Synthesis of Symmetrical and Unsymmetrical N-Aryl-Substituted Cyclic Ureas through Copper(I) Iodide Catalyzed Goldberg–Buchwald–Nandakumar C–N Coupling Reactions

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Abstract: The catalytic conditions of copper(I) iodide/potassium carbonate/trans-N,N¢-dimethylcyclohexane-1,2-diamine, either in toluene at reflux temperature, or by heating neat at 150 °C effectively promoted the C–N coupling of aryl bromides with cyclic ureas. By employing a protection–deprotection strategy, unsymmetrical diaryl-substituted cyclic ureas could also be synthesized.

Key words: arylation, copper, cross-coupling, homogeneous catalysis, heterocycles

N-Aryl-substituted ureas have attracted investigations by many synthetic chemists because of their wide applications in different fields such as medicinal chemistry,1 host-guest chemistry,2 and anion sensors.3 Conventional methods4 for urea synthesis usually involve hazardous and toxic reagents such as isocyanates,5 phosgene,6 or carbon monoxide.7 Alternative strategies utilizing transition-metal-catalyzed C–N bond-formation have been developed. A few examples of the palladium-catalyzed arylation of ureas with aryl halides have been reported.8 These included the cross-coupling of N-alkyl- and N-phenyl-substituted acyclic ureas and cyclic ureas with aryl halides8i,9 or heteroaryl halides,10 and intramolecular palladium-catalyzed arylation of ureas.11 In spite of the accessibility of the palladium-catalyzed reactions, some limitations still remain. For example, the C–N coupling of ureas with electron-rich aryl halides, and ortho-substituted aryl halides could be difficult.9a,12 Moreover, the removal of the palladium residues from polar reaction products, particularly in the latter stages of the synthesis of pharmaceutical substances, could be challenging.12 The high cost of palladium has invited the investigation of less expensive synthetic alternatives.

The well-documented Goldberg reaction,13,14 using copper(I) iodide catalyzed N-arylation, provided a less expensive route for C–N bond formation in amide synthesis; however, the reaction conditions were relatively harsh. Ligand-assisted Goldberg reactions were therefore developed.12,15–17 It is worth mentioning that the presence of strongly electron-donating substituents at the ortho or para positions has no deleterious effects on the arylation of amides.15 In contrast, examples of the diarylation of ureas are rare.18 Buchwald has reported the copper-catalyzed 1,3-diarylation of imidazolidin-2-one with ethylenediamine as a ligand in N,N-dimethylformamide under microwave irradiation.18a Nandakumar has recently reported the arylation of urea using copper(I) iodide/cyclohexane-1,2-diamine (CHDA)/tripotassium phosphate in N,N-dimethylformamide at 80 °C, which gave arylureas in moderate yields.18b

Continuing our interest in the chemistry of ureas,19 we have recently investigated alternative conditions for the copper(I) iodide promoted N,N¢-diarylurea synthesis. Although Goldberg reactions usually proceeded effectively in coordinating solvents such as N,N-dimethylformamide or dioxane,20 we are looking for catalytic conditions that would proceed smoothly in other solvents such as toluene. It has been known that the reactivity of the copper catalyst strongly relies on the ligand system used in the reaction.17a–f Effective ligands, including ethylenediamine and derivatives such as trans-N,N¢-dimethylcyclohexane-1,2-diamine (DMCHDA), are known to promote the Goldberg reaction.12,15

Table 1 Copper(I) Iodide Catalyzed Cross-Coupling of 4-Bromo-toluene with Imidazolidin-2-one in Toluene under Different Base-Ligand Assisted Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Diamine ligand</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K3PO4</td>
<td>CHDA</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>K2CO3</td>
<td>CHDA</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>Cs2CO3</td>
<td>CHDA</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>K3PO4</td>
<td>DMCHDA</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>K2CO3</td>
<td>DMCHDA</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>Cs2CO3</td>
<td>DMCHDA</td>
<td>44</td>
</tr>
</tbody>
</table>

a 1 (1.2 mmol), Cul (10 mol%), ligand (20 mol%), base (2.5 mmol), toluene (1 mL).

