EFFICIENT AND DIVERGENT SYNTHESIS OF BENZOXAZOLES AND 1,2-BENZISOXAZOLES FROM o-HYDROXYARYL KETOXIMES

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Abstract – A bis(trichloromethyl) carbonate (BTC) / triphenylphosphine oxide (TPPO) system promoting tunable cyclization of a variety of o-hydroxyaryl ketoximes to benzoxazoles and benzisoxazoles was developed. The synthetic switch was enabled by base-free or the use of Et$_3$N. Under base-free conditions, o-hydroxyaryl ketoximes were treated with BTC/TPPO giving corresponding 2-substituted benzoxazoles via cascaded Beckmann rearrangement and intramolecular oxa-cyclization. Analogously, the 3-substituted benzisoxazoles were obtained via intramolecular nucleophilic substitution reactions in the presence of Et$_3$N. This process features mild reaction conditions, high chemoselectivity, and good functional groups tolerance.

INTRODUCTION

The heterocyclic structures of isomeric benzoxazoles and benzisoxazoles are ubiquitously found in the fields of pharmacologically active substances and natural products (Figure 1). For example, the benzoxazole motif makes up the core structure of numerous bioactive compounds and drugs, including flunoxaprofen$^1$ and benoxaprofen$^2$, which are widely used to treat osteoarthritis and rheumatoid arthritis.$^3$ Additionally, the benzoxazole ring occurs in antiviral agents and elastase inhibitor agents.$^4$

Figure 1. Benzoxazoles and benzisoxazoles as medicinal agents
Meanwhile, the 1,2-benzisoxazole derivatives also have luxurious biological properties, especially in the realms of central nervous system diseases. Four 1,2-benzisoxazoles (zonisamide, risperidone, paliperidone, and iloperidone) have been clinically used and identified as active therapeutic agents. Benzoisoxazole is also an essential structure for the development of atypical antipsychotics. It is for these critical pharmacological properties of benzoxazoles and benzisoxazoles that milder and more efficient synthetic strategy is sought for their synthesis.

A survey of the literature reveals a variety of preparative protocols have been developed for the synthesis of 2-substituted benzoxazoles. One of the most commonly used methods undergoes a Beckmann rearrangement process of o-hydroxyaryl ketoximes. To accomplish this transformation, various reagents and techniques had been utilized, such as zeolite, ZnCl₂, (EtO)₂POCl, titanium cation-exchanged montmorillonite and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl). On the other hand, numerous approaches towards the formation of benzisoxazoles from o-hydroxyaryl ketoximes have also been presented using different systems including SOCl₂/pyridine, Ac₂O/K₂CO₃, Ac₂O/pyridine, Ga(OTf)₃, Ph₃P/DDQ, and Tf₂O. However, to the best of our knowledge, the previous reports mainly focused on the synthesis of benzoxazoles and benzisoxazoles respectively. The divergent synthetic strategy based on the same oximes is rare reported. It remains a challenging task to develop an operationally tunable and straightforward synthetic method for benzoxazoles and benzisoxazoles.

Over the past decades, bis(trichloromethyl) carbonate (BTC) has been gradually dawned as the most popular alternative of phosgene. The popularity of BTC is probably related to the fact that it exists as a stable nonhygroscopic crystalline material at room temperature, and this permits easy and safe handling. Driven by our continuous interests and efforts in expanding the chemistry of BTC, we recently developed several eco-friendly methods for the construction of dichloropyrimidine-fused heterocycles by transforming notorious triphenylphosphine oxide (TPPO) to a versatile chlorination reagent triphenylphosphine dichloride (TPPDC, Ph₃PCl₂). As part of our ongoing research in developing the BTC system to synthesize biologically relevant heterocyclic compounds, we demonstrated herein an efficient strategy for the divergent synthesis of benzoxazoles and benzisoxazoles from o-hydroxyacetophenone oximes promoted by BTC/TPPO system controlled by Et₃N providing moderate to excellent yields.

RESULTS AND DISCUSSION

Initially, o-hydroxyacetophenone oxime (1a) was selected as a model compound for the subsequent investigation in the presence of different BTC systems. To our delight, 2-methylbenzoxazole 2a was afforded with 60% yields in the presence of 1.0 equiv of BTC/TPPO (Table 1, Entry 1). Then the reaction conditions, including the ratio of 1a to BTC/TPPO and reaction temperature were optimized (Table1,
Entries 1-5). A series of experiments indicated that 1.5 equiv of BTC/TPPO was sufficient for the synthesis of 2a, and the optimal reaction conditions were built when the reaction of 1a was performed at 25 °C for 0.5 h, whereby the yield of 2a reached 85% (Table 1, Entry 2).

