Ruthenium-catalyzed intramolecular selective halogenation of O-methylbenzohydroximoyl halides: a new route to halogenated aromatic nitriles

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Electronic Supplementary Information (ESI)

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Experimental Section

General Procedure for the Preparation of Starting Materials 1 and 3.

**Method A**

\[ \text{R} - \text{N}=\text{C}=\text{O} \xrightarrow{\text{NCS or NBS}} \text{R} - \text{N}=\text{C}=\text{Cl, Br} \]

The appropriate \( O \)-alkyl benzaldehyde oxime (20 mmol, 1.0 equiv) and DMF (50 mL) was charged in a 250 mL round-bottom flask. Then, \( N \)-chlorosuccinimide (NCS, 20 mmol, 1.0 equiv) or \( N \)-bromosuccinimide (NBS, 20 mmol, 1.0 equiv) was slowly added to the reaction mixture. After the addition was complete, the reaction mixture was stirred at room temperature for 48 h. Then, the reaction mixture was poured into ice water (70 mL) and the resulting mixture was extracted three times with dichloromethane. The combined organic layers were dried over \( \text{MgSO}_4 \), filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure 1 or 3.


**Method B**

\[ \text{R} - \text{N}=\text{C}=\text{O} \xrightarrow{\text{H}_2\text{NOMeHCl, K}_2\text{CO}_3} \xrightarrow{\text{PCl}_5 \text{ or PBr}_5} \text{R} - \text{N}=\text{C}=\text{Cl, Br} \]

\( O \)-Methylhydroxylamine hydrochloride (2.0 g, 24.0 mmol, 1.2 equiv) and \( \text{K}_2\text{CO}_3 \) (5.98 g, 48.0 mmol, 2 equiv) were dissolved in 120 mL of mixture of ethyl acetate and water (2:1) in a round-bottomed flask. The solution was cooled to 0 °C in an ice bath. The corresponding benzoyl chloride (20.0 mmol, 1.0 equiv) was added via syringe and the reaction mixture was stirred at room temperature for 8 h. Then, the aqueous layer in the reaction mixture was separated out and organic layer was washed with water and then brine. After drying over \( \text{MgSO}_4 \), solvents were evaporated under reduced pressure. The crude reaction mixture was transferred into a round-bottom flask with a stir bar, and dry benzene (60 mL) was added. The solution was cooled to 5 °C and \( \text{PCl}_5 \) (6.25 g, 30.0 mmol, 1.5 equiv) or \( \text{PBr}_5 \) (6.50 g, 30.0 mmol, 1.5 equiv) was added. The reaction mixture was stirred at 5 °C for 2 h and then allowed to warm at room temperature for 30 min. The resulting mixture was extracted three
times with hexane. The combined organic layers were dried over MgSO₄, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure 1 or 3.


**General Procedure for Intramolecular Halogenation of O-Methylbenzohydroximoyl Halides Catalyzed by Ruthenium Complex.**

A 15-mL pressure tube equipped with a magnetic stirrer and septum containing [{RuCl₂(p-cymene)}₂] (0.03 mmol, 3 mol %) and diphenylacetylene (30 mol %) or methyl acrylate (50 mol %) was evacuated and purged with nitrogen gas three times. To the tube were then added O-methylbenzohydroximoyl halides 1 or 3 (1.00 mmol) and iso-propanol (3.0 mL) via syringes and again the tube was evacuated and purged with nitrogen gas three times. Then, in the pressure tube, septum was taken out and covered with a screw cap immediately under nitrogen atmosphere and the reaction mixture was allowed to stir at 100 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with CH₂Cl₂, filtered through Celite and silica gel, and the filtrate was concentrated. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure 2 and 4.

**General Procedure for the Preparation of Substituted Tetrazoles.**

A 50-mL two-neck round bottom flask equipped with a magnetic stirrer, septum and condenser containing I₂ (20 mol %), NaN₃ (1.5 mmol) and aromatic nitriles 2 (1.0 mmol). To the round bottom flask was then added solvent DMF (3.0 mL) via syringe. Then, the reaction mixture was allowed to stir at 120 °C for 24 h. After cooling to ambient temperature, the reaction mixture was extracted three times with DCM. The combined organic layers were dried over MgSO₄, filtered and the filtrate was concentrated under reduced pressure. The crude residue was purified through a silica gel column using hexanes and ethyl acetate as eluent to give pure 5.

