Copper(II) Triflate Catalyzed Synthesis of 2,4-Disubstituted Oxazoles from α-Diazoketones

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Abstract A novel method is devised for the synthesis of 2,4-disubstituted oxazole derivatives via the coupling of α-diazoketones with amides using copper(II) triflate as the catalyst. The synthetic versatility of this approach is exemplified in the synthesis of an analogue of balsoxin.

Key words α-diazoketones, amides, copper(II) triflate, oxazoles

The oxazole motif is often found in biologically active natural products (Figure 1), agrochemicals and medicinally important compounds.1,2 In particular, di- and trisubstituted oxazoles are known to exhibit promising antibacterial,1a antimycobacterial,1b antiviral,3c hypoglycemia3d and anticancer activities.3e Consequently, numerous methods have been developed for the synthesis of oxazole derivatives, which include intramolecular cyclization of amides,4 domino reactions of ketones,5 oxidative cyclization of imines,6 transition-metal-catalyzed cross-coupling reactions,7 Fischer oxazole synthesis8a and the Robinson–Gabriel synthesis of oxazoles.8b Moses et al. have reported the one-step synthesis of oxazoles from α-haloketones, a method which shows broad substrate scope and tolerance to a variety of functional groups.9a Recently, Wang et al. reported an oxidative domino reaction for the synthesis of functionalized oxazoles from aryl methyl ketones and benzyl amines.9c More recently, Zhang and co-workers reported the synthesis of functionalized oxazoles from α-bromoketones and benzyl amine using the iodine–potassium carbonate (I2–K2CO3) reagent system,9b however, this method only worked with aryl ketones. Though numerous procedures have been reported for the synthesis of oxazoles, simple and expedient approaches still remain scarce.

Figure 1 Examples of biologically active natural products containing an oxazole motif

The relative stability and facile decomposition of α-diazocarbonyl compounds under thermal, photochemical and transition-metal-catalysis conditions make them useful intermediates in organic synthesis.10 Inspired by the synthet-
ates and phosphonates with aryl carboxamides to produce 2,4,5-trisubstituted oxazoles by N–H insertion followed by cyclodehydration. However, the scope was limited to the synthesis of oxazoles carrying an additional acceptor group such as carboxylate, phosphonate or sulfone.

In continuation of our interest in the application of α-diazoketones, we herein report a simple and convenient approach for the synthesis of 2,4-disubstituted oxazoles through the coupling of α-diazoketones with amides. As a model reaction, we first attempted the cross-coupling of 2-diazo-1-phenylethanone (1a) with benzamide (2a) in the presence of copper(II) triflate [Cu(OTf)₂] (10 mol%) in 1,2-dichloroethane. The reaction was sluggish at room temperature, however, by increasing the temperature from 25 to 80 °C, the desired product, 2,4-diphenyloxazole (3a), was obtained in 87% yield (Scheme 1).

In order to optimize the reaction conditions, several metal catalysts including dirhodium tetraacetate, copper(II) triflate, copper(I) triflate (CuOTf), scandium(III) triflate [Sc(OTf)₃], indium(III) triflate [In(OTf)₃], bismuth(III) triflate [Bi(OTf)₃], copper(II) hexafluoroacetylacetonate [Cu(hfacac)₂], copper(II) acetate [Cu(OAc)₂], copper(II) acetylacetonate [Cu(acac)₂], copper(I) iodide (CuI) and copper(II) sulfate [CuSO₄] were screened. Among them, copper(II) triflate (10 mol%) gave the best results in terms of conversion (Table 1, entry 1). In addition, dirhodium tetraacetate (10 mol%) was also effective for this transformation (Table 1, entry 4), however, its use here cannot be recommended as rhodium is significantly more expensive than copper. Furthermore, metal triflates such as scandium(III) triflate, indium(III) triflate, and bismuth(III) triflate were found to be less effective (Table 1, entries 11–13). Solid acids such as clays, heteropolyacids and ion-exchange resins failed to give the desired product. Of the different solvents tested, toluene and tetrahydrofuran were found to be less effective resulting in the formation of product 3a in lower yields (Table 1, entries 2 and 3).

