Electronic Supplementary Information

Aryne Cycloaddition with 3-Oxidopyridinium Species

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Table of Contents

Preparation of the 3-Oxidopyridinium Species........................................................................ESI2-ESI5
Preparation of the 3- Amidopyridinium Species......................................................................ESI6
References and Notes ..................................................................................................................ESI17
Copies of $^1$H and $^{13}$C NMR Spectra, including 2D NMR Spectra........................................ESI18-ESI74
Preparation of the 3-Oxidopyridinium Species

Method A, representatively outlined for the preparation of 1a:1,2

To a stirred solution of furfural (1.00 g, 10.5 mmol) in absolute ethanol (25 mL) was added benzylamine (1.07 g, 10 mmol) at room temperature. After stirring for 1 h, sodium borohydride was added (0.76 g, 20 mmol, 2 equiv.) and stirring continued overnight. The reaction was concentrated in vacuo and 10 wt % K₂CO₃ (30 mL) was added. The aqueous layer was extracted with CH₂Cl₂. Combined extracts were dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography (petroleum ether/EtOAc 4:1, with 1 vol % of Et₃N) to afford N-benzyl-N-(2-furylmethyl)amine (1.75 g, 94%) as an oil.

To a solution of the amine obtained from the above reaction (0.37 g, 2 mmol) in 1:1 acetic acid/water (20 mL) at 0 °C was added bromine (2.2 mL of 1 M solution in acetic acid, 2.2 mmol, 1.1 equiv) over 1 min. The reaction mixture was stirred for 1 h and concentrated in vacuo. The residue was taken up in 3:1 THF/water (40 mL) and neutralized by Amberlite IRA-400 resin (OH form, 30 g). After the mixture was stirred for 30 min, the resin was filtered off and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (10 vol % MeOH in CH₂Cl₂ with 1 vol % of NH₄OH) to afford 1a (255 mg, 69%) as white crystals, mp 82–83 °C (lit107–111 °C);1 H NMR (300 MHz, CDCl₃) δ 7.47 (dd, J = 2.3, 2.2 Hz, 1 H), 7.44–7.37 (m, 3 H), 7.31–7.19 (m, 4 H), 7.07–7.05 (m, 1 H), 5.19 (s, 2 H); 13C NMR (75 MHz, CDCl₃) δ 169.9, 134.4, 134.2, 132.9, 129.5, 129.4, 128.1, 126.9, 121.4, 64.1; HRMS (ESI) calcd for C₁₂H₁₂NO (M+H) 186.0913, found 186.0914.

Per the above procedure, the following 3-oxidopyridinium species were prepared:

**Compound 1d**: prepared from 5-methylfurfural and BnNH₂, yield 50%, white solid, mp 166–168 °C;1 H NMR (300 MHz, CDCl₃) δ 7.50 (d, J = 2.8 Hz, 1 H), 7.43–7.31 (m, 4 H), 7.11–7.06 (m, 3 H), 5.25 (s, 2 H), 2.34 (s, 3 H); 13C NMR (100 MHz, CDCl₃) δ 168.1, 136.2, 134.9, 132.7, 130.7, 129.3, 129.2, 128.8, 126.5, 60.7, 18.3; HRMS (ESI) calcd for C₁₃H₁₄NO (M+H) 200.1070, found 200.1066.

**Compound 1g**: prepared from furfural and CyNH₂, yield 95%, white solid, mp 168–170 °C;1 H NMR (300 MHz, CDCl₃) δ 7.48 (t, J = 2.2 Hz, 1 H), 7.16–7.25 (m, 2 H), 7.06 (dt, J = 5.4, 1.5 Hz, 1 H), 3.88 (tt, J = 12.2, 3.7 Hz, 1 H), 2.19–2.09 (m, 2 H), 2.03–1.93 (m, 2 H), 1.82–1.68 (m, 3 H), 1.52–1.21 (m, 3 H); 13C NMR (75 MHz, CDCl₃) δ 169.9, 134.0, 132.1, 126.6, 119.5, 70.6, 33.6, 25.3, 24.6; HRMS (ESI) calcd for C₁₁H₁₆NO (M+H) 178.1226, found 178.1223.
**Compound 1h**: prepared from furfural and \( \text{BuNH}_2 \), yield 62%, brown oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.74 (s, 1 H), 7.27–7.24 (m, 1 H), 7.23–7.21 (m, 2 H), 1.68 (s, 9 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 169.5, 133.0, 131.6, 126.4, 118.2, 65.6, 30.0; HRMS (ESI) calcd for \( \text{C}_{18}\text{H}_{27}\text{N}_{2}\text{O}_{2} \) (2M+H) 303.2067, found 303.2068.

