained in the absence of catalysts, which also further proved that scandium triflate does play an important role in this reaction.

In order to optimise the reaction parameters, we carried out several reactions using scandium triflate as the catalyst to study the effect of solvents and reaction temperature. The results are summarised in Table 2. In addition, we further studied the influence of the amount of scandium triflate on the reaction yields. In the presence of 5, 3, and 1 mol% scandium triflate, the corresponding yields were 92%, 91%, and 74%, respectively. The results show that 3 mol% of scandium triflate was sufficient to catalyse the reaction and excessive amount of catalyst did not increase the yields. In the light of this, subsequent studies were carried out under the following optimised conditions, that is, 3 mol% $Sc(OTf)_3$, dioxane at 100 °C.

To evaluate the scope of the protocol's application, we first applied the above-mentioned optimised conditions to a variety of aromatic amines and the results are summarised in Table 3.



Scheme 1 Clauson–Kass pyrrole synthesis.

Table 1 Effect of catalysts for the synthesis of pyrroles[a]

Entry	Catalyst	Yield/%[b]
1	None	No reaction
2	$FeCl_3$	20
3	$CuCl_2$	43
4	$InCl_3$	18
5	$Cu(OTf)_2$	79
6	$Mg(OTf)_2$	70
7	$Zn(OTf)_2$	78
8	$Yb(OTf)_3$	80
9	$Y(OTf)_3$	81
10	$Bi(OTf)_3$	83
11	$La(OTf)_3$	82
12	$Sc(OTf)_3$	84

[a]Reaction conditions: aniline (1 mmol), 2,5-dimethoxy-tetrahydrofuran (1 mmol), catalyst (5 mol%) and toluene (2 ml), 110 °C, 40 min.
[b]Isolated yields.

Table 2 $Sc(OTf)_3$-catalysed synthesis of pyrrole from aniline under different reaction conditions[a]

Entry	Solvent	Temp./°C	Yield/%[b]
1	CH_2Cl_2	110	81
2	$CHCl_3$	110	67
3	CH_3CN	110	71
4	Dioxane	110	86
5	CH_3NO_2	110	69
6	n-Hexane	110	14
7	Dioxane	90	60
8[c]	Dioxane	100	92, 91,[c] 74[d]

[a]Reaction conditions: aniline (1 mmol), 2,5-dimethoxy-tetrahydrofuran (1 mmol) and $Sc(OTf)_3$ (5 mol%) were run for 40 min.
[b]Isolated yields.
[c]$Sc(OTf)_3$ (3 mol%).
[d]$Sc(OTf)_3$ (1 mol%).

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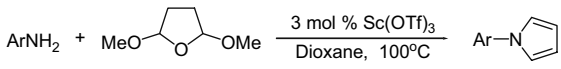
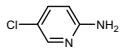
Table 3 Formation of pyrroles from various aromatic amines[a]



1 **2** **3**

Entry	$ArNH_2$	Product	Time/min	Yield/%[b]
1	$C_6H_5NH_2$	**3a**	40	91
2	4-$(CH_3)C_6H_4NH_2$	**3b**	40	90
3	2-$(CH_3)C_6H_4NH_2$	**3c**	40	86
4	4-$(Cl)C_6H_4NH_2$	**3d**	40	83
5	3-$(Cl)C_6H_4NH_2$	**3e**	40	85
6	4-$(NO_2)C_6H_4NH_2$	**3f**	30	77
7	2-$(NO_2)C_6H_4NH_2$	**3g**	30	74
8	2-$(OCH_3)C_6H_4NH_2$	**3h**	90	88
9	4-$(I)C_6H_4NH_2$	**3i**	30	81
10	2-$(CN)C_6H_4NH_2$	**3j**	20	80
11	2-(Cl)-5-$(NO_2)C_6H_3NH_2$	**3k**	30	80
12		**3l**	30	94
13		**3m**	240	84
14		**3n**	300	74

[a]Reaction conditions: aromatic amines (1 mmol), 2,5-dimethoxytetrahydrofuran (1 mmol), dioxane (2 ml), and $Sc(OTf)_3$ (3 mol%) were heated at 100 °C.
[b]Isolated yields.