Spectral data and copies of ¹H and ¹³C NMR spectra of all compounds are listed below (pages S16 – S75).
Optimization Studies

Table 1. Optimization Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ru cat.</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ru cat</td>
<td>No ligand</td>
<td>MeOH</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Ru cat</td>
<td>PPh₃ (20 mol %)</td>
<td>MeOH</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>Ru cat</td>
<td>dppe (10 mol %)</td>
<td>MeOH</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>Ru cat</td>
<td>diphenylacetylene (30 mol %)</td>
<td>MeOH</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>Ru cat</td>
<td>styrene (30 mol %)</td>
<td>MeOH</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Ru cat</td>
<td>methyl acrylate (50 mol %)</td>
<td>MeOH</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>Ru cat</td>
<td>norbornadiene (50 mol %)</td>
<td>MeOH</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>Ru cat</td>
<td>cyclooctadiene (50 mol %)</td>
<td>MeOH</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>Ru cat</td>
<td>norbornene (50 mol %)</td>
<td>MeOH</td>
<td>NR</td>
</tr>
<tr>
<td>10</td>
<td>No Ru cat</td>
<td>diphenylacetylene (30 mol %)</td>
<td>MeOH</td>
<td>NR</td>
</tr>
<tr>
<td>11</td>
<td>Ru cat</td>
<td>diphenylacetylene (30 mol %)</td>
<td>iso-PrOH</td>
<td>93</td>
</tr>
<tr>
<td>12</td>
<td>Ru cat</td>
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<td>tert-BuOH</td>
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</tr>
<tr>
<td>13</td>
<td>Ru cat</td>
<td>diphenylacetylene (30 mol %)</td>
<td>DMF</td>
<td>60</td>
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<tr>
<td>14</td>
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<td>THF</td>
<td>NR</td>
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<td>NR</td>
</tr>
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<td>toluene</td>
<td>NR</td>
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<tr>
<td>17</td>
<td>Ru cat</td>
<td>diphenylacetylene (30 mol %)</td>
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<td>18</td>
<td>Ru cat</td>
<td>diphenylacetylene (30 mol %)</td>
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<td>NR</td>
</tr>
<tr>
<td>19</td>
<td>Ru cat</td>
<td>diphenylacetylene (30 mol %)</td>
<td>1,4-dioxane</td>
<td>NR</td>
</tr>
</tbody>
</table>

All reactions were carried out using 1a (1.0 mmol), ligand and [{RuCl₂(p-cymene)}₂] (3 mol %) in solvent (3.0 mL) at 100 ºC for 16 h. Yields were determined by the ¹H NMR integration method, using mesitylene as an internal standard.

In the beginning of the project, the intramolecular chlorination of 1a was examined in the presence of [{RuCl₂(p-cymene)}₂] (3 mol %) in MeOH at 100 ºC for 16 h. However, in the reaction, no chlorination product 2a was observed (Table 1, entry 1). Then, the catalytic reaction was tested in the presence of phosphine ligands PPh₃ and dppe and carbon-carbon π-component ligands such as diphenylacetylene, styrene, methyl acrylate, norbornene, norbornadiene and cyclooctadiene (entries 2-9). The corresponding chlorination product 2a was observed in the presence of ligand, diphenylacetylene, in 72% yield (entry 4). The yield of product 2a was determined by the ¹H NMR integration methods using mesitylene as an internal standard. Methyl acrylate (50 mol %) also worked equally, giving 2a in 71% yield (entry 6). Other ligands were totally inactive for the reaction. Usually, less coordinating carbon-carbon π-component moieties are suitable ligands for C-H bond activation reaction.
Importantly, diphenylacetylene or methyl acrylate was not involved in the reaction. In the crude reaction mixture, diphenylacetylene or methyl acrylate was found. This was isolated and confirmed by NMR spectroscopy. The reaction was tested without ruthenium catalyst and just only in the presence of ligand. In the reaction, no 2a was observed (entry 10). This result clearly revealed that both ruthenium and ligand such as diphenylacetylene or methyl acrylate are crucial for the reaction. In order to increase the yield of 2a, the catalytic reaction was tested with various solvents such as iso-PrOH, tert-BuOH, DMF, THF, CH3CN, toluene, 1,2-dichloroethane, acetic acid and 1,4-dioxane (entries 11-19). Among them, iso-PrOH was the best solvent, providing 2a in excellent 93% yield (entry 11). tert-BuOH and DMF were also partially active solvent, giving 2a in 55% and 60% yields, respectively (entries 12 and 13). The remaining solvents were totally ineffective for the reaction. In the meantime, the halogenation reaction was also tested with N-hydroxybenzimidoyl chloride instead of N-methoxybenzimidoyl chloride 1b under the optimized reaction conditions (eq. 1). However, in the reaction, no halogenation compound was observed and only methyl 4-methoxybenzoate was observed in 85% yield (eq. 1). In the reaction, imidoyl chloride moiety was converted into ester under the reaction conditions.
Regioselective Studies

A. X-Ray Analysis

3-Chloro-4-ethoxybenzonitrile (2c).

Table 1. Crystal data and structure refinement for (2c).