**Compound 1m**: prepared from furfural and 3-aminopyridine, yield 51%, light-gray solid, mp 90–92 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.87 (dd, \( J = 4.8, 1.4 \) Hz, 1 H), 8.83 (d, \( J = 2.5 \) Hz, 1 H), 7.87 (ddd, \( J = 8.2, 2.7, 1.5 \) Hz, 1 H), 7.58 (ddd, \( J = 8.2, 4.8, 0.6 \) Hz, 1 H), 7.56 (t, \( J = 2.3 \) Hz, 1 H), 7.46 (left side of a dd of ABq, \( J_{AB} = 9.1 \) Hz, \( J = 2.6, 1.1 \) Hz, 1 H), 7.40 (right side of a dd of ABq, appearing as a d of ABq, \( J_{AB} = 9.1 \) Hz, \( J = 5.3, 1 \) Hz, 1 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 169.8, 151.9, 144.5, 140.3, 136.0, 133.9, 131.3, 127.1, 124.6, 121.2; HRMS (ESI) calcd for \( \text{C}_{10}\text{H}_{9}\text{N}_{2} \) 173.0709, found 173.0705.

**Compound 1o**: prepared from 5-hydroxymethylfurfural and BnNH\(_2\), yield 41%, light-gray solid, mp 164–166 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.45 (d, \( J = 2.8 \) Hz, 1 H), 7.43–7.33 (m, 3 H), 7.30 (d, \( J = 9.0 \) Hz, 1 H), 7.21 (d, \( J = 7.3 \) Hz, 2 H), 6.93 (dd, \( J = 9.1, 2.8 \) Hz, 1 H), 5.84 (br, 1 H), 5.55 (s, 2 H), 4.41 (s, 2 H); \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)) \( \delta \) 170.0, 134.6, 133.9, 126.7, 121.7, 47.1; HRMS (ESI) calcd for \( \text{C}_{13}\text{H}_{14}\text{NO} \) (M+H) 216.1019, found 216.1019.

**Method B**, representatively outlined for the preparation of 1e:

A mixture of 475 mg (5 mmol) of 3-hydroxypyridine and 709 mg (5 mmol) of Mel in 1-propanol (3 mL) was heated under reflux for 8 h. Solvent was then removed and the residue was taken up in 3:1 THF/water (80 mL). The mixture was neutralized by Amberlite IRA-400 resin (OH form, 60 g). After the mixture was stirred for 30 min, the resin was filtered off and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (10 vol % MeOH in CH\(_2\)Cl\(_2\) with 1 vol % NH\(_4\)OH) to afford 1e (440 mg, 68%) as a dark oil; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.35 (t, \( J = 2.2 \) Hz, 1 H), 7.24–7.15 (m, 2 H), 6.96 (d, \( J = 5.2 \) Hz, 1 H), 3.96 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 170.0, 134.6, 133.9, 126.7, 121.7, 47.1; HRMS (ESI) calcd for \( \text{C}_{6}\text{H}_{8}\text{NO} \) (M+H) 100.0600, found 100.0597.

Per the above procedure, the following 3-oxidopyridinium species were prepared:
**Compound 1b:** prepared from 2-methyl-3-hydroxy-5-pyridine and BnBr, yield 95%, purple solid, mp 71–73 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.40–7.32 (m, 3 H), 7.28–7.24 (m, 1 H), 7.19–7.15 (m, 2 H), 7.05–7.02 (m, 2 H), 5.41 (s, 2 H), 2.49 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 167.9, 145.9, 133.0, 129.9, 129.3, 128.8, 126.2, 124.6, 123.1, 61.2, 13.1; HRMS (ESI) calcd for C$_{13}$H$_{14}$NO (M+H) 200.1070, found 200.1072.

**Compound 1c:** prepared from 3-chloro-5-hydroxy-5-pyridine and BnBr, yield 73%, yellow-green solid, mp 156–158 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.46–7.41 (m, 3 H), 7.38 (t, $J = 2.1$ Hz, 1 H), 7.32–7.27 (m, 2 H), 7.19 (dd, $J = 2.4, 1.7$ Hz, 1 H), 7.03 (t, $J = 1.7$ Hz, 1 H), 5.17 (s, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 169.4, 134.6, 133.6, 133.4, 132.1, 129.9, 129.5, 128.3, 119.3, 64.4; HRMS (ESI) calcd for C$_{12}$H$_{11}$NOCl (M+H) 220.0524, found 220.0524.