b Isolated yield.
Therefore, we first attempted to carry out phenylation of \(N,N'\)-dimethylurea with bromobenzene under the catalytic conditions of copper(I) iodide (10 mol%), tripotassium phosphate (2.2 equiv), and trans-\(N,N'\)-dimethylcyclohexane-1,2-diamine (DMCHDA, 20 mol%) in toluene at reflux temperature, but these conditions failed and the starting materials were recovered according to NMR analysis. When the reagents Cu/K$_2$CO$_3$/DMCHDA were used, only some unidentified products were obtained. Since cesium carbonate has been known to effectively promote C–N coupling reactions,\textsuperscript{24} we, therefore, attempted to use cesium carbonate as the base in our synthesis. Interestingly, when cesium carbonate was applied, around 5% of \(N\)-methylaniline was isolated. We suspected that the phenylation process might proceed first to give the urea products, followed by in situ hydrolysis or aminolysis with the diamine ligand to give \(N\)-methylaniline. This result urged us to investigate the cross-coupling of aryl halides with imidazolidin-2-one, a cyclic urea with higher resistance against hydrolysis. When similar conditions were applied to imidazolidin-2-one with 4-bromotoluene in toluene, using cyclohexane-1,2-diamine as the ligand and potassium carbonate as the base, 2\textsuperscript{21} was obtained in 62% yield (Table 1). Other bases such as tripotassium phosphate or cesium carbonate were less effective.\textsuperscript{22}

When trans-\(N,N'\)-dimethylcyclohexane-1,2-diamine was employed, the yields of 2 were boosted significantly. Among the bases we tried, potassium carbonate gave the best yield of 92%. On the other hand, when cesium carbonate was used, a stoichiometric amount of copper(I) iodide was required to afford the desired ureas in moderate yield (Table 2). Other bases such as tripotassium phosphate or cesium carbonate were less effective.\textsuperscript{22}

The reaction could be applied to a large variety of aryl halides. Many functional groups, including ether, sulfide, nitrile, nitro, ester, and carbonyl groups, were compatible with the copper(I) iodide catalyzed N-arylation protocol. The reaction could also be applied to heterocyclic halides such as 2-bromopyridine to give 12 in good yield. Although substituent electronic effects were less significant, the yield of 3\textsuperscript{21} (73%) and 4 (54%) in the cross-coupling reaction were noticeably low, indicating that the C–N coupling reactions were less effective if aryl halides bearing electron-withdrawing groups were used. This tendency in its reactivity is the reverse of that for other known methods.\textsuperscript{9,12}

The C–N coupling reaction also proceeded smoothly when sterically hindered aryl halides were used. For example, ortho-substituted 2-bromoanisole reacted to give 10 in 95% yield. In addition, 1-bromonaphthalene could also react to give 11 in 83% yield. The structural identification of 11 was further supported by X-ray crystallographic analysis. Single crystals of 11 were successfully prepared by slow diffusion of hexane into the corresponding chloroform solution (Figure 1). The result also confirmed that N,N'-diarylation, rather than N,O-diarylation, of imidazolidin-2-one was obtained.

![Figure 1 ORTEP of 11 proved the success of the C–N coupling reaction](image)

The method could be extended to other cyclic and acyclic urea substrates, such as 2-hydroxy-1\(H\)-benzimidazole and 1,3-diphenylurea. The reactions were conducted smoothly under the same conditions, which gave 13–15 in moderate yields (Scheme 1). A single crystal of 15 was successfully prepared by slow evaporation of the solvents from the corresponding dichloromethane–ethyl acetate solution for X-ray crystallographic analysis (Figure 2). The result also