<table>
<thead>
<tr>
<th>Identification code</th>
<th>2c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C9 H8 Cl NO</td>
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<tr>
<td>Formula weight</td>
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</tr>
<tr>
<td>Temperature</td>
<td>200(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>‘Monoclinic’</td>
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<tr>
<td>Space group</td>
<td>‘C1c1’</td>
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<tr>
<td>Unit cell dimensions</td>
<td></td>
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<tr>
<td>a</td>
<td>8.511(5) Å</td>
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<tr>
<td>b</td>
<td>17.062(10) Å</td>
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<tr>
<td>c</td>
<td>7.200(4) Å</td>
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<tr>
<td>Volume</td>
<td>868.6(9) Å³</td>
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<tr>
<td>Z</td>
<td>4</td>
</tr>
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Density (calculated) 1.389 Mg/m$^3$
Absorption coefficient 0.386 mm$^{-1}$
F(000) 376
Crystal size 0.16 x 0.12 x 0.08 mm$^3$
Theta range for data collection 2.39 to 28.29°
Index ranges -11<=h<=11, -18<=k<=22, -9<=l<=9
Reflections collected 2102
Independent reflections 1251 [R(int) = 0.0411]
Completeness to theta = 25.00° 84.0 %
Max. and min. transmission 0.9698 and 0.9408
Refinement method Full-matrix least-squares on F$^2$
Data / restraints / parameters 1251 / 2 / 110
Goodness-of-fit on F$^2$ 1.001
Final R indices [I>2sigma(I)] R1 = 0.0571, wR2 = 0.1374
R indices (all data) R1 = 0.0838, wR2 = 0.1513
Absolute structure parameter 0.02(17)
Largest diff. peak and hole 0.571 and -0.268 e.Å$^{-3}$
6-Chlorobenzod[1,3]dioxole-5-carbonitrile (2l).

![Chemical structure of 6-Chlorobenzod[1,3]dioxole-5-carbonitrile (2l).]

Table 1. Crystal data and structure refinement for 2l.

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<thead>
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<th>Value</th>
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<tbody>
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<td>2l</td>
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<tr>
<td>Empirical formula</td>
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<tr>
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<tr>
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<td>Space group</td>
<td>P2(1)/n</td>
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<td></td>
<td>b = 380.23(10) pm</td>
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<td>F(000)</td>
<td>368</td>
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<td>Crystal size</td>
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<tr>
<td>Theta range for data collection</td>
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<td>Index ranges</td>
<td>-15&lt;=h&lt;=16, -4&lt;=k&lt;=5, -20&lt;=l&lt;=20</td>
</tr>
</tbody>
</table>
Reflections collected: 7021
Independent reflections: 1788 [R(int) = 0.0263]
Completeness to theta = 28.41°: 98.7%
Absorption correction: Semi-empirical from equivalents
Max. and min. transmission: 0.927 and 0.834
Refinement method: Full-matrix least-squares on F²
Data / restraints / parameters: 1788 / 0 / 110
Goodness-of-fit on F²: 1.075
Final R indices [I>2sigma(I)]: R1 = 0.0262, wR2 = 0.0719
R indices (all data): R1 = 0.0275, wR2 = 0.0729
Extinction coefficient: 0.006(3)
Largest diff. peak and hole: 0.352 and -0.227 e.Å⁻³
3-Bromo-4-hydroxy-5-methoxybenzonitrile (4f).

Table 1. Crystal data and structure refinement for (4f).

<table>
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<th>Value</th>
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<tbody>
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<tr>
<td>Crystal system</td>
<td>‘Triclinic’</td>
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</tbody>
</table>
Space group

‘P-1’

Unit cell dimensions

\[ a = 7.2030(10) \text{ Å} \quad \alpha = 85.645(3)^\circ. \]
\[ b = 9.5004(12) \text{ Å} \quad \beta = 89.563(3)^\circ. \]
\[ c = 12.9717(16) \text{ Å} \quad \gamma = 70.248(3)^\circ. \]

Volume

832.88(19) Å³

Z

2

Density (calculated)

1.819 Mg/m³

Absorption coefficient

4.889 mm⁻¹

F(000)

448

Crystal size

0.16 x 0.13 x 0.11 mm³

Theta range for data collection

1.57 to 28.53°.

Index ranges

-9<=h<=6, -12<=k<=12, -17<=l<=17

Reflections collected

13496

Independent reflections

4127 [R(int) = 0.0244]

Completeness to theta = 28.53°

97.4 %

Max. and min. transmission

0.6153 and 0.5084

Refinement method

Full-matrix least-squares on F²

Data / restraints / parameters

4127 / 0 / 225

Goodness-of-fit on F²

1.043

Final R indices [I>2sigma(I)]

R1 = 0.0255, wR2 = 0.0592

R indices (all data)

R1 = 0.0325, wR2 = 0.0613

Largest diff. peak and hole

1.059 and -0.417 e.Å⁻³
B. NOESY Studies

Copy of NOESY Experiment of Compound 2j.