### Table 1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>1a/BTC/TPPO ratio</th>
<th>Base</th>
<th>Solvent</th>
<th>2a&lt;sup&gt;b&lt;/sup&gt;</th>
<th>3a&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:0.33:1</td>
<td>/</td>
<td>DCM</td>
<td>60%</td>
<td>N.D.</td>
</tr>
<tr>
<td>2</td>
<td>1:0.5:1.5</td>
<td>/</td>
<td>DCM</td>
<td>85%</td>
<td>N.D.</td>
</tr>
<tr>
<td>3</td>
<td>1:0.67:2</td>
<td>/</td>
<td>DCM</td>
<td>86%</td>
<td>N.D.</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1:0.5:1.5</td>
<td>/</td>
<td>DCM</td>
<td>85%</td>
<td>N.D.</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1:0.5:1.5</td>
<td>/</td>
<td>DCM</td>
<td>37%</td>
<td>N.D.</td>
</tr>
<tr>
<td>6</td>
<td>1:0.5:1.5</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N (2 eq.)</td>
<td>DCM</td>
<td>83%</td>
<td>N.D.</td>
</tr>
<tr>
<td>7&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0.5:1.5</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N (2 eq.)</td>
<td>DCM</td>
<td>21%</td>
<td>46%</td>
</tr>
<tr>
<td>8&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N (2 eq.)</td>
<td>DCM</td>
<td>39%</td>
<td>52%</td>
</tr>
<tr>
<td>9&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N (3 eq.)</td>
<td>DCM</td>
<td>30%</td>
<td>62%</td>
</tr>
<tr>
<td>10&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N (4 eq.)</td>
<td>DCM</td>
<td>14%</td>
<td>80%</td>
</tr>
<tr>
<td>11&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N (5 eq.)</td>
<td>DCM</td>
<td>9%</td>
<td>87%</td>
</tr>
<tr>
<td>12&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N (6 eq.)</td>
<td>DCM</td>
<td>10%</td>
<td>86%</td>
</tr>
<tr>
<td>13&lt;sup&gt;d,f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N (5 eq.)</td>
<td>DCM</td>
<td>9%</td>
<td>88%</td>
</tr>
<tr>
<td>14&lt;sup&gt;e,f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>Et&lt;sub&gt;3&lt;/sub&gt;N (5 eq.)</td>
<td>DCM</td>
<td>3%</td>
<td>19%</td>
</tr>
<tr>
<td>15&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>DABCO (5 eq.)</td>
<td>DCM</td>
<td>24%</td>
<td>N.D.</td>
</tr>
<tr>
<td>16&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>DBU (5 eq.)</td>
<td>DCM</td>
<td>39%</td>
<td>N.D.</td>
</tr>
<tr>
<td>17&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>pyridine (5 eq.)</td>
<td>DCM</td>
<td>77%</td>
<td>N.D.</td>
</tr>
<tr>
<td>18&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0.67:2</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt; (5 eq.)</td>
<td>THF</td>
<td>trace</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions unless specified otherwise: 1a (1 mmol, 1 eq.), BTC, and TPPO in solvent were premixed under an ice bath and stirred at rt for further 0.5 h. Then, 1a was dropwise into the mixture within 0.5 h. <sup>b</sup>Isolated yield based on 1a. <sup>c</sup>N.D. for Not detected. <sup>d</sup>Reaction temperature 39 °C. <sup>e</sup>Reaction temperature -10 °C. <sup>f</sup>The reaction mixture of BTC/TPPO was dropwise into the solution of 1a and base.

Next, encouraged by the above results, we turned our attention to select appropriate reaction conditions that favored the formation of benzisoxazoles. Considering Beckmann rearrangement commonly catalyzed
by acids, we explored whether the addition of a base could inhibit the Beckmann rearrangement progress. However, the product of benzoisoxazole 3a was not detected when the reaction solution of 1a and Et₃N was dropped into the solution of BTC/TPPO (Table 1, Entry 6). Surprisingly, when the reaction mixture of BTC/TPPO was dropped into the solution of 1a and Et₃N, the reaction proceeded smoothly as indicated by TLC and the product was characterized as 3a by the spectral and analytical data (Table 1, Entry 7). Subsequently, the usage of BTC/TPPO and Et₃N was further investigated (Table 1, Entries 8-12). When the ratio of 1a: BTC: TPPO: Et₃N was 1: 0.67: 2: 5, the yield of 3a was improved to 87% after reacting about 1 h at 25 °C (Table 1, Entry 11). No significant improvement in the yield of 3a was achieved by changing the reaction temperature (Table 1, Entries 13-14). Finally, several bases, including DABCO, DBU, pyridine, and K₂CO₃ were explored (Table 1, Entries 15-18), and it was observed that Et₃N was more suitable for this reaction.