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArBr</th>
<th>Product</th>
<th>Yield(^a) (%)</th>
<th>K$_2$CO$_3$$^b$</th>
<th>Cs$_2$CO$_3$$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeC$_6$H$_4$</td>
<td>2\textsuperscript{21}</td>
<td>92</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4-EtO$_2$CC$_6$H$_4$</td>
<td>3\textsuperscript{9}</td>
<td>73</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4-O$_2$NC$_6$H$_4$</td>
<td>4\textsuperscript{21}</td>
<td>54</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4-MeOC$_6$H$_4$</td>
<td>5\textsuperscript{21,24}</td>
<td>88</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4-MeSC$_6$H$_4$</td>
<td>6</td>
<td>76</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4-NCC$_6$H$_4$</td>
<td>7</td>
<td>84</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4-AcC$_6$H$_4$</td>
<td>8</td>
<td>81</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>9\textsuperscript{21,25}</td>
<td>85</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2-MeOC$_6$H$_4$</td>
<td>10</td>
<td>95</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1-naphthyl</td>
<td>11</td>
<td>83</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>2-pyridyl</td>
<td>12\textsuperscript{10}</td>
<td>82</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yield.
\textsuperscript{b} 1 (1.2 mmol), CuI (10 mol%), ligand (20 mol%), base (2.5 mmol), toluene (1 mL), reflux, 24 h.
\textsuperscript{c} 1 (1.2 mmol), CuI (100 mol%), ligand (200 mol%), base (2.5 mmol), mesitylene (1 mL), reflux, 48 h.

Table 2 Copper(I) Iodide Catalyzed Cross-Coupling of Aryl Bromides with Imidazolidin-2-one in Toluene
revealed the stereochemistry of 15, in which two phenyl rings were located in the Z,Z-positions.

This reaction could be further applied to 1,3-diaryltetrahydropyrimidin-2-one synthesis. However, both 4-bromoanisole and 1-bromo-4-nitrobenzene were coupled with tetrahydropyrimidin-2-one in low yields. According to the NMR analysis of the crude products, both unreacted tetrahydropyrimidin-2-one and the monoarylation product were found, implying that tetrahydropyrimidin-2-one was less reactive than imidazolidin-2-one. By modifying the catalyst loading, concentration, and reaction temperature, the best yield of 16 was obtained when the reactions were conducted in the presence of 0.3 equivalents of copper(I) iodide and excess aryl bromide (6 equiv) under neat condition at 150 °C (Scheme 2).

To extend the scope of the C–N coupling method to unsymmetrical cyclic urea synthesis, we attempted the preparation of 1-arylimidazolidin-2-one by limiting the number of equivalents of the aryl halides used in the reaction. In the first trial, we prepared 4-(methylsulfanyl)phenyl-substituted 18 by reacting equivalent amounts of 4-bromoanisole and 1. However, 1H NMR analysis of the crude mixture revealed that the ratio of 18 and 6 was 1:1.65, indicating that the preference for mono- versus diarylation was low (Scheme 3).

Similar results were also obtained when 2-bromopyridine was employed. In this trial, almost equal amounts of 12 and 19 were identified even when excess imidazolidin-2-one (5 equiv) was used (Scheme 4).

To make the synthesis of unsymmetrical cyclic urea successful, another approach, protection–deprotection strategy, was adopted to bypass this problem (Scheme 4). Commercially available 1-tert-butylimidazolidin-2-one (20) was employed as the starting material. The coupling of 20 with 4-bromoanisole afforded 21 in high yield. Deprotection of 21 by removal of the tert-butyl group in aqueous hydrochloric acid (20%) afforded 18. Finally, the cross-coupling of 18 with ethyl 4-bromobenzoate afforded unsymmetrical 1,3-diarylimidazolidin-2-one 22 in moderate yield (Scheme 5).

In summary, the foregoing methodology offers a highly accessible approach for the synthesis of mono- and disubstituted cyclic ureas. Either symmetrical or unsymmetrical cyclic ureas could be successfully prepared.
1,3-Bis(4-(ethoxycarbonyl)phenyl)imidazolidin-2-one (3)\textsuperscript{9f}

Purified by flash chromatography (CHCl\textsubscript{3}); white solid; yield: 76%; mp 222 °C.