There is a NOE correlation between Ha ($\delta$ 6.89, s) and Hd ($\delta$ 3.85, s). In meantime, there is also a correlation between Hb ($\delta$ 7.01, s) and Hc ($\delta$ 3.90, s). These results clearly revealed that the regiochemistry of compound 2j is correct.
Copy of NOESY Experiment of Compound 4c.

There is a NOE correlation between Hb (δ 6.89, d) and Hd (δ 4.14, q). In meantime, there is also a very weak NOE correlation between Hc (δ 7.54, dd) and Hd (δ 4.14, d). However, there is no correlation between Ha (δ 7.79, s) and Hd (δ 4.14, q). These results clearly revealed that the regiochemistry of compound 4c is correct.
Copy of NOESY Experiment of Compound 4d.

There is a NOE correlation between Hb (δ 6.88, d) and Hd (δ 4.01, q). In meantime, there is also a very weak NOE correlation between Hc (δ 7.52, dd) and Hd (δ 4.01, d). However, there is no correlation between Ha (δ 7.77, s) and Hd (δ 4.01, q). These results clearly revealed that the regiochemistry of compound 4d is correct.
Copy of NOESY Experiment of Compound 4g.

There is a NOE correlation between Ha (δ 7.12, s) and Hb (δ 3.80, s). In meantime, there is also a correlation between Hc (δ 6.98, dd) and Hb (δ 3.80, s). These results clearly revealed that the regiochemistry of compound 4g is correct. If there is a no correlation between Hc (δ 6.98, dd) and Hb (δ 3.80, s), then the other regiochemistry is possible. But, there is a signal.
Spectral Data of all Compounds

3-Chloro-4-hydroxybenzonitrile (2a).

Colorless solid; eluent (10% ethyl acetate in hexanes).

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 3419, 2234, 1593, 1411, 1305, 1123 and 1044.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.63 (s, 1 H), 7.46 (dd, $J = 8.0, 4.0$, Hz, 1 H), 7.06 (d, $J = 8.0$ Hz, 1 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 155.8, 133.3, 132.7, 121.0, 117.9, 117.3, 104.7.

HRMS (ESI): calc. for [(C$_7$H$_4$ClNO)H] (M+H) 154.0060, measured 154.0063.

3-Chloro-4-methoxybenzonitrile (2b).

Colorless solid; eluent (5% ethyl acetate in hexanes).

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 2923, 2228, 1595, 1500, 1270, 1192 and 1064.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.62 (s, 1 H), 7.53 (dd, $J = 8.0, 4.0$ Hz, 1 H), 6.96 (d, $J = 8.0$ Hz, 1 H), 3.94 (s, 3 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 158.6, 133.6, 132.5, 123.6, 117.9, 112.2, 104.7, 56.5.

HRMS (ESI): calc. for [(C$_8$H$_6$ClNO)H] (M+H) 168.0217 measured 168.0217.

3-Chloro-4-ethoxybenzonitrile (2c).

Colorless solid; eluent (5% ethyl acetate in hexanes).

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 2229, 1591, 1477, 1298, 1262, 1167, 1125 and 1033.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.61 (s, 1 H), 7.50 (dd, $J = 8.0, 4.0$ Hz, 1 H), 6.93 (d, $J = 8.0$ Hz, 1 H), 4.14 (q, $J = 8.0$ Hz, 2 H), 1.48 (t, $J = 8.0$ Hz, 3 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 158.1, 133.6, 132.4, 123.7, 118.1, 112.9, 104.4, 65.2, 14.5.
3-Chloro-4-propoxybenzonitrile (2d).

Brown liquid; eluent (5% ethyl acetate in hexanes).

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 2968, 2228, 1690, 1594, 1463, 1394, 1270 and 1061.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.62 (s, 1 H), 7.50 (dd, $J$ = 8.0, 4.0 Hz, 1 H), 6.92 (d, $J$ = 8.0 Hz, 1 H), 4.02 (t, $J$ = 4.0 Hz, 2 H), 1.89 – 1.84 (m, 2 H), 1.06 (t, $J$ = 8.0 Hz, 3 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 158.3, 133.6, 132.4, 123.8, 118.1, 113.0, 104.3, 70.9, 22.3, 10.4.

HRMS (ESI): calc. for [(C$_9$H$_8$ClNO)H] (M+H) 182.0373, measured 182.0371.

3-Chloro-4-(dimethylamino)benzonitrile (2e).

Brown liquid; eluent (5% ethyl acetate in hexanes).

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 2968, 2228, 1690, 1594, 1463, 1270, 1195 and 1061.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.54 (s, 1 H), 7.42 (dd, $J$ = 8.0 Hz, 1 H), 6.96 (d, $J$ = 8.0 Hz, 1 H), 2.89 (s, 6 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 154.1, 134.4, 131.5, 126.4, 119.4, 118.4, 104.4, 42.9.