In all cases, the corresponding *N*-substituted pyrroles are formed in good to excellent yields.

As shown in Table 3, a series of aromatic amines bearing either electron-donating (Table 3, entries 2–3, 8) or electron-withdrawing (Table 3, entries 4–7, 10–11) groups on the aromatic ring was investigated. The reaction occurred smoothly without showing a marked substituent effect in the presence of scandium triflate. The substitution groups on the aromatic ring have no obvious effect on the yield and the reaction time under the above optimal conditions. Note that the same substituent group at different positons of the phenyl ring also did not make a significant difference in this protocol (Table 3, entries 2–3, 4–5, 6–7).

Furthermore, we examined the reactivity of heteroaromatic amines with 2,5-dimethoxytetrahydrofuran (**2**) in the presence of scandium triflate. However, good yields were only obtained by prolonged reaction time (Table 3, entries 13–14). For example, the reaction of 5-chloropyridin-2-amine with **2** in the presence of scandium triflate for 240 minutes furnished 5-chloro-2-(1*H*-pyrrol-1-yl)pyridine (**3m**) in 84% yield (Table 3, entry 13). Simiarly, when pyrimidin-2-amine was employed for 300 minutes, 2-(1*H*-pyrrol-1-yl)pyrimidine (**3n**) was obtained in 74% yield (Table 3, entry 14).

To extend the scope of this scandium triflate-catalysed method of *N*-substituted pyrrole formation, 4-methylbenzenesulfonamide and 2-chlorobenzamide were used under the same conditions. The desired product of **3o** was obtained in excellent yield (95%) for a short time (30 min) and the product of **3p** was also obtained in good yield (85%) for 300 min (Scheme 2). Moreover, we also examined the reaction of aliphatic amines with **2**. Unfortunately, scandium triflate failed to promote the condensation of aliphatic amines and 2,5-dimethoxytetrahydrofuran.

In summary, an efficient protocol for the synthesis of *N*-substituted, 2- and 3-unsubstituted pryyoles has been achieved with good to excellent yields. Compared with reported methods, the reaction using scandium triflate as catalyst has exhibited the accelerated reaction time, mild conditions, improved yields, simple work-up and avoidance of strong acidic reaction conditions. In additional, this method demonstrated good functional group tolerance and amines such as aromatic amines, sulfonamide, and benzamide could be good substrates.

Experimental

Chemicals were purchased and used without further purification. All the melting points were uncorrected. ^1H NMR and ^{13}C NMR spectra were measured on a FT-Bruker AT-300 spectrometer (^1H: 300 MHz, ^{13}C: 75 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, the coupling constants *J* are given in Hz. Mass spectra were measured in a Shimadzu GC-MS QP 2010. Elemental analyses were carried out using a Carlo-Erba EA1112 instrument. Column chromatography was performed using EM Silica gel 60 (300–400 mesh)

General procedure for preparation of **3a–p**

A Schlenk reaction tube was charged with amine (1 mmol), 2,5-dimethoxytetrahydrofuran (1 mmol), $Sc(OTf)_3$ (3 mol%), and dioxane (2 ml). The mixture was stirred at 100 °C for a certain period of time as indicated in Table 1 and Scheme 2. The progress of the reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on a silica gel to give the desired, pure product. The physical and spectra data of the compounds **3a–p** are as follows.

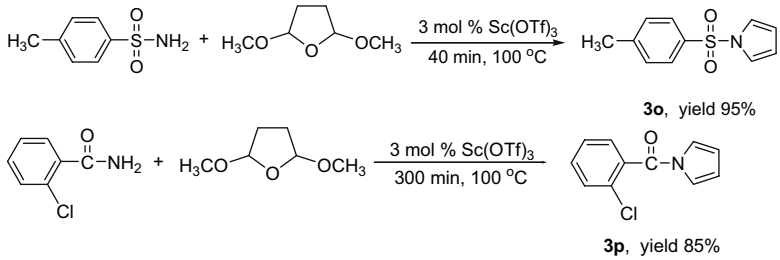
1-phenyl-1H-pyrrole (**3a**): Pale yellow solid, m.p. 58–59 °C (lit.[24] 62 °C); ^1H NMR: δ 7.39–7.47 (m, 4H), 7.23–7.29 (m, 1H), 7.11 (t, *J* = 2.2 Hz, 2H), 6.37 (t, *J* = 2.2 Hz, 2H). ^{13}C NMR: δ 140.5, 129.2, 125.3, 120.2, 119.0, 110.0.

