Efficient Synthesis of Pyrrolo[1,2-a]quinoxalines Catalyzed by Brønsted Acid through Cleavage of C-C Bond

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1. Preparation of starting materials

1.1 General procedure for preparation of 2-(1H-pyrrol-1-yl)anilines.

Scheme 1 General procedure for preparation of 2-(1H-pyrrol-1-yl)anilines.

2-(1H-pyrrol-1-yl)anilines were prepared according to a modified literature procedure.\(^1\) A mixture of substituted 2-nitroaniline (20 mmol) and 2,5-dimethoxytetrahydrofuran (20 mmol) in acetic acid (100 mL) was refluxed for 2 h with vigorous stirring. After cooling, the reaction mixture was poured into water (300 mL) and extracted with EtOAc three times (3×50 mL). The combined organic layers were dried with MgSO\(_4\) and the solvent was removed in vacuo to afford a residue. The residue was added to iron powder (80 mmol) and NH\(_4\)Cl (20 mmol) in water (50 mL) and reflux for 4 h. After cooling, the reaction mixture was poured into water (300 mL) and extracted with ethyl acetate time times (3×50 mL). The combined organic layers were dried with MgSO\(_4\) and the solvent was removed in vacuo to afford a residue. The residue was purified by column chromatography on silica gel using petroleum ether / EtOAc as eluent to provide the desired product. The spectra data are shown in 2 part.

1.2 General procedure for preparation of 2-(1H-indol-1-yl)aniline.

Scheme 2 General procedure for preparation of 2-(1H-indol-1-yl)anilines

2-(1H-indol-1-yl)anilines were prepared according to a modified literature procedure.\(^2\) A
mixture of 2-nitroaniline (2 mmol), N-heterocycle (2 mmol) and NaOH (2 mmol) in DMSO (4 mL) was stirred vigorously for 2 h. After cooling, the reaction mixture was poured into water (30 mL) and extracted with EtOAc three times (3×30 mL). The combined organic layers were dried with MgSO₄ and the solvent was removed in vacuo to afford a residue. The residue was added to iron powder (16 mmol) and NH₄Cl (1 mmol) in water (30 mL) and refluxed for 4 h. After cooling, the reaction mixture was poured into water (100 mL) and extracted with ethyl acetate twice (3×30 mL). The combined organic layers were dried with MgSO₄ and the solvent was removed in vacuo to afford a residue. The residue was purified by column chromatography on silica gel using petroleum ether / ethyl acetate as eluent to provide the desired product. The spectra data are shown in 2 part.

1.3 General procedure for preparation of Benzhydryl 3-oxobutanoate

![Scheme 3 General procedure for preparation of Benzhydryl 3-oxobutanoate](image)

Benzhydryl 3-oxobutanoate was prepared according to a modified literature procedure.³ In a 100 mL round-bottom flask, equipped with a magnetic stir bar and a reflux condenser, 2,2,6-trimethyl-4H-1,3-dioxin-4-one (2 mmol, 0.28 g) and benzyl alcohol (2 mmol, 0.36 g) was dissolved in 5 mL xylene. The reaction was heated to vigorous reflux for 4 h, then cooled to room temperature. Xylene was removed in vacuo. The residue was purified by column chromatography on silica gel using petroleum ether / ethyl acetate as eluent to provide the desired product. This compound is literature known.³
2. Spectra data of starting materials

2-(1H-pyrrol-1-yl)aniline (1a)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.16$-$7.12$ (m, 2H), 6.82 (t, $J = 2.1$ Hz, 2H), 6.79-$6.75$ (m, 2H), 6.33 (t, $J = 2.0$, 2H), 3.68 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 142.07$, 128.59, 127.54, 127.20, 121.74, 118.43, 116.13, 109.42; HRMS calcd for C$_{10}$H$_{10}$N$_2$ [(M+H)$^+$]: 159.0917; found, 159.0916.

5-methyl-2-(1H-pyrrol-1-yl)aniline (1b)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.03$ (d, $J = 7.7$ Hz, 1H), 6.80 (t, $J = 2.1$ Hz, 2H), 6.60 (d, $J = 9.2$ Hz, 2H), 6.32 (t, $J = 2.0$ Hz, 2H), 3.61 (s, 2H), 2.29 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 141.86$, 138.62, 126.98, 125.27, 121.86, 119.20, 116.60, 109.24, 21.20; HRMS calcd for C$_{11}$H$_{12}$N$_2$ [(M+H)$^+$]: 173.1073; found, 173.1081.