3-Chloro-4-(methylamino)benzonitrile (2f).

Colorless solid; eluent (20% ethyl acetate in hexanes).

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 3325, 2361, 1517, 1235 and 1037.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.46 (s, 1 H), 7.40 (d, $J$ = 8.0 Hz, 1 H), 6.58 (d, $J$ = 8.0 Hz, 1 H), 4.91 (bs, 1 H), 2.93 (s, 3H).
$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 148.9, 132.5, 132.3, 119.3, 118.5, 109.9, 98.7, 30.0. HRMS (ESI): calc. for [(C$_8$H$_7$ClN$_2$)H] (M+H) 167.0376, measured 167.0371.

3-Chloro-4-hydroxy-5-methoxybenzonitrile (2g).

![Chemical Structure](image)

Colorless solid; eluent (10% ethyl acetate in hexanes).

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 3427, 2215, 1588, 1500, 1415, 1363, 1293, 1124 and 1044.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.29 (s, 1 H), 7.00 (s, 1 H), 3.93 (s, 3 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 147.5, 146.5, 126.9, 120.4, 118.1, 112.4, 103.6, 56.8. HRMS (ESI): calc. for [(C$_8$H$_6$ClNO$_2$)H] (M+H) 184.0165, measured 184.0164.

3-Chloro-4,5-dihydroxybenzonitrile (2h).

![Chemical Structure](image)

Colorless solid; eluent (20% ethyl acetate in hexanes).

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 3433, 2234, 1593, 1411, 1305, 1123 and 1044.

$^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ 7.43 (s, 1 H), 7.03 (s, 1 H).

$^{13}$C NMR (DMSO-d$_6$, 100 MHz): $\delta$ 148.8, 146.9, 127.9, 118.7, 117.6, 110.2, 102.4. HRMS (ESI): calc. for [(C$_7$H$_4$ClNO$_2$)H] (M+H) 170.0009, measured 170.0005.

2-Chloro-5-methoxybenzonitrile (2i).

![Chemical Structure](image)

Colorless solid; eluent (5% ethyl acetate in hexanes).

**IR (ATR)** $\tilde{\nu}$ (cm$^{-1}$): 2365, 1599, 1265, and 1121.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.36 (d, $J = 8.0$ Hz, 1 H), 7.12 (s, 1 H), 7.05 (dd, $J = 8.0$, 4.0 Hz, 1 H), 3.81 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 158.1, 130.9, 120.7, 118.2, 116.0, 115.8, 113.7, 55.9.

2-Chloro-4,5-dimethoxybenzonitrile (2j).

Colorless solid; eluent (7% ethyl acetate in hexanes).

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\))**: 2229, 1595, 1459, 1382, 1274, 1220, 1121 and 1042.

\(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) 7.01 (s, 1 H), 6.89 (s, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H).

\(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta \) 153.3, 148.0, 130.2, 116.5, 114.6, 112.6, 104.2, 56.5, 56.4.

HRMS (ESI): calc. for [(C₉H₈ClNO₂)H] (M+H) 198.0322, measured 198.0319.

2-Chloro-3,5-dimethoxybenzonitrile (2k).

Colorless solid; eluent (7% ethyl acetate in hexanes).

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\))**: 2230, 1589, 1387, 1225 and 1123.

\(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) 6.71 (s, 1 H), 6.67 (s, 1 H), 3.88 (s, 3 H), 3.81 (s, 3 H).

\(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta \) 159.2, 156.4, 117.8, 116.1, 114.2, 108.3, 104.6, 56.5, 56.0.

HRMS (ESI): calc. for [(C₉H₈ClNO₂)H] (M+H) 198.0322, measured 198.0320.

6-Chlorobenzo[d][1,3]dioxole-5-carbonitrile (2l).

Yellow solid; eluent (7% ethyl acetate in hexanes).

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\))**: 2235, 1590, 1472, 1414, 1261, 1121 and 1036.

\(^1\)H NMR (CDCl₃, 400 MHz): \( \delta \) 6.99 (s, 1 H), 6.90 (s, 1 H), 6.08 (s, 2 H).

\(^{13}\)C NMR (CDCl₃, 100 MHz): \( \delta \) 152.3, 146.9, 131.8, 116.2, 111.9, 110.6, 105.3, 103.2.

HRMS (ESI): calc. for [(C₈H₄ClNO₂)H] (M+H) 182.0009, measured 182.0009.
2-Chloro-1-naphthonitrile (2m).

![Image of 2-Chloro-1-naphthonitrile]

Colorless solid; eluent (5% ethyl acetate in hexanes).

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\))**: 2355, 1597, 1479, 1135 and 1051.