Next, we extended this method to other aromatic α-diazoketones including 3,4,5-trimethoxyphenyl and 3-methylphenyl derivatives. In most cases, the corresponding oxazole derivatives were obtained in good yields (Table 2, entries 3, 4, 7 and 8). Furthermore, we also examined the reactivity of different aliphatic diazoketones. Interestingly, alkyl α-diazoketones such as 1-diazo-3,3-dimethylbutan-2-one, 1-diazo-3-methylbutan-2-one and 1-diazo-3-methylbutan-2-one afforded the corresponding oxazoles in good yields (Table 2, entries 5, 6 and 10). In addition, this method worked with aliphatic amides. However, the reaction was not successful if both substrates were aliphatic. With aliphatic amides, the corresponding alkyl-substituted oxazoles were obtained in relatively lower yields (Table 2, entries 2, 4 and 8) compared with their aromatic counterparts. In all the cases, the reactions proceeded efficiently in the presence of copper(II) triflate (10 mol%) at 80 °C in 1,2-dichloroethane, and the corresponding products were obtained in good yields. No side products arising from Wolff rearrangements were observed under the present reaction conditions.

![Scheme 1](image1.png)

**Scheme 1** Synthesis of 2,4-diphenyloxazole (3a)

![Scheme 2](image2.png)

**Scheme 2** A plausible reaction pathway

### Table 1 Screening of Different Catalysts for the Formation of 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)₂</td>
<td>DCE</td>
<td>1</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)₂</td>
<td>THF</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)₂</td>
<td>toluene</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Rh₂(OAc)₄</td>
<td>DCE</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>Cu(hfacac)₂</td>
<td>DCE</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>Cu(acac)₂</td>
<td>DCE</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>CuOTf</td>
<td>DCE</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)₂</td>
<td>DCE</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>Cu</td>
<td>DCE</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>CuSO₄</td>
<td>DCE</td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>Sc(OTf)₃</td>
<td>DCE</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>In(OTf)₃</td>
<td>DCE</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>Bi(OTf)₃</td>
<td>DCE</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

*Reactions were performed on 0.5 mmol scale with respect to 1a using 10 mol% of the catalyst.*

*Yield of isolated pure product after column chromatography.*
Table 2  Synthesis of 2,4-Disubstituted Oxazoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-Diazoketone</th>
<th>Amide</th>
<th>Product*</th>
<th>Time (h)</th>
<th>Yield (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>3a</td>
<td>1</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>3b</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>MeO-</td>
<td>MeO-</td>
<td>3c</td>
<td>1</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>MeO-</td>
<td>MeO-</td>
<td>3d</td>
<td>1.5</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>Me-</td>
<td>Me-</td>
<td>3e</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>Me-</td>
<td>Me-</td>
<td>3f</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
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<td>75</td>
</tr>
<tr>
<td>9</td>
<td>MeO-</td>
<td>MeO-</td>
<td>3i</td>
<td>1</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>Me-</td>
<td>Me-</td>
<td>3j</td>
<td>2</td>
<td>76</td>
</tr>
</tbody>
</table>

* The structures of the products were established from their NMR and IR spectra.

b Yield of isolated pure product after column chromatography.
To show the synthetic utility, we applied the present protocol to the synthesis of an analogue of balsoxin. The 2,5-diaryloxazole motif is found in various natural products such as taxamine and balsoxin (Figure 1), which were isolated from the roots of *Amyris texana* and *A. plumieri*, respectively. Accordingly, the coupling of commercially available benzamide (2a) with 2-diazo-1-(3,4-dimethoxyphenyl)ethanone (1i) in the presence of copper(II) triflate (10 mol%) gave the balsoxin analogue 3i in 73% yield (Table 2, entry 9). This procedure is efficient and practical compared to previous methods.

A plausible mechanism for this reaction is proposed in Scheme 2. In the presence of a catalytic amount of copper(II) triflate in 1,2-dichloroethane, diazoketone 1 decomposes with evolution of nitrogen to form a copper carbonyl species, which reacts rapidly with carbazole 2. Subsequent attack of the carbonyl group, in preference to N–H insertion on the copper carbonyl, followed by cyclohydration gives the desired 2,4-disubstituted oxazole (Scheme 2).

In the case of carbamides, N–H insertion, with formation of a C–N bond, is generally a favorable reaction pathway. However, there are a few examples reported involving the formation of a C–O bond in the reaction of a carbene with a carbamid in which an N–H bond is also available for insertion. In the present case, the change in selectivity is presumably electronic in nature, reflecting the changes in the electrophilicity of the carbene.

In conclusion, we have developed a novel protocol for the synthesis of 2,4-disubstituted oxazoles. This method offers several advantages such as good yields, the use of cost-effective reagents, and a low catalyst loading, which should make it an attractive procedure for the synthesis of a wide range of 2,4-disubstituted oxazoles.

The α-diazoketones were prepared using reported conditions. CH₂Cl₂ was distilled from CaH under an N₂ atmosphere. Column chromatography was performed using silica gel (mesh size?). Melting points were measured on a Thermo Scientific Micro melting point apparatus. IR spectra were recorded on a Shimadzu FT-IR spectrometer and absorptions are reported in reciprocal centimeters (cm⁻¹). ¹H and ¹³C NMR spectra were recorded on Bruker Avance spectrometers and absorptions are reported in absolute parts per million (ppm). HRMS spectra were obtained using a VG Autospec triple sector mass spectrometer.