1-p-tolyl-1H-pyrrole (**3b**): White solid, m.p. 80–81 °C (lit.[25] 81.5–83 °C); ^1H NMR: δ 7.20–7.30 (m, 4H), 7.06 (t, *J* = 1.7 Hz, 2H), 6.34 (t, *J* = 1.6 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR: δ 138.2, 135.0, 129.7, 120.2, 119.1, 109.7, 20.5.

1-o-tolyl-1H-pyrrole (**3c**): Yellow oil, ^1H NMR: δ 7.23–7.29 (m, 4H), 6.79 (t, *J* = 2.1 Hz, 2H), 6.31–6.33 (m, 2H), 2.21 (s, 3H). ^{13}C NMR: 140.3, 133.5, 130.7, 127.2, 126.3, 126.2, 121.7, 108.4, 17.5. EI-MS: *m/z* (%): 157 (95). Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.09; H, 7.01; N, 8.90.

1-(4-chlorophenyl)-1H-pyrrole (**3d**):[26] Yellow solid, m.p. 88 °C; ^1H NMR: δ 7.22–7.40 (m, 4H), 7.03 (t, *J* = 2.2 Hz, 2H), 6.35 (t, *J* = 2.1 Hz, 2H). ^{13}C NMR: δ 139.3, 131.0, 129.6, 121.6, 119.2, 110.8.

1-(3-chlorophenyl)-1H-pyrrole (**3e**): White solid, ^1H NMR: δ 7.20–7.39 (m, 4H), 7.05 (t, *J* = 2.2 Hz, 2H), 6.35 (t, *J* = 2.2 Hz, 2H). ^{13}C NMR: 141.4, 134.9, 130.3, 125.3, 120.3, 118.9, 118.1, 110.7. EI-MS: *m/z* (%): 77 (91). Anal. Calcd for $C_{10}H_8ClN$: C, 67.62; H, 4.54; N, 7.89. Found: C, 67.55; H, 4.56; N, 7.93.



Scheme 2 Reaction of 2,5-dimethoxytetrahydrofuranm with 4-methylbenzenesulfonamide or 2-chlorobenzamide.

1-(4-nitrophenyl)-1H-pyrrole (**3f**):[27] Yellow solid, m.p. 187 °C; ^{1}H NMR: δ 8.29–8.34 (m, 2H), 7.49–7.55 (m, 2H), 7.16–7.19 (m, 2 H), 6.42–6.44 (m, 2H). ^{13}C NMR: δ 144.9, 144.4, 125.3, 119.1, 118.8, 112.2.

1-(2-nitrophenyl)-1H-pyrrole (**3g**):[28] Yellow oil, ^{1}H NMR: δ 7.82 (t, *J* = 0.7 Hz, 1H), 7.63–7.64 (d, *J* = 0.4 Hz, 1H), 7.43–7.48 (m, 2H), 6.79 (m, 2H), 6.35 (m, 2H). ^{13}C NMR: δ 145.0, 133.9, 132.9, 127.5, 127.3, 124.6, 121.0, 110.7.

1-(2-methoxyphenyl)-1H-pyrrole (**3h**): Dark yellow oil, ^{1}H NMR: δ 7.03–7.12 (m, 2H), 6.79–6.85 (m, 4H), 6.17 (t, *J* = 2.2 Hz, 2H), 3.58 (s, 3H). ^{13}C NMR: δ 152.6, 130.2, 127.3, 125.6, 121.9, 120.8, 112.3, 108.7, 55.6. EI-MS: *m/z* (%): 173 (100). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.35; H, 6.32; N, 8.08.

1-(4-iodophenyl)-1H-pyrrole (**3i**): White crystalline solid, M.p. 130–131 °C (lit.[29] 128–129 °C); ^{1}H NMR: δ 7.68–7.72 (m, 2H), 7.10–7.14 (m, 2H), 7.01–7.04 (m, 2H), 6.34 (t, *J* = 2.0 Hz, 2H). ^{13}C NMR: δ 140.1, 138.2, 121.9, 118.8, 110.6, 89.1.