Table 2. Synthesis of 2-substituted benzoxazoles

<table>
<thead>
<tr>
<th>R²</th>
<th>R²</th>
<th>TPPO (1.5 eq.), BTC (0.5 eq.)</th>
<th>DCM, 25 °C</th>
<th>2a-2p</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Me</td>
<td>-Me</td>
<td>85%</td>
<td></td>
<td>2a</td>
</tr>
<tr>
<td>-Me</td>
<td>-Me</td>
<td>82%</td>
<td></td>
<td>2b</td>
</tr>
<tr>
<td>-Me</td>
<td>-Me</td>
<td>78%</td>
<td></td>
<td>2c</td>
</tr>
<tr>
<td>-Me</td>
<td>-Me</td>
<td>79%</td>
<td></td>
<td>2d</td>
</tr>
<tr>
<td>-Me</td>
<td>-Cl</td>
<td>81%</td>
<td></td>
<td>2e</td>
</tr>
<tr>
<td>-Me</td>
<td>-Br</td>
<td>76%</td>
<td></td>
<td>2f</td>
</tr>
<tr>
<td>-Me</td>
<td>-F</td>
<td>74%</td>
<td></td>
<td>2g</td>
</tr>
<tr>
<td>-Me</td>
<td>-Me</td>
<td>86%</td>
<td></td>
<td>2h</td>
</tr>
<tr>
<td>-Me</td>
<td>-Cl</td>
<td>86%</td>
<td></td>
<td>2i</td>
</tr>
<tr>
<td>-Me</td>
<td>-Br</td>
<td>85%</td>
<td></td>
<td>2j</td>
</tr>
<tr>
<td>-Me</td>
<td>-Et</td>
<td>87%</td>
<td></td>
<td>2l</td>
</tr>
<tr>
<td>-Me</td>
<td>-n-Pr</td>
<td>85%</td>
<td></td>
<td>2m</td>
</tr>
<tr>
<td>-Me</td>
<td>-Me</td>
<td>88%</td>
<td></td>
<td>2n</td>
</tr>
<tr>
<td>-Me</td>
<td>-Cl</td>
<td>90%</td>
<td></td>
<td>2o</td>
</tr>
<tr>
<td>-Me</td>
<td>-Cl</td>
<td>92%</td>
<td></td>
<td>2p</td>
</tr>
</tbody>
</table>

*Reactions were performed using reaction conditions A: 1a (1 mmol, 1 eq.) TPPO (1.5 mmol, 1.5 eq.), BTC (0.5 mmol, 0.5 eq.) in 25 °C, *b* isolated yield.

With these optimized conditions in hand, we turned to examine the scope and limitations of this method. Generally, a range of substituents on the aromatic ring, including -Me, -OMe, -F, -Cl, and -Br were all
well-tolerated in this process, producing the desired benzoxazoles with satisfactory yields (Table 2, 2b-2f, 2h-2k). As expected, the strong electron-withdrawing group -NO₂ afforded a relatively lower yield (Table 2, 2g). o-Hydroxyaryl ketoximes with the same substituent groups in the meta position of the hydroxy group gave relatively higher yields than those in the para position because of the reactive tendency of Beckmann rearrangement. (Table 2, 2h-2k vs 2c-2f). The reaction was not dramatically influenced when the R² was linear alkyl (Table 2, 2l and 2m). The yield was slightly increased when the R² was aryl group (Table 2, 2n-2p). The migration of an aryl group might explain it predominates over that of an alkyl group during Beckmann rearrangement.²⁸