IR (KBr): 2981, 2906, 1708, 1606 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \(\delta = 8.26\) (d, J = 9.4 Hz, 4 H, H3\'), 7.88 (d, J = 9.4 Hz, 4 H, H2\'), 4.07 (s, 4 H, H4).

\textsuperscript{13}C NMR (125 MHz, DMSO-d\textsubscript{6}); \(\delta = 153.6, 145.4, 141.7, 124.7, 117.4, 41.4\).

HRMS (EI): \(m/z\) ccalc for C\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}: 298.1317; found: 298.1320.

1,3-Bis(4-nitrophenyl)imidazolidin-2-one (4)\textsuperscript{23}

Purified by flash chromatography (CHCl\textsubscript{3}); yellow solid; yield: 54%; mp 306 °C (Lit.\textsuperscript{23} 299 °C).

IR (KBr): 1725, 1607 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \(\delta = 7.69\) (d, J = 9.2 Hz, 4 H, H3\'), 7.70 (d, J = 9.2 Hz, 4 H, H2\'), 3.95 (s, 4 H, H4), 2.47 (s, 6 H, SCH\textsubscript{3}.

\textsuperscript{13}C NMR (125 MHz, DMSO-d\textsubscript{6}); \(\delta = 154.8, 137.7, 132.1, 128.3, 118.6, 41.9, 17.0\).

HRMS (EI): \(m/z\) ccalc for C\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}: 298.1317; found: 298.1320.

Anal. Cacld for C\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}: C, 68.23; H, 6.09; N, 9.38. Found: C, 68.23; H, 6.09; N, 9.38.

1,3-Di-4-tolylimidazolidin-2-one (2)\textsuperscript{21}

Purified by flash chromatography (silica gel); white solid; yield: 84%; mp 274–276 °C (Lit.\textsuperscript{21} 266 °C).

IR (KBr): 2925, 2908, 1874, 1685, 1522 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \(\delta = 7.46\) (d, J = 9.0 Hz, 4 H, H2\'), 6.89 (d, J = 9.0 Hz, 4 H, H3\'), 3.91 (s, 4 H, H4), 3.78 (s, 6 H, OCH\textsubscript{3}.

\textsuperscript{13}C NMR (125 MHz, DMSO-d\textsubscript{6}); \(\delta = 155.4\) (2 C based on HMBC experiment).

HRMS (EI): \(m/z\) ccalc for C\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}: 278–279 °C (Lit.\textsuperscript{21} 266 °C).

1,3-Diarylimidazolidin-2-ones 2–12, 1,3-Diaryl-1,3-dihydro-2H-benzimidazol-2-ones 13,14 and 1,3-Diphenyl-1,3-di-2-pyridylurea (15); General Procedure

To a 2-necked flask were charged imidazolidin-2-one (1, 0.10 g, 1.2 mmol), Cu (0.02 g, 10 mol%), K\textsubscript{2}CO\textsubscript{3} (0.35 g, 2.5 mmol), and toluene (1 mL, 1 M) under argon. The mixture was refluxed for 24 h and then cooled to r.t., diluted with CHCl\textsubscript{3} (10 mL), and filtered through Celite and washed with CHCl\textsubscript{3} (3 × 15 mL). Solvents were evaporated under reduced pressure by using a rotary evaporator. All yields given refer to as isolated yields. NMR spectra were recorded on a 400 MHz spectrometer. IR spectra were recorded on a FT-IR spectrophotometer. MS and HRMS experiments were performed on a high-/low-resolution magnetic sector mass spectrometer.

1,3-Di-4-tolylimidazolidin-2-one (2)\textsuperscript{21}

Purified by flash chromatography (CHCl\textsubscript{3}); white solid; yield: 92%; mp 233–234 °C (Lit.\textsuperscript{21} 224 °C).

IR (KBr): 3032, 2991, 2912, 2857, 1686 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}); \(\delta = 8.04\) (dd, J = 7.0, 3.8 Hz, 4 H, H3\'), 7.67 (dd, J = 7.0, 3.8 Hz, 4 H, H2\'), 4.35 (q, J = 7.1 Hz, 4 H, OCH\textsubscript{2}CH\textsubscript{3}.