**Compound 1f:** prepared from 3-hydroxy-5-pyridine and cyclopropylmethyl bromide, yield 48%, pink solid, mp 133–135 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 (m, 1 H), 7.17–7.09 (m, 2 H), 7.04 (m, 1 H), 3.86 (d, $J = 7.3$ Hz, 2 H), 1.27–1.16 (m, 1 H), 0.74–0.62 (m, 2 H), 0.42–0.34 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.4, 134.6, 133.6, 133.4, 132.1, 129.9, 129.5, 128.3, 119.3, 64.4; HRMS (ESI) calcd for C$_9$H$_{12}$NO (M+H) 150.0913, found 150.0910.

**Compound 1l:** prepared from 3-hydroxy-5-pyridine and 2-bromopyridine, recrystallized from methanol/EtOAc, yield 56%, beige solid, mp 182–184 °C; $^1$H NMR (400 MHz, D$_2$O) δ 8.85–8.81 (m, 2 H), 8.62 (dd, $J = 4.9, 0.7$ Hz, 1 H), 8.18 (td, $J = 7.9, 1.8$ Hz, 1 H), 8.17 (left side of a dd of ABq, $J_{AB} = 8.7$ Hz, $J = 2.5, 0.9$ Hz, 1 H), 7.97 (right side of a dd of ABq, appearing as a d of ABq, $J_{AB} = 8.7$ Hz, $J = 6.0$ Hz, 1 H), 7.90 (dt, $J = 8.2, 0.8$ Hz, 1 H), 7.72 (dd, $J = 7.6, 4.9$ Hz, 1 H), $^{13}$C NMR (100 MHz, D$_2$O) δ 156.8, 151.9, 149.5, 141.4, 134.2, 134.1, 130.9, 128.5, 127.1, 118.2; HRMS (ESI) calcd for C$_{10}$H$_9$N$_2$O (M+H) 173.0709, found 173.0707.
Compound 1n: prepared from 3-hydroxypyridine and chloromethyl methyl ether, yield 26%, brown oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.56 (s, 1 H), 7.38 (dd, $J = 8.9$, 1.8 Hz, 1 H), 7.31 (dd, $J = 8.8$, 5.6 Hz, 1 H), 7.20 (d, $J = 5.4$ Hz, 1 H), 5.33 (s, 2 H), 3.43 (s, 3 H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 168.1, 134.2, 132.3, 127.0, 121.7, 89.0, 57.0. HRMS (ESI) calcd for C$_7$H$_{10}$NO (M+H) 140.0706, found 140.0701.

Method C, representatively outlined for the preparation of 1i:

A mixture of 535 mg (5 mmol) of 4-methylaniline and 720 mg (7.5 mmol) of furfural in ethanol/H$_2$O (1:1, 12.5 mL) was heated under reflux under air overnight. Solvent was then removed. The crude product was purified by flash chromatography (10 vol % MeOH in CH$_2$Cl$_2$ with 1 vol % of NH$_4$OH) to afford 1i (102 mg, 11%) as brown oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.53–7.52 (m, 1 H), 7.31–7.23 (m, 6 H), 7.23–7.19 (m, 1 H), 2.34 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.1, 141.2, 140.8, 134.5, 133.8, 130.5, 126.5, 123.0, 122.0, 20.8; HRMS (ESI) calcd for C$_{12}$H$_{12}$NO (M+H) 186.0913, found 186.0910.

Per the above procedure, the following 3-oxidopyridinium species were prepared:

Compound 1j: prepared from furfural and 4-chloroaniline, yield 12%, brown solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57 (s, 1 H), 7.52 (d, $J = 8.6$ Hz, 2 H), 7.42 (d, $J = 8.6$ Hz, 2 H), 7.39–7.30 (m, 2 H), 7.22 (d, $J = 4.8$ Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.3, 141.2, 140.8, 134.5, 133.8, 130.5, 126.5, 123.0, 122.0, 20.8; HRMS (ESI) calcd for C$_{11}$H$_9$ClNO (M+H) 206.0863, found 206.0859.