### Table 3. Synthesis of 3-substituted benzisoxazoles²ᵃ,ᵇ

<table>
<thead>
<tr>
<th></th>
<th>R¹</th>
<th>R²</th>
<th>TPPO (2 eq.), BTC (0.67 eq.), Et₂N (5 eq.)</th>
<th>DCM, 25 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>Me</td>
<td>Me</td>
<td>87% (9%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>Me</td>
<td>Me</td>
<td>83% (12%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>Me</td>
<td>Me</td>
<td>91% (5%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>Me</td>
<td>Me</td>
<td>92% (6%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>Cl</td>
<td>Me</td>
<td>83% (11%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3f</td>
<td>Br</td>
<td>Me</td>
<td>91% (6%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3g</td>
<td>O₂N</td>
<td>Me</td>
<td>82% (7%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3h</td>
<td>Cl</td>
<td>Me</td>
<td>84% (10%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3i</td>
<td>F</td>
<td>Me</td>
<td>80% (15%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3j</td>
<td>n-Pr</td>
<td>Me</td>
<td>76% (13%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3k</td>
<td>Cl</td>
<td>Me</td>
<td>74% (18%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3l</td>
<td>n-Pr</td>
<td>Me</td>
<td>88% (10%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3m</td>
<td>Cl</td>
<td>Me</td>
<td>70% (24%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3n</td>
<td>Cl</td>
<td>Me</td>
<td>70% (23%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3o</td>
<td>Cl</td>
<td>Me</td>
<td>65% (30%ᵇ)</td>
<td></td>
</tr>
<tr>
<td>3p</td>
<td>Cl</td>
<td>Me</td>
<td>83% (10%ᵇ)</td>
<td></td>
</tr>
</tbody>
</table>

²ᵃReaction conditions B: 1a (1 mmol, 1 eq.), Ph₃PO (2 mmol, 2 eq.), BTC (0.67 mmol, 0.67 eq.), Et₂N (5 mmol), DCM (10 mL). ²ᵇIsolated yield. ²ᶜYield of the corresponding side product 2.
On the other hand, we explored the substrate scope for the selective synthesis of 3-substituted benzisoxazoles. Here again, a variety of o-hydroxyaryl methyl ketoximes containing electron-donating and electron-withdrawing groups were tolerated. Both electron-donating groups such as -Me, -OMe (Table 2, 3b, 3c, and 3h) and electron-withdrawing groups such as -F, -Cl, -Br and -NO₂ (Table 3, 3d-3g, 3i-3k) gave the particular benzisoxazoles products in good to high yields (74-92%). Similarly, o-hydroxyaryl ethyl ketoxime reacted well, giving a yield of 88% (Table 2, 3l). Due to the migration reactivity of Beckmann rearrangement, o-hydroxyaryl propyl- and aryl ketoximes gave the desired products with lower yields, while the corresponding rearrangement products 2 were isolated in yields ranging from 10 to 30% yields (Table 2, 3m-3p).

To demonstrate the practicality of our different protocols in the synthesis of benzoazoles and benzisoxazoles, higher-scale reactions were carried out. When the oxime 1a was magnified to 10 mmol (1.51 g), the product 2a was still afforded in 1.16 g, 84% isolated yield (Scheme 1). Furthermore, when the oxime 1a was magnified to 10 mmol (1.51 g), the product 3a was afforded in 1.18 g, 86% isolated yield (Scheme 1).

![Scheme 1. Higher-Scale Reaction](image)

To further demonstrate the hypothetical inhibiting role of Et₃N, control experiments were carried out (Scheme 2). Acetophenone oxime was added to the activated BTC/Ph₃PO mixture at room temperature. The corresponding Beckmann rearrangement product acetonilide was obtained in 80% yield. While the reaction mixture of BTC/Ph₃PO was added to the solution of acetophenone oxime and Et₃N, the yield of acetonilide was severely decreased to 10%. The experimental results showed that Et₃N could well inhibit Beckmann rearrangement progress in this procedure.

![Scheme 2. Control experiments](image)
Based on the above results and previous literature reports, a plausible reaction mechanism was proposed (Scheme 3). Firstly, the nucleophilic attack from TPPO to BTC generates \([\text{Ph}_3\text{PCl}]^+\text{Cl}^-\). Secondly, two pathways are possible for the following steps. In path a, \([\text{Ph}_3\text{PCl}]^+\text{Cl}^-\) reacts with the hydroxy group of the oxime 1 to form intermediate A. Then, the Beckmann rearrangement is followed to give the critical intermediate C. A nucleophilic attack leads to giving 2 as the final product with the elimination of hydrogen chloride. On the other hand, in path b, 1 reacts with TPPDC, due to the presence of Et₃N, Beckmann rearrangement is sufficiently inhibited, nucleophilic attack naturally takes place to form compound 3.

In summary, we have developed a practical and efficient protocol for selective synthesis of 2-substituted benzoxazoles 2 and 3-substituted benzisoxazoles 3 from readily available \(\alpha\)-hydroxyaryl ketoximes 1. A
series of benzoxazoles were synthesized via sequential Beckmann rearrangement and intramolecular oxa-cyclization under BTC/TPPO conditions, and the benzisoxazoles were obtained via intramolecular nucleophilic substitution reactions conducted by the addition of Et$_3$N. Mild reaction conditions, high chemoselectivity and simple execution are the notable advantages of this method. This result could provide an exciting alternative to prepare benzoxazoles and benzisoxazoles for medicinal agents.