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}); \(\delta = 155.1, 137.6, 132.4, 129.3, 118.0, 42.0, 20.7\).

HRMS (EI): \(m/z\) ccalc for C\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}: 306.1175; found: 306.1176.

Anal. Calcd for C\textsubscript{17}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}: C, 68.23; H, 6.85; N, 10.49.
1.3-Bis(4-acetylphenyl)imidazolidin-2-one (8)

Purified by flash chromatography (CHCl₃); white solid; yield: 81%; mp 284 °C.

IR (KBr): 2989, 2917, 1686, 1673, 1605 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.99 (d, J = 8.8 Hz, 4 H, H₃'), 7.70 (d, J = 8.8 Hz, 4 H, H₂), 4.06 (s, 4 H, H₄), 2.58 (s, 6 H, COCH₃).

13C NMR (100 MHz, CDCl₃): δ = 196.9, 154.1, 143.7, 132.0, 129.6, 117.1, 41.6, 26.4.

HRMS (EI): m/z calcd for C₁₉H₁₈N₂O₃: 288.1011; found: 288.1012.

Anal. Calcd for C₁₉H₁₈N₂O₃: C, 70.82; H, 4.20; N, 19.43. Found: C, 70.70; H, 4.18; N, 19.67.

1.3-Diphenylimidazolidin-2-one

1H NMR (400 MHz, CDCl₃): δ = 7.59–7.57 (m, 4 H, H₂, H₃'). 7.37–7.34 (m, 4 H, H₂), 7.09–7.06 (m, 2 H, H₄'), 3.95 (s, 4 H, H₄).

13C NMR (100 MHz, CDCl₃): δ = 155.0, 140.0, 128.9, 123.0, 118.1, 42.0.

HRMS (EI): m/z calcd for C₂₃H₁₈N₂O: 322.1317; found: 322.1313.

Anal. Calcd for C₂₃H₁₈N₂O: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.71; H, 5.61; N, 8.52.

1.3-Diphenylimidazolidin-2-one (9)²¹²⁵

Purified by flash chromatography (CHCl₃); white solid; yield: 85%; mp 219–220 °C (Lit.²¹ 212–213 °C).

IR (KBr): 2292, 2904, 1687, 1601 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.59–7.57 (m, 4 H, H₂, H₃'), 7.37–7.34 (m, 4 H, H₂), 7.09–7.06 (m, 2 H, H₄'), 3.95 (s, 4 H, H₄).

13C NMR (100 MHz, CDCl₃): δ = 153.7, 151.5, 146.9, 136.9, 118.0, 113.1, 40.9.

HRMS (EI): m/z calcd for C₁₉H₁₂N₄O₅: 328.0978; found: 328.0966.


1.3-Bis(2-methoxyphenyl)imidazolidin-2-one (10)

Purified by flash chromatography (CHCl₃); yellow liquid; yield: 95%.

IR (CHCl₃): 3011, 2400, 1713 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.44 (dd, J = 7.8, 1.6 Hz, 2 H, H₆'), 7.22–7.18 (m, 2 H, H₄'), 6.98–6.93 (m, 4 H, H₃, H₅'), 3.90 (s, 4 H, H₄), 3.86 (s, 6 H, OCH₃).

13C NMR (100 MHz, CDCl₃): δ = 158.5, 154.9, 128.6, 128.3, 127.3, 120.8, 112.0, 55.6, 45.0.

HRMS (EI): m/z calcd for C₂₅H₂₈N₂O₄: 380.2047; found: 380.2046.


1.3-Di-1-naphthylimidazolidin-2-one (11)

Purified by flash chromatography (CHCl₃); white solid; yield: 83%; mp 198–200 °C.