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 8.33 (d, \( J = 8.0 \) Hz, 1 H), 8.23 (d, \( J = 8.0 \) Hz, 1 H), 7.80 (d, \( J = 8.0 \) Hz, 1 H), 7.77 – 7.69 (m, 2 H), 7.60 (d, \( J = 8.0 \) Hz, 1 H).

\(^1\)C NMR (CDCl\(_3\), 100 MHz): \( \delta \) 138.0, 133.3, 132.2, 130.6, 129.5, 128.7, 125.7, 125.6, 125.3, 117.3, 109.4.

HRMS (ESI): calc. for [(C\(_{11}\)H\(_6\)ClN)H] (M+H) 188.0267, measured 188.0265.

(E)-Methyl 3-((Z)-chloro(methoxyimino)methyl)phenylacrylate (2n).

![Image of (E)-Methyl 3-((Z)-chloro(methoxyimino)methyl)phenylacrylate]

Pale yellow semisolid; eluent (15% ethyl acetate in hexanes).

\(^1\)H NMR (CDCl\(_3\), 200 MHz): \( \delta \) 8.01 (s, 1 H), 7.86 (d, \( J = 8.0 \) Hz, 1 H), 7.72 (d, \( J = 16.0 \) Hz, 1 H), 7.56 (d, \( J = 8.0 \) Hz, 1 H), 7.43 (d, \( J = 8.0 \) Hz, 1 H), 6.51 (d, \( J = 16.0 \) Hz, 1 H), 4.13 (s, 3 H), 3.82 (s, 3 H).

\(^1\)C NMR (CDCl\(_3\), 50 MHz): \( \delta \) 167.2, 143.9, 136.5, 134.8, 133.5, 129.8, 129.1, 128.7, 126.6, 119.0, 63.4, 51.8.

HRMS (ESI): calc. for [(C\(_{12}\)H\(_{12}\)ClNO\(_3\))H] (M+H) 254.0584, measured 254.0579.

3-Bromo-4-hydroxybenzonitrile (4a).

![Image of 3-Bromo-4-hydroxybenzonitrile]

Brown solid; eluent (10% ethyl acetate in hexanes).

**IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\))**: 3431, 2237, 1600, 1507, 1410, 1303, 1222 and 1046.

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta \) 7.77 (s, 1 H), 7.48 (dd, \( J = 8.0, 4.0 \) Hz, 1 H), 7.04 (d, \( J = 8.0 \) Hz, 1 H).
$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 156.7, 136.3, 133.3, 117.7, 116.9, 110.6, 105.0. HRMS (ESI): calc. for [(C$_7$H$_4$BrNO)H] (M+H) 197.9555, measured 197.9559.

3-Bromo-4-methoxybenzonitrile (4b).

\[ \text{MeO} \quad \text{CN} \]

Colorless solid; eluent (5% ethyl acetate in hexanes).

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 2235, 1589, 1488, 1294, 1190, 1121 and 1046.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.79 (s, 1 H), 7.58 (dd, $J = 8.0$, 4.0 Hz, 1 H), 6.90 (d, $J = 8.0$ Hz, 1 H), 3.94 (s, 3 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 159.1, 136.7, 133.2, 117.8, 112.3, 111.9, 105.2, 56.6. HRMS (ESI): calc. for [(C$_8$H$_6$BrNO)H] (M+H) 211.9711, measured 211.9713.

3-Bromo-4-ethoxybenzonitrile (4c).

\[ \text{EtO} \quad \text{CN} \]

Colorless solid; eluent (5% ethyl acetate in hexanes).

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 2224, 1594, 1471, 1295, 1266, 1161, 1120 and 1036.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.79 (s, 1 H), 7.54 (dd, $J = 8.0$, 4.0 Hz, 1 H), 6.89 (d, $J = 8.0$ Hz, 1 H), 4.14 (d, $J = 8.0$ Hz, 2 H), 1.48 (t, $J = 8.0$ Hz, 3 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 159.0, 136.7, 133.1, 117.9, 112.7, 112.6, 104.9, 65.3, 14.5. HRMS (ESI): calc. for [(C$_9$H$_8$BrNO)H] (M+H) 225.9868, measured 225.9863.

3-Bromo-4-propoxybenzonitrile (4d).

\[ \text{PrO} \quad \text{CN} \]

Brown liquid; eluent (5% ethyl acetate in hexanes).

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 2971, 2227, 1593, 1491, 1267, 1191 and 1051.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.77 (s, 1 H), 7.52 (dd, $J = 8.0$, 4.0 Hz, 1 H), 6.88 (d, $J = 8.0$ Hz, 1 H), 4.01 (t, $J = 8.0$ Hz, 2 H), 1.88 – 1.83 (m, 2 H), 1.05 (t, $J = 8.0$ Hz, 3 H).
$^{13}$C NMR (CDCl$_3$, 100 MHz): δ 159.1, 136.6, 133.1, 117.9, 112.7, 112.6, 104.8, 71.0, 22.3, 10.5.