EXPERIMENTAL

Unless otherwise noted, synthetic reagents were purchased from Aladdin and used without further purification. Analytical TLC (thin-layer chromatography) was performed with 0.25 mm silica gel G with a 254 nm fluorescent indicator. Silica gel (100-200 mesh) was used for column chromatography. Melting points (mp) were obtained on a digital melting point apparatus and uncorrected.$^1$H, $^{13}$C, and $^{19}$F NMR spectra were recorded on Brüker (400 MHz & 101 MHz & 376 MHz) spectrometer. Spectra were referenced internally to the residual proton resonance in CDCl$_3$ (δ 7.26 ppm), with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. $^{13}$C NMR spectra were referenced to CDCl$_3$ (δ 77.16 ppm, the middle peak). Coupling constants are expressed in Hz. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublets, dt = doublet of triplets, m = multiplet, br = broad.

General Procedure for the Synthesis of Benzoxazoles 2

A solution of BTC (0.148 g, 0.5 mmol) in 5 mL DCM was added to a stirred solution of TPPO (0.417 g, 1.5 mmol) in 5 mL DCM dropwise under ice bath. After addition completed, the mixture was stirred for 30 min at room temperature. Then the oxime (1 mmol) in 5 mL DCM was added dropwise into the solution. After the addition, the mixture was stirred at room temperature, monitored by TLC until the reaction completed. The reaction mixture was neutralized by the aqueous solution of Na$_2$CO$_3$, diluted with DCM (4 × 10 mL), washed with water (2 × 10 mL) and brine (10 mL), dried over anhydrous Na$_2$SO$_4$. The combined extracts were dried and the solvent was removed in vacuo. The residue was purified by column chromatography to afford the pure product.

2-Methylbenzo[d]oxazole (2a)$^{29}$

Colorless oil; 113 mg, 85% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.66-7.64 (m, 1H), 7.46 (m, 1H), 7.29-7.27 (m, 2H), 2.63 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 163.8, 151.0, 141.5, 124.4, 124.1, 119.4, 110.2, 14.5; MS (ESI): m/z 133.97 [M+H]$^+$. 
2,5-Dimethylbenzo[d]oxazole (2b)\(^\text{29}\)
Colorless oil; 120 mg, 82% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.42 (s, 1H), 7.32 (d, \(J = 8.4\) Hz, 1H), 7.08 (dd, \(J = 8.4, 1.6\) Hz, 1H), 2.60 (s, 3H), 2.44 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 164.0, 149.3, 141.8, 134.0, 125.5, 119.5, 109.6, 21.5, 14.7; MS (ESI): \(m/z\) 148.01 [M+H]\(^+\).

5-Methoxy-2-methylbenzo[d]oxazole (2c)\(^\text{29}\)
Colorless oil; 127 mg, 78% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.23 (d, \(J = 8.8\) Hz, 1H), 7.05 (d, \(J = 2.5\) Hz, 1H), 6.78 (dd, \(J = 8.8, 2.5\) Hz, 1H), 3.73 (s, 3H), 2.50 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 164.5, 156.9, 145.5, 142.3, 112.5, 110.1, 102.6, 55.7, 14.4; MS (ESI): \(m/z\) 164.11 [M+H]\(^+\).

5-Fluoro-2-methylbenzo[d]oxazole (2d)\(^\text{29}\)
Colorless oil; 119 mg, 79% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.37 (dd, \(J = 8.6, 4.3\) Hz, 1H), 7.31 (dd, \(J = 8.6, 2.6\) Hz, 1H), 7.24 (dd, \(J = 8.6, 2.0\) Hz, 1H), 2.61 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 165.8, 159.9 (d, \(J = 239.8\) Hz), 147.3, 142.4 (d, \(J = 13.1\) Hz), 112.0 (d, \(J = 26.2\) Hz), 110.5 (d, \(J = 10.0\) Hz), 106.0 (d, \(J = 25.7\) Hz), 14.6; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): δ -118.59; MS (ESI): \(m/z\) 152.03 [M+H]\(^+\).

5-Chloro-2-methylbenzo[d]oxazole (2e)\(^\text{29}\)
White solid; mp 61-62°C; 135 mg, 81% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.61 (d, \(J = 2.0\) Hz, 1H), 7.36 (d, \(J = 8.6\) Hz, 1H), 7.24 (dd, \(J = 8.6, 2.0\) Hz, 1H), 2.62 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 165.4, 149.6, 142.7, 129.7, 124.8, 119.6, 111.0, 14.7; MS (ESI): \(m/z\) 167.98 [M+H]\(^+\).