IR (KBr): 3042, 2878, 1697, 1595 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 8.13 (dd, J = 8.4, 0.6 Hz, 2 H, H₆'), 7.91–7.88 (m, 2 H, H₅'), 7.82 (d, J = 8.0 Hz, 2 H, H₇'), 7.60–7.50 (m, 8 H, H₂', H₃', H₄', H₆'), 4.12 (s, 4 H, H₄).

13C NMR (100 MHz, CDCl₃): δ = 159.1, 136.5, 134.6, 130.5, 128.4, 127.7, 126.4, 126.2, 125.7, 123.1, 47.4.

HRMS (EI): m/z calcd for C₆₁H₄₁N₂O₂: 338.1419; found: 338.1411.


X-ray crystal structure analysis: formula C₆₁H₄₁N₂O₂, M = 338.39, T = 295(2) K, λ = 0.71073 Å, crystal system: monoclinic, space group P2₁/c. Unit cell dimensions: a = 13.2790(3) Å, b = 10.8498(3) Å, c = 12.4770(4) Å, β = 107.042(17)°, V = 1718.68(8) Å³, Z = 4. p₁₀₀ is 1.308 mg/m³; absorption coefficient: 0.081 mm⁻¹. F(000) = 712. Crystal size: 0.30 x 0.20 x 0.15 mm. 0 Range for data collection: 2.47 to 27.49°. Limiting indices: −17 ≤ h ≤ 17, −14 ≤ k ≤ 16, −16 ≤ l ≤ 16. Reflections collected: 12289. Independent reflections: 3938 [R(int) = 0.0767]. Completeness to θ = 27.49°: 99.8%. Refinement method: Full-matrix least-squares on F². Data/restraints/parameters: 3938/0/236. Goodness-of-fit on F²: 1.018. Final R indices (I > 2σ(I)): R1 = 0.0534, wR2 = 0.1191. R indices (all data) R1 = 0.1052, wR2 = 0.1451. Largest diff. peak and hole: 0.212 and −0.252 e Å⁻³. Selected bond lengths (Å) and angles (°): C1–C1 1.321(9), C1–H1 1.09(1), C1–C2 1.375(11), C1–N1 1.276(11), C1–N2 1.274(11), C1–N3 1.272(11), C1–N4 1.271(11), C1–N5 1.270(11).
HRMS (EI): m/z calc. for C_{32}H_{33}N_{4}O_2: 529.2481; found: 529.2462. Anal. Calcd for C_{32}H_{33}N_{4}O_2: C, 78.46; H, 5.91; N, 14.73. Found: C, 78.32; H, 5.87; N, 14.71.

X-ray crystal structure analysis: formula C_{32}H_{33}N_{4}O_2, M = 566.41, T = 295(2) K, Z = 4, λ = 0.71073 Å, crystal system: orthorhombic, space group Pbcn. Unit cell dimensions: a = 11.3440(2) Å, b = 11.7670(2) Å, c = 14.1680(3) Å, V = 1891.21(6) Å\(^3\), Z = 4, \(\rho_{calc} = 1.287 \text{ mg mm}^{-3}\), absorption coefficient: 0.082 mm\(^{-1}\), \(F(000) = 768\). Crystal size: 0.30 \times 0.15 \times 0.10 mm. Data/restraints/parameters: 2159/0/129. Goodness-of-fit on F\(^2\): 1.071. Final R indices (I > 2\(\sigma(I)\)): R1 = 0.0493, wR2 = 0.1103. R values (all data) R1 = 0.0692, wR2 = 0.1215. Largest diff. peak and hole: 0.290 and –0.338 e Å\(^{-3}\). Selected bond lengths (Å) and angles (°): O1–C1 1.217(2), N1–C1 1.388(2), N1–C7 1.466(2), C1–N1–C7 118.59(12), C2–N1–C7 114.06(12), C1–N1–C2 121.78(11), C2–N1–C7 114.03(12), C3–N1–C2 115.05(11). Structure factor range for reflections collected: 11964. Refinement method: Full-matrix least-squares on F\(^2\).