2-(1H-pyrrol-1-yl)benzonitrile (**3j**): Yellow oil, ^{1}H NMR: δ 7.64–7.77 (m, 2H), 7.36–7.46 (m, 2H), 7.11–7.14 (m, 2H), 6.41–6.43 (m, 2H). ^{13}C NMR: δ 142.7, 134.2, 133.8, 126.3, 124.8, 120.8, 116.7, 110.9, 106.5. EI-MS: *m/z* (%): 168 (100). Anal. Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.60; H, 4.77; N, 16.63.

1-(2-chloro-5-nitrophenyl)-1H-pyrrole (**3k**): Yellow oil, ^{1}H NMR: δ 8.13–8.25 (m, 2H), 7.72 (d, *J* = 8.8 Hz, 1H), 6.99 (t, *J* = 2.1 Hz, 2H), 6.41 (t, *J* = 2.1 Hz, 2H). ^{13}C NMR: δ 146.5, 139.2, 135.9, 131.4, 122.2, 122.1, 121.7, 110.3. EI-MS: *m/z* (%): 222 (71). Anal. Calcd for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58. Found: C, 53.91; H, 3.20; N, 12.55.

1-(naphthalen-1-yl)-1H-pyrrole (**3l**)[26]: Yellow oil, ^{1}H NMR: δ 7.79–7.96 (m, 3H), 7.46–7.56 (m, 4H), 7.04 (t, *J* = 2.1 Hz, 2H), 6.46 (t, *J* = 2.1 Hz, 2H). ^{13}C NMR: δ 137.9, 133.9, 129.5, 127.7, 127.5, 126.6, 126.2, 124.9, 122.94, 122.91, 122.8, 108.7.

5-chloro-2-(1H-pyrrol-1-yl)pyridine (**3m**): White crystalline solid, m.p. 68–69 °C; ^{1}H NMR: δ 8.37 (d, *J* = 2.5 Hz, 1H), 7.66–7.70 (m, 1H), 7.46 (t, *J* = 2.3 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 1H), 6.37 (t, *J* = 2.3 Hz, 2H). ^{13}C NMR: δ 149.3, 147.0, 137.8, 127.3, 117.8, 111.6, 111.4. EI-MS: *m/z* (%): 178 (100). Anal. Calcd for $C_9H_7ClN_2$: C, 60.52; H, 3.95; N, 15.68. Found: C, 60.48; H, 4.03; N, 15.70.

2-(1H-pyrrol-1-yl)pyrimidine (**3n**): Pale yellow solid, m.p. 81–82 °C; ^{1}H NMR: δ 8.59 (d, *J* = 4.8 Hz, 2H), 7.78 (t, *J* = 2.4 Hz, 2H), 6.99–7.03 (m, 1H), 6.34 (t, *J* = 2.3 Hz, 2H). ^{13}C NMR: δ 158.3, 156.3, 119.0, 117.0, 112.0. EI-MS: *m/z* (%): 145 (100). Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.11; H, 4.50; N, 29.39.

1-tosyl-1H-pyrrole (**3o**): White solid, m.p. 101–102 °C (lit.[9] 96.9–97.5 °C); ^{1}H NMR: δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.25–7.29 (m, 2H), 7.15 (t, *J* = 2.3 Hz, 2H), 6.28 (t, *J* = 2.3 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR: δ 144.6, 135.8, 129.6, 126.5, 120.4, 113.2, 21.3.

(2-chlorophenyl)(1H-pyrrol-1-yl)methanone (**3p**): Pale yellow oil, ^{1}H NMR: δ 7.33–7.46 (m, 4H), 7.10 (s, 2H), 6.30 (t, *J* = 2.3 Hz, 2H). ^{13}C NMR: δ 164.9, 133.4, 131.5, 131.2, 129.8, 128.7, 126.5, 120.1, 113.6. EI-MS: *m/z* (%): 205 (16). Anal. Calcd for $C_{11}H_8ClNO$: C, 64.25; H, 3.92; N, 6.81. Found: C, 64.16; H, 3.82; N, 6.87.

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