### 2.4-Disubstituted Oxazoles; General Procedure

A mixture of a diazoketone (1.2 mmol), amide (1 mmol) and Cu(OTf)₂ (0.1 mmol) in DCE (10 mL) was stirred at 80 °C for the appropriate period of time (see Table 2). After completion, as indicated by TLC, the mixture was quenched with H₂O and extracted with EtOAc (2 × 15 mL). Evaporation of the solvent followed by purification over silica gel (77–77) afforded the pure oxazole 3.

#### 2.4-Diphenyl oxazole (3a)

Yield: 190 mg (87%); white solid; mp 72–74 °C.

- **¹H NMR (500 MHz, CDCl₃)**: δ = 8.14–8.06 (m, 2 H, Ar-H), 7.92 (s, 1 H, oxaz-CH), 7.80–7.77 (m, 3 H, Ar-H), 7.48–7.36 (m, 4 H, Ar-H), 7.31–7.25 (m, 1 H, Ar-H).
- **¹³C NMR (75 MHz, CDCl₃)**: δ = 160.8, 141.2, 132.7, 130.4, 129.7, 128.0, 127.4, 126.9, 125.9, 125.0.
- **MS (ESI)**: m/z = 312 [M + H]+.


#### 2-Methyl-4-phenyloxazole (3b)

Yield: 127 mg (80%); semi-solid.

- **¹H NMR (500 MHz, CDCl₃)**: δ = 7.75 (s, 1 H, oxaz-CH), 7.64 (d, J = 8.0 Hz, 2 H, Ar-H), 7.34 (t, J = 7.5 Hz, 2 H, Ar-H), 7.25–7.21 (m, 1 H, Ar-H), 2.50 (s, 3 H, CH₃).
- **¹³C NMR (75 MHz, CDCl₃)**: δ = 160.7, 139.8, 132.4, 128.0, 127.2, 124.7, 14.7.

MS (ESI): m/z = 160 [M + H]+.


#### 2-Phenyl-4-(3,4,5-trimethoxyphenyl)oxazole (3c)

Yield: 264 mg (85%); semi-solid.

- **¹H NMR (500 MHz, CDCl₃)**: δ = 8.11–8.09 (m, 2 H, Ar-H), 7.86 (s, 1 H, oxaz-CH), 7.47–7.42 (m, 3 H, Ar-H), 6.99 (s, 2 H, Ar-H), 3.94 (s, 6 H, OCH₃), 3.84 (s, 3 H, OCH₃).
- **¹³C NMR (75 MHz, CDCl₃)**: δ = 161.7, 153.5, 141.8, 133.1, 130.4, 128.7, 127.3, 126.7, 126.4, 106.0, 102.7, 60.9, 56.2, 56.1.

MS (ESI): m/z = 312 [M + H]+.


#### 2-Methyl-4-(3,4,5-trimethoxyphenyl)oxazole (3d)

Yield: 194 mg (78%); semi-solid.

- **¹H NMR (500 MHz, CDCl₃)**: δ = 7.70 (s, 1 H, oxaz-CH), 7.64 (d, J = 8.0 Hz, 2 H, Ar-H), 7.25–7.21 (m, 1 H, Ar-H), 2.50 (s, 3 H, CH₃).
- **¹³C NMR (75 MHz, CDCl₃)**: δ = 160.7, 152.5, 139.7, 137.1, 132.1, 126.1, 124.7, 14.6.

MS (ESI): m/z = 272 [M + Na]+.


#### 4-tert-Butyl-2-phenyloxazole (3e)

Yield: 150 mg (75%); semi-solid.

- **¹H NMR (300 MHz, CDCl₃)**: δ = 8.02–7.97 (m, 2 H, Ar-H), 7.46–7.31 (m, 3 H, Ar-H), 7.23 (s, 1 H, oxaz-CH), 1.30 (s, 9 H, C(CH₃)$_₃$).
13C NMR (75 MHz, CDCl3): δ = 160.8, 160.5, 129.7, 128.6, 127.8, 125.9, 120.9, 32.4, 28.6.

MS (ESI): m/z = 202 [M + H]+.


4-Isopropyl-2-phenyloxazole (3f)

Yield: 199 mg (85%); brown solid; mp 91–93 °C.

IR (KBr): 2983, 1675, 1496, 1378, 1031, 948, 754 cm–1.

MS (ESI): m/z = 174 [M + H]+.

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Supporting Information

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