5-Bromo-2-methylbenzo[d]oxazole (2f)\(^\text{29}\)
White solid; mp 71-72°C; 161 mg, 76% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.76 (d, \(J = 1.9\) Hz, 1H), 7.38 (dd, \(J = 8.6, 1.9\) Hz, 1H), 7.32 (d, \(J = 8.6\) Hz, 1H), 2.62 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 165.2, 150.1, 143.2, 127.6, 122.6, 116.9, 111.5, 14.7; MS (ESI): \(m/z\) 212.05 [M+H]\(^+\).

2-Methyl-5-nitrobenzo[d]oxazole (2g)\(^\text{30}\)
White solid; mp 154-155°C; 132 mg, 74% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.51 (d, \(J = 2.3\) Hz, 1H), 8.25 (dd, \(J = 8.9, 2.3\) Hz, 1H), 7.56 (d, \(J = 8.9\) Hz, 1H), 2.70 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 167.2, 154.6, 145.2, 142.1, 120.8, 116.0, 110.5, 14.8; MS (ESI): \(m/z\) 179.10 [M+H]\(^+\).

6-Methoxy-2-methylbenzo[d]oxazole (2h)\(^\text{29}\)
White solid; mp 51-52°C; 140 mg, 86% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.49 (d, \(J = 8.7\) Hz, 1H), 6.98 (d, \(J = 2.4\) Hz, 1H), 6.87 (dd, \(J = 8.7, 2.4\) Hz, 1H), 3.82 (s, 3H), 2.58 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): δ 162.9, 157.8, 151.9, 135.3, 119.4, 112.1, 95.4, 56.0, 14.5; MS (ESI): \(m/z\) 164.00 [M+H]\(^+\).
6-Fluoro-2-methylbenzo[d]oxazole (2i)\textsuperscript{29}

Colorless oil; 129 mg, 86% yield; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.56 (dd, \( J = 8.6, 5.1 \) Hz, 1H), 7.22 (dd, \( J = 8.6, 2.1 \) Hz, 1H), 7.06 (td, \( J = 8.8, 2.1 \) Hz, 1H), 2.56 (s, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): δ 164.5 (d, \( J = 3.3 \) Hz), 160.4 (d, \( J = 243.0 \) Hz), 151.0 (d, \( J = 14.6 \) Hz), 137.8 (d, \( J = 1.7 \) Hz), 119.7 (d, \( J = 10.1 \) Hz), 112.0 (d, \( J = 24.6 \) Hz), 98.4 (d, \( J = 28.1 \) Hz), 14.6; \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}): δ -116.48; MS (ESI): \textit{m/z} 152.04 [M+H]\textsuperscript{+}.

6-Chloro-2-methylbenzo[d]oxazole (2j)\textsuperscript{31}

White solid; mp 42-43 °C; 143 mg, 86% yield; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.53 (d, \( J = 8.5 \) Hz, 1H), 7.48-7.45 (m, 1H), 7.28-7.24 (m, 1H), 2.61 (s, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): δ 164.7, 151.3, 140.4, 130.3, 124.9, 120.1, 111.1, 14.7; MS (ESI): \textit{m/z} 168.15 [M+H]\textsuperscript{+}.

6-Bromo-2-methylbenzo[d]oxazole (2k)\textsuperscript{32}

White solid; mp 47-48 °C; 180 mg, 85% yield; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.64-7.57 (m, 1H), 7.47 (d, \( J = 8.4 \) Hz, 1H), 7.42-7.36 (m, 1H), 2.60 (s, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): δ 164.5, 151.6, 140.8, 127.6, 120.5, 117.5, 113.9, 14.6; MS (ESI): \textit{m/z} 212.05 [M+H]\textsuperscript{+}.

2-Ethylbenzo[d]oxazole (2l)\textsuperscript{30}

Brown oil; 128 mg, 87% yield; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.66 (dd, \( J = 6.3, 2.8 \) Hz, 1H), 7.47 (dd, \( J = 6.3, 3.0 \) Hz, 2H), 7.31-7.27 (m, 1H), 2.96 (q, \( J = 7.6 \) Hz, 2H), 1.45 (t, \( J = 7.6 \) Hz, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): δ 168.2, 150.9, 141.5, 124.5, 124.1, 119.6, 110.3, 22.2, 11.0; MS (ESI): \textit{m/z} 148.00 [M+H]\textsuperscript{+}.