HRMS (ESI): calc. for [(C$_{10}$H$_{10}$BrNO)$_2$H] (M+H) 240.0024, measured 240.0020.

3-Bromo-4-(dimethylamino)benzonitrile (4e).

[Image: molecular structure of 3-Bromo-4-(dimethylamino)benzonitrile]

Brown liquid; eluent (5% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2223, 1593, 1445, 1339, 1133 and 1045.

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.75 (s, 1 H), 7.48 (dd, $J$ = 8.0, 4.0 Hz, 1 H), 6.98 (d, $J$ = 8.0 Hz, 1 H), 2.88 (s, 6 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ 155.7, 137.7, 132.1, 119.8, 118.2, 116.5, 105.3, 43.4.

HRMS (ESI): calc. for [(C$_9$H$_9$BrN$_2$)$_2$H] (M+H) 225.0027, measured 225.0028.

3-Bromo-4-hydroxy-5-methoxybenzonitrile (4f).

[Image: molecular structure of 3-Bromo-4-hydroxy-5-methoxybenzonitrile]

Colorless solid; eluent (10% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3454, 2223, 1587, 1492, 1285, 1175, 1126 and 1040.

$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.42 (s, 1 H), 7.03 (s, 1 H), 3.92 (s, 3 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): δ 147.6, 147.2, 129.7, 117.9, 112.9, 108.6, 104.2, 56.8.

HRMS (ESI): calc. for [(C$_8$H$_6$BrNO$_2$)$_2$H] (M+H) 227.9660, measured 227.9664.

2-Bromo-5-methoxybenzonitrile (4g).

[Image: molecular structure of 2-Bromo-5-methoxybenzonitrile]

Colorless solid; eluent (5% ethyl acetate in hexanes).

IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2237, 1587, 1425, 1141 and 1045.
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.52 (d, $J = 8.0$ Hz, 1 H), 7.12 (s, 1 H), 6.98 (dd, $J = 8.0$, 4.0 Hz, 1 H), 3.80 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 158.7, 134.0, 120.9, 118.9, 117.1, 116.2, 115.6, 55.9.

HRMS (ESI): calc. for [(C$_8$H$_6$BrNO)H] (M+H) 211.9711, measured 211.9710.

2-Bromo-4,5-dimethoxybenzonitrile (4h).

![Structure](image)

Colorless solid; eluent (7% ethyl acetate in hexanes).

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 2925, 2227, 1980, 1590, 1419, 1349, 12367, 1122 and 1036.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.04 (s, 1 H), 7.02 (s, 1 H), 3.90 (s, 3 H), 3.86 (s, 3 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 153.2, 148.5, 117.7, 117.6, 115.5, 115.3, 106.9, 56.5, 56.4.

HRMS (ESI): calc. for [(C$_9$H$_8$BrNO$_2$)H] (M+H) 241.9817, measured 241.9812.

6-Bromobenzo[b][1,3]dioxole-5-carbonitrile (4i).

![Structure](image)

Yellow solid; eluent (7% ethyl acetate in hexanes).

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 2360, 1591, 1470, 1259, 1119 and 1031.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.05 (s, 1 H), 6.99 (s, 1 H), 6.08 (s, 2 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 152.3, 147.5, 119.0, 117.4, 113.4, 112.6, 107.9, 103.1.

HRMS (ESI): calc. for [(C$_8$H$_4$BrNO$_2$)H] (M+H) 225.9504, measured 225.9500.

Methyl 4-methoxybenzoate.

![Structure](image)

Colorless solid; eluent (5% ethyl acetate in hexanes)

**IR (ATR) $\tilde{\nu}$ (cm$^{-1}$):** 1711, 1609, 1448, 1321, 1288, 1263, 1170, 1022.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.97 (d, $J = 8.0$ Hz, 2 H), 6.89 (d, $J = 8.0$ Hz, 2 H), 3.86 (s, 3 H), 3.83 (s, 3 H).

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 166.5, 163.3, 131.6, 122.6, 113.6, 55.4, 51.9.

2-Chloro-N,N-dimethyl-4-(1H-tetrazol-5-yl)aniline (5a).³

![Chemical Structure Image]

Yellow solid; eluent (20% ethyl acetate in hexanes).

¹H NMR (CDCl₃, 500 MHz): δ 7.56 (s, 1 H), 7.49 (dd, J = 10.0, 5.0 Hz, 1 H), 6.67 (d, J = 10.0 Hz, 1 H), 4.98 (bs, 1 H), 3.02 (s, 3 H), 3.01 (s, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 148.1, 132.5, 132.3, 119.3, 118.5, 109.9, 98.7, 30.0.