Compound 1k: prepared from furfural and 2-methoxyaniline, yield 6%, brown solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52–7.42 (m, 2 H), 7.37 (d, $J = 9.0$ Hz, 1 H), 7.31–7.25 (m, 2 H), 7.11–7.02 (m, 3 H), 3.77 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.1, 152.1, 136.0, 134.7, 132.3, 131.8, 126.1, 126.0, 123.7, 121.0, 112.6, 55.9; HRMS (ESI) calcd for C$_{12}$H$_{12}$NO$_2$ (M+H) 202.0863, found 202.0859.
Preparation of the 3-aminopyridinium Species

General procedures representatively outlined for the preparation of 5a

A mixture of 496 mg (2 mmol) of 3-tosylamidopyridine and 357 mg (2.1 mmol) of BnBr in toluene (1.5 mL) was heated under reflux for 3 h. Solvent was then removed and the residue was recrystallized from EtOH to afford 5a (652 mg, 78%) as white solid, mp 204–205 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 8.84–8.79 (m, 1 H), 8.65 (s, 1 H), 8.08 (d, $J$ = 8.6 Hz, 1 H), 7.95 (t, $J$ = 6.5 Hz, 1 H), 7.65 (d, $J$ = 8.2 Hz, 2 H), 7.51–7.39 (m, 5 H), 7.31 (d, $J$ = 8.1 Hz, 2 H), 5.83 (s, 2 H), 2.33 (s, 3 H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 157.5, 143.6, 137.9, 136.4, 134.11, 134.06, 133.7, 129.9, 129.4, 129.2, 128.9, 128.7, 126.7, 63.4, 21.0; HRMS (ESI) calcd for C$_{19}$H$_{19}$N$_2$O$_2$S (M$^+$) 339.1162, found 339.1166.

**Compound 5b:** prepared from 3-tosylamidopyridine and cyclopropylmethyl bromide, recrystallized from EtOH, yield 89%, white solid, mp 171–172 °C; $^1$H NMR (400 MHz, D$_2$O) $\delta$ 8.59 (s, 1 H), 8.54 (d, $J$ = 6.0 Hz, 1 H), 8.09 (dd, $J$ = 8.6, 1.4 Hz, 1 H), 7.83 (dd, $J$ = 8.6, 6.0 Hz, 1 H), 7.69 (d, $J$ = 8.4 Hz, 2 H), 7.36 (d, $J$ = 8.4 Hz, 2 H), 4.35 (d, $J$ = 7.6 Hz, 2 H), 2.32 (s, 3 H), 1.35–1.20 (m, 1 H), 0.74–0.62 (m, 2 H), 0.51–0.36 (m, 2 H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 144.6, 139.7, 138.3, 135.3, 134.05, 133.99, 130.2, 128.7, 127.0, 64.9, 21.0, 11.9, 4.0; HRMS (ESI) calcd for C$_{16}$H$_{19}$N$_2$O$_2$S (M$^+$) 303.1162, found 303.1159.

**Compound 5c:** prepared from 3-(Boc-amido)pyridine and BnBr, recrystallized from EtOH/EtOAc, yield 56%, brown solid, mp 181–182 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 9.23 (s, 1 H), 8.91 (d, $J$ = 5.9 Hz, 1 H), 8.36 (dd, $J$ = 8.7, 1.2 Hz, 1 H), 8.06 (dd, $J$ = 8.7, 5.9 Hz, 1 H), 7.56–7.47 (m, 2 H), 5.92 (s, 2 H), 1.47 (s, 9 H); $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 152.6, 140.9, 137.9, 134.2, 133.3, 133.2, 129.3, 129.2, 128.8, 128.3, 81.1, 63.5, 27.9; HRMS (ESI) calcd for C$_{17}$H$_{23}$N$_2$O$_2$ (M$^+$) 285.1598, found 285.1598.
References and Notes:


4. Our compound is pure judged by NMR. The melting range is sharp. The inconsistency with literature value might come from different forms of crystals.

Copies of $^1$H and $^{13}$C NMR Spectra:
Please note the small signal at 9.7 ppm.
Please note the small signal at 9.72 ppm.
NOESY spectrum for this compound (2r):
NOESY spectrum for this compound (2r'):
The signals at 1.26 and 0.87 ppm are petroleum ether residue. Our previous experience with the same supplier of petroleum ether indicated that this residue contains mostly $C_{12}$ paraffin.
The signals at 29.8 ppm is petroleum ether residue.
NOESY spectrum for this compound (7):

Expansion 1
List of NOE correlations

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Calculated dihedral angles (Spartan 08):

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Both angles correlate well with the observed coupling constants.