IR (KBr): 2925, 2851, 1651, 1505 cm\(^{-1}\). Anal. Calcd for C_{18}H_{20}N_{2}O_{3}: C, 69.21; H, 5.64; N, 8.97. Found: C, 68.72; H, 5.65; N, 8.79.

1-3-Diaryltetrahydropyrimidin-2(1H)-ones 16, 17; General Procedure
To a double-necked flask were charged tetrahydropyrimidin-2-one (2 mL) was reacted according to the general procedure to give 16, 17, and further purified by flash chromatography (silica gel, CHCl\(_3\)–EtOAc, 2:1). IR (KBr): 2950, 2906, 2834, 1685, 1498 cm\(^{-1}\). Anal. Calcd for C_{18}H_{19}N_{2}O_{3}: C, 68.79; H, 6.65; N, 8.83. HRMS (FAB): m/z [M + H]\(^+\)calc. for C_{30}H_{24}N_{4}O_{2}: 468.1607; found: 468.1602.

1-4-Tert-Butyl-3-[4-(methylsulfonyl)phenyl]phenylimidazolidin-2-one (21)
To an oven-dried flask (25 mL) was added a solution of 21 (1.15 g, 4 mmol) in 20% HCl (26 mL). The mixture was heated at 110 °C for 18 h. The resulting suspension was cooled, and neutralized with aq NaOH. The mixture was extracted with CHCl\(_3\) (3 × 30 mL). The collected organic extracts were dried (anhyd MgSO\(_4\)) and concentrated. The crude products were purified by recrystallization (CH\(_2\)Cl\(_2\)) to give 21 as a white solid; yield: 64%; mp 210–214 °C.

1-{4-[4-(Methylsulfonyl)phenyl]phenylimidazolidin-2-yl}benzoate (22)
A solution of 18 (0.08 g, 0.4 mmol), Cu (0.01 g, 10 mol%), K\(_2\)CO\(_3\) (0.3022 g, 2.2 mmol), DMCHDA (0.01 mL, 20 mol%), and 4-Bromohippuric acid (0.45 g, 2.4 mmol) in toluene (1 mL) was reacted according to the general procedure and further purified by flash chromatography (silica gel, CHCl\(_3\)–EtOAc, 2:1) to give 22 as a white solid; yield: 67%; mp 165–166 °C (Lit.\(^{10}\) 165–167 °C).

HRMS (FAB): m/z [M + H]\(^+\)calc. for C_{40}H_{33}N_{3}O_{3}: 624.2196; found: 624.2194.

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matography (silica gel, CHCl₃) to give 22 as a white solid; yield: 76%; mp 199–200 °C.

IR (KBr): 2978, 2918, 1702, 1612 cm⁻¹.

3¹H NMR (400 MHz, CDCl₃): δ = 8.02 (d, J = 9.0 Hz, 2 H, H3), 7.65 (d, J = 9.0 Hz, 2 H, H2), 7.51 (d, J = 8.8 Hz, 2 H, H2), 7.28 (d, J = 8.8 Hz, 2 H, H3'), 4.34 (q, J = 7.1 Hz, 2 H, OCH₂CH₃), 3.98–3.96 (m, 4 H, NCH₂CH₂N), 2.46 (s, 3 H, SCH₃), 1.37 (t, J = 7.1 Hz, 3 H, OCH₂CH₃).

3¹C NMR (100 MHz, CDCl₃): δ = 166.3, 154.4, 143.9, 137.3, 132.7, 130.6, 128.1, 124.5, 118.9, 116.7, 60.8, 41.3, 41.7, 16.8, 14.4.

HRMS (EI): m/z calcd for C₈H₇N₂O₃S: 356.1195; found: 356.1198.

Anal. Calcd for C₈H₇N₂O₃S: C, 64.02; H, 5.66; N, 7.86; S, 9.00.

Found: C, 64.19; H, 5.79; N, 7.83; S, 9.22.

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References


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Synthesis of N-Aryl-Substituted Cyclic Ureas


(20) While DMF is a teratogen, dioxane is a carcinogen suspect agent.