5-Chloro-2-propylbenzo[d]oxazole (2m)\textsuperscript{33}

Colorless oil; 166 mg, 85% yield; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.63-7.62 (m, 1H), 7.38-7.35 (m, 1H), 7.26-7.22 (m, 1H), 2.89 (t, \( J = 8.2 \) Hz, 2H), 1.90 (q, \( J = 7.4 \) Hz, 2H), 1.03 (t, \( J = 7.4 \) Hz, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): δ 168.8, 149.5, 142.6, 129.6, 124.8, 119.7, 111.1, 30.6, 20.3, 13.8; MS (ESI): \textit{m/z} 196.06 [M+H]\textsuperscript{+}.

2-Phenylbenzo[d]oxazole (2n)\textsuperscript{29}

White solid; mp 102-103 °C; 172 mg, 88% yield; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 8.27 (dd, \( J = 6.7, 3.0 \) Hz, 2H), 7.79 (dd, \( J = 6.3, 2.8 \) Hz, 1H), 7.58 (dd, \( J = 6.3, 3.0 \) Hz, 1H), 7.52 (dd, \( J = 5.1, 1.5 \) Hz, 3H), 7.37-7.33 (m, 2H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): δ 163.1, 150.9, 142.2, 131.6, 129.0, 127.7, 127.3, 125.2, 124.7, 120.1, 110.7; MS (ESI): \textit{m/z} 196.11 [M+H]\textsuperscript{+}. 
6-Methoxy-2-phenylbenzo[d]oxazole (2o)\textsuperscript{29}
White solid; mp 82-84 °C; 202 mg, 90% yield; \( ^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 8.24-8.15 (m, 2H), 7.63 (d, \( J = 8.7 \) Hz, 1H), 7.48 (s, 3H), 7.09 (s, 1H), 6.94 (d, \( J = 8.7 \) Hz, 1H), 3.85 (s, 3H); \( ^{13}\)C NMR (101 MHz, CDCl\textsubscript{3}): \( \delta \) 162.3, 158.4, 151.7, 136.0, 131.0, 128.0, 127.4, 127.3, 120.1, 112.9, 95.5, 56.0; MS (ESI): \( m/z \) 226.11 [M+H]\textsuperscript{+}.

5-Chloro-2-(2-chlorophenyl)benzo[d]oxazole (2p)
White solid; mp 102-105 °C; 242 mg, 92% yield; \( ^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 8.12 (d, \( J = 7.6 \) Hz, 1H), 7.80 (s, 1H), 7.56-7.38 (m, 4H), 7.34 (d, \( J = 8.6 \) Hz, 1H); \( ^{13}\)C NMR (101 MHz, CDCl\textsubscript{3}): \( \delta \) 162.4, 149.2, 142.9, 133.7, 132.3, 132.0, 131.6, 130.3, 127.1, 126.0, 125.9, 120.5, 111.6; HRMS (ESI): calcd for C\textsubscript{13}H\textsubscript{8}Cl\textsubscript{2}NO [M+H]\textsuperscript{+} 263.9982, found 263.9977.

General Procedure for the Synthesis of Benzisoxazoles 3
BTC (0.197 g, 0.67 mmol in 5 mL of DCM) was added to a stirred solution of TPPO (0.556 g, 2 mmol in 5 mL of DCM) dropwise under an ice bath. After complete addition, the mixture was stirred for 30 min at room temperature. Then the reaction mixture was dropwise added slowly into a solution of oxime (1 mmol) and Et\textsubscript{3}N (5 mmol, 0.505 g). After the addition, the mixture was stirred at room temperature, monitored (TLC) until completion. The reaction mixture was neutralized by the aqueous solution of Na\textsubscript{2}CO\textsubscript{3}, diluted with DCM (4 \( \times \) 10 mL), washed with water (2 \( \times \) 10 mL) and brine (10 mL), dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. The combined extracts were dried and the solvent was removed in vacuo. The residue was purified by a silica gel column chromatography to afford the pure product.

3-Methylbenzo[d]isoxazole (3a)\textsuperscript{23}
Colorless oil; 116 mg, 87% yield; \( ^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 7.63 (d, \( J = 7.9 \) Hz, 1H), 7.54-7.53 (m, 2H), 7.30 (m, 1H), 2.58 (s, 3H); \( ^{13}\)C NMR (101 MHz, CDCl\textsubscript{3}): \( \delta \) 162.8, 155.0, 129.8, 123.2, 122.3, 121.2, 109.8, 10.1; MS (ESI): \( m/z \) 134.01 [M+H]\textsuperscript{+}.