5-chloro-2-(1H-pyrrol-1-yl)aniline (1c)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.05$ (d, $J = 8.3$ Hz, 1H), 6.78-$6.76$ (m, 3H), 6.74 (dd, $J = 8.3$ Hz, 2.2 Hz, 1H), 6.34 (t, $J = 2.06$ Hz, 2H), 3.76 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 143.15$, 133.97, 128.17, 125.95, 121.65, 118.23, 115.62, 109.77; HRMS calcd for C$_{10}$H$_{9}$ClN$_2$ [(M+H)$^+$]: 193.0527; found, 193.0528.

5-fluoro-2-(1H-pyrrol-1-yl)aniline (1d)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.08$-$7.04$ (m, 1H), 6.76 (t, $J = 2.0$ Hz, 2H), 6.47-$6.42$ (m, 2H), 6.33 (t, $J = 2.0$ Hz, 2H), 3.78 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 163.98$ ($^1$J$_{C,F}$ = 243 Hz), 143.93 ($^3$J$_{C,F}$ = 12 Hz), 128.61 ($^3$J$_{C,F}$ = 11 Hz), 123.64, 121.91, 109.60, 104.93 ($^2$J$_{C,F}$ = 23 Hz), 102.57 ($^2$J$_{C,F}$ = 26 Hz); HRMS calcd for C$_{10}$H$_9$FN$_2$ [(M+H)$^+$]: 177.0823; found, 177.0827.

5-methoxy-2-(1H-pyrrol-1-yl)aniline (1e)
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.07 (dd, $J$ = 8.8 Hz, 3.6 Hz, 1H), 6.77 (t, $J$ = 2.8Hz, 2H ), 6.35-6.31 (m, 4H), 3.78 (s, 3H ), 3.67 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 159.94, 143.36, 128.15, 122.12, 121.24, 109.17, 103.66, 102.13, 55.40; HRMS calcd for C$_{11}$H$_{12}$ON$_2$ [(M+H)$^+$]: 189.1022; found, 189.1024.

4-chloro-2-(1H-pyrrol-1-yl)aniline (1g)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.13-7.09 (m, 2H), 6.80 (m, $J$ = 1.8 Hz, 2H), 6.71 (d, $J$ = 8.4 Hz, 1H), 6.33 (d, $J$ = 2.1 Hz, 2H), 3.70 (s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 140.67, 128.38, 128.06, 126.98, 122.58, 121.51, 116.94, 109.88; HRMS calcd for C$_{10}$H$_9$ClN$_2$ [(M+H)$^+$]: 193.0527; found, 193.0529.

4-fluoro-2-(1H-pyrrol-1-yl)aniline (1h)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 6.93-6.86 (m, 2H), 6.83 (t, $J$ = 2.1 Hz, 2H), 6.35 (d, $J$ = 9.6 Hz, 5.1 Hz, 1H), 6.34-6.31 (m, 2H), 3.65 (s, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 157.14 ($^1$J$_{C,F}$ = 236 Hz), 137.91, 127.88 ($^3$J$_{C,F}$ = 9 Hz), 121.53, 116.89 ($^3$J$_{C,F}$ = 8 Hz), 115.29 ($^2$J$_{C,F}$ = 23 Hz), 114.10 ($^2$J$_{C,F}$ = 23 Hz), 109.85; HRMS calcd for C$_{10}$H$_9$FN$_2$ [(M+H)$^+$]: 177.0823; found, 177.0821.

2-(1H-indol-1-yl)aniline (1i)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.69-7.67 (m, 1H), 7.23-7.14 (m, 6H), 6.83-6.80 (m, 2H), 6.67 (d, $J$ = 3.16 Hz, 1H), 3.49 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 143.21, 136.42, 129.24, 128.69, 128.62, 124.90, 122.30, 121.04, 120.24, 118.58, 116.31, 110.83, 103.28. HRMS calcd for C$_{14}$H$_{12}$N$_2$ [(M+H)$^+$]: 209.1072; found, 209.1071.