2-Chloro-N-methyl-4-(1H-tetrazol-5-yl)aniline (5b).³

![Chemical Structure Image]

Pale yellow solid; eluent (45% ethyl acetate in hexanes).

¹H NMR (CDCl₃, 200 MHz): δ 7.52 (s, 1 H), 7.32 (t, J = 8.0 Hz, 1 H), 6.72 (d, J = 8.0 Hz, 1 H), 4.62 (bs, 2 H), 2.94 (d, J = 16.0 Hz, 3 H).

¹³C NMR (CDCl₃, 100 MHz): δ 147.1, 133.2, 131.9, 118.9, 118.4, 115.1, 100.7, 36.7.


5-(6-Bromobenzo[d][1,3]dioxol-5-yl)-1H-tetrazole (5c).

![Chemical Structure Image]

Colorless solid; eluent (25% ethyl acetate in hexanes).

¹H NMR (CDCl₃, 400 MHz): δ 7.25 (s, 1 H), 7.23 (s, 1 H), 6.36 (bs, 1H), 5.23 (s, 2 H).

¹³C NMR (CDCl₃, 100 MHz): δ 150.9, 143.0, 120.4, 120.1, 119.1, 117.2, 106.7, 81.0.

HRMS (ESI): calc. for [(C₈H₅BrN₄O₂)H] (M+H) 268.9674, measured 268.9670.

S24
$^1$H and $^{13}$C NMR Spectra of Compound 2a.
DEPT (135) NMR Spectrum of Compound 2a.
$^1$H and $^{13}$C NMR Spectra of Compound 2b.
DEPT (135) NMR Spectrum of Compound 2b.
$^1$H and $^{13}$C NMR Spectra of Compound 2c.
DEPT (135) NMR Spectrum of Compound 2c.
$^1$H and $^{13}$C NMR Spectra of Compound 2d.
DEPT (135) NMR Spectrum of Compound 2d.
$^1$H and $^{13}$C NMR Spectra of Compound 2e.

![NMR Spectra](image-url)
DEPT (135) NMR Spectrum of Compound 2e.
$^1$H and $^{13}$C NMR Spectra of Compound 2f.
DEPT (135) NMR Spectrum of Compound 2f.
$^1$H and $^{13}$C NMR Spectra of Compound 2g.
DEPT (135) NMR Spectrum of Compound 2g.
$^1$H and $^{13}$C NMR Spectra of Compound 2h ($d$-DMSO solvent was used).
$^1$H and $^{13}$C NMR Spectra of Compound 2i.
DEPT (135) NMR Spectrum of Compound 2i.
$^1$H and $^{13}$C NMR Spectra of Compound 2j.
DEPT (135) NMR Spectrum of Compound 2j.
$^1$H and $^{13}$C NMR Spectra of Compound 2k.
DEPT (135) NMR Spectrum of Compound 2k.
$^1$H and $^{13}$C NMR Spectra of Compound 21.

[Image of NMR spectra]
DEPT (135) NMR Spectrum of Compound 2l.
$^1$H and $^{13}$C NMR Spectra of Compound 2m.
DEPT (135) NMR Spectrum of Compound 2m.
$^1$H and $^{13}$C NMR Spectra of Compound 2n.
DEPT (135) NMR Spectrum of Compound 2n.
$^1$H and $^{13}$C NMR Spectra of Compound 4a.
DEPT (135) NMR Spectrum of Compound 4a.
$^1$H and $^{13}$C NMR Spectra of Compound 4b.
DEPT (135) NMR Spectrum of Compound 4b.
$^1$H and $^{13}$C NMR Spectra of Compound 4c.
DEPT (135) NMR Spectrum of Compound 4c.
$^1$H and $^{13}$C NMR Spectra of Compound 4d.
DEPT (135) NMR Spectrum of Compound 4d.
$^1$H and $^{13}$C NMR Spectra of Compound 4e.
DEPT (135) NMR Spectrum of Compound 4e.
$^1$H and $^{13}$C NMR Spectra of Compound 4f.

![NMR Spectra Image]
DEPT (135) NMR Spectrum of Compound 4f.
$^1$H and $^{13}$C NMR Spectra of Compound 4g.
DEPT (135) NMR Spectrum of Compound 4g.
$^1$H and $^{13}$C NMR Spectra of Compound 4h.
DEPT (135) NMR Spectrum of Compound 4h.
$^1$H and $^{13}$C NMR Spectra of Compound 4i.
DEPT (135) NMR Spectrum of Compound 4i.
$^1$H NMR Spectrum of Compound 5a.
DEPT (135) NMR Spectrum of Compound 5a.
$^1$H NMR Spectrum of Compound 5b.
$^1$H and $^{13}$C NMR Spectra of Compound 5c.
DEPT (135) NMR Spectrum of Compound 5c.