3, 5-Dimethylbenzo[d]isoxazole (3b)\textsuperscript{23}
Yellow oil; 122 mg, 83% yield; \( ^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 7.42-7.38 (m, 2H), 7.34 (d, \( J = 8.5 \) Hz, 1H), 2.54 (s, 3H), 2.46 (s, 3H); \( ^{13}\)C NMR (101 MHz, CDCl\textsubscript{3}): \( \delta \) 161.5, 154.8, 132.9, 131.4, 122.5, 120.5, 109.4, 21.2, 10.2; MS (ESI): \( m/z \) 148.01 [M+H]\textsuperscript{+}.
5-Methoxy-3-methylbenzo[d]isoxazole (3c)
White solid; mp 28-29 °C; 148 mg, 91% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.41 (d, $J = 9.0$ Hz, 1H), 7.14 (dd, $J = 9.0$, 2.5 Hz, 1H), 6.94 (d, $J = 2.5$ Hz, 1H), 3.85 (s, 3H), 2.53 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 158.4, 156.3, 155.0, 122.6, 120.2, 110.6, 101.4, 56.0, 10.2; MS (ESI): $m/z$ 164.08 [M+H]$^+$. 

5-Fluoro-3-methylbenzo[d]isoxazole (3d)
White solid. mp 72-73 °C; 139 mg, 92% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.47 (dd, $J = 8.9$, 3.8 Hz, 1H), 7.29-7.22 (m, 2H), 2.54 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 159.5, 159.1 (d, $J = 241.3$ Hz), 155.3 (d, $J = 4.6$ Hz), 122.9 (d, $J = 10.2$ Hz), 118.5 (d, $J = 27.0$ Hz), 110.9 (d, $J = 9.3$ Hz), 106.1 (d, $J = 24.8$ Hz), 10.2; $^{19}$F NMR (376 MHz, CDCl$_3$): δ -120.2. MS (ESI): $m/z$ 152.07 [M+H]$^+$. 

5-Chloro-3-methylbenzo[d]isoxazole (3e)
White solid; mp 51-52 °C; 138 mg, 83% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.58-7.55 (m, 1H), 7.47-7.41 (m, 2H), 2.53 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 161.4, 154.7, 130.2, 128.9, 123.6, 120.7, 111.0, 10.1; MS (ESI): $m/z$ 167.93 [M+H]$^+$. 

5-Bromo-3-methylbenzo[d]isoxazole (3f)
White solid; mp 41-42 °C; 193 mg, 91% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.72-7.71 (m, 1H), 7.59-7.55 (m, 1H), 7.40-7.36 (m, 1H), 2.53 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 161.7, 154.5, 132.8, 124.2, 123.8, 116.0, 111.3, 10.1; MS (ESI): $m/z$ 212.03 [M+H]$^+$. 

3-Methyl-5-nitrobenzo[d]isoxazole (3g)
White solid; mp 127-128 °C; 146 mg, 82% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.59 (d, $J = 1.7$ Hz, 1H), 8.45 (dd, $J = 9.1$, 1.7 Hz, 1H), 7.64 (d, $J = 9.1$ Hz, 1H), 2.66 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 165.2, 156.3, 144.5, 125.5, 123.1, 118.6, 110.6, 10.1; MS (ESI): $m/z$ 179.10 [M+H]$^+$. 

6-Methoxy-3-methylbenzo[d]isoxazole (3h)
White solid; mp 95-96 °C; 137 mg, 84% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.43 (d, $J = 8.7$ Hz, 1H), 6.94 (d, $J = 2.0$ Hz, 1H), 6.88 (dd, $J = 8.7$, 2.0 Hz, 1H), 3.86 (s, 3H), 2.51 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 164.8, 162.2, 154.8, 121.5, 115.7, 113.9, 92.6, 55.8, 10.0; MS (ESI): $m/z$ 164.04 [M+H]$^+$. 

6-Fluoro-3-methylbenzo[d]isoxazole (3i)
White solid; mp 50-51 °C; 121 mg, 80% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.56 (dd, $J = 8.5$, 5.1 Hz, 1H), 7.22 (d, $J = 8.5$ Hz, 1H), 7.04-7.09 (m, 1H), 2.56 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 164.4 (d, $J$
6-Chloro-3-methylbenzo[d]isoxazole (3j)
White solid; mp 70-71 °C; 127 mg, 76% yield; ¹H NMR (400 MHz, CDCl₃): δ 7.52 (d, J = 8.4 Hz, 2H), 7.27 (dd, J = 8, 4, 1.6Hz, 1H), 2.55 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 163.2, 155.0, 136.5, 124.4, 121.9, 121.1, 110.4, 10.1; HRMS (ESI): calcd for C₈H₇ClNO [M+H]+ 168.0216, found 168.0211.

6-Bromo-3-methylbenzo[d