2-(3-methyl-1H-indol-1-yl)aniline (1j)
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.80-7.77 (m, 1H), 7.35-7.24 (m, 5H), 7.09 (s, 1H), 6.96-6.89 (m, 2H), 3.48 (s, 2H), 2.54 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 143.27, 136.85, 129.14, 129.00, 128.71, 126.28, 125.24, 122.35, 119.69, 119.20, 118.62, 116.37, 112.50, 110.79, 9.81. HRMS calcd for C$_{15}$H$_{14}$N$_2$ [(M+H)$^+$]: 223.1230; found, 223.1232.

2-(1H-imidazol-1-yl)aniline (1k)

$^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ = 7.75 (s, 1H), 7.30 (s, 1H), 7.17-7.11 (m, 1H), 7.11 (s, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 4.94 (s, 2H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ = 143.21, 137.42, 129.02, 128.89, 126.74, 122.44, 120.28, 116.32, 116.05. HRMS calcd for C$_9$H$_9$N$_3$ [(M+H)$^+$]: 160.0869; found, 160.0864.

3.$^1$H NMR, $^{13}$C NMR and HRMS spectra

3.1 The spectra of starting materials

2-(1H-pyrrol-1-yl)aniline (1a)
5-methyl-2-(1H-pyrrol-1-yl)aniline (1b)
5-chloro-2-(1H-pyrrol-1-yl)aniline (1c)
5-fluoro-2-(1H-pyrrol-1-yl)aniline (1d)
5-methoxy-2-(1H-pyrrol-1-yl)aniline (1e)
4-chloro-2-(1H-pyrrol-1-yl)aniline (1g)
4-fluoro-2-(1H-pyrrol-1-yl)aniline (1h)
2-(1H-indol-1-yl)aniline (1i)
2-(3-methyl-1H-indol-1-yl)aniline (1j)
2-(1H-imidazol-1-yl)aniline (1k)
3.2 The spectra of products

4-phenylpyrrolo[1,2-a]quinoxaline (4a)
7-methyl-4-phenylpyrrolo[1,2-α]quinoxaline (4b)
7-methoxy-4-phenylpyrrolo[1,2-α]quinoxaline (4c)
7-chloro-4-phenylpyrrolo[1,2-a]quinoxaline (4d)
8-chloro-4-phenylpyrrolo[1,2-a]quinoxaline (4e)
7-fluoro-4-phenylpyrrolo[1,2-α]quinoxaline (4f)
8-fluoro-4-phenylpyrrolo[1,2-a]quinoxaline (4g)
6-phenylindolo[1,2-α]quinoxaline (4i)
7-methyl-6-phenylindolo[1,2-α]quinoxaline (4j)
4-methylpyrrolo[1,2-α]quinoxaline (4k)
4-ethylpyrrolo[1,2-α]quinoxaline (4l)
4,7-dimethylpyrrolo[1,2-a]quinoxaline (4n)
7-chloro-4-methylpyrrolo[1,2-\text{a}]quinoxaline (4o)
7-methoxy-4-methylpyrrolo[1,2-α]quinoxaline (4p)
4-(4-methoxyphenyl)pyrrolo[1,2-a]quinoxaline (4q)
4-(3-fluorophenyl)pyrrolo[1,2-\(a\)]quinoxaline (4r)
4-(4-fluorophenyl)pyrrolo[1,2-α]quinoxaline (4s)
4-(4-fluorophenyl)-7-methylpyrrolo[1,2-α]quinoxaline (4t)
4-(4-methoxyphenyl)-7-methylpyrrolo[1,2-α]quinoxaline (4u)
7-chloro-4-(3-fluorophenyl)pyrrolo[1,2-\(\alpha\)]quinoxaline (4v)
7-chloro-4-(4-fluorophenyl)pyrrolo[1,2-α]quinoxaline (4w)
7-methoxy-4-(4-methoxyphenyl)pyrrolo[1,2-α]quinoxaline (4x)
4-(3-fluorophenyl)-7-methoxypyrrolo[1,2-\(a\)]quinoxaline (4y)
5-(pyrrolo[1,2-α]quinoxalin-4-yl)pentan-2-one (4z)
(Z)-1,3-diphenyl-3-(phenylamino)prop-2-en-1-one (5e)
Acetophenone (5f)

4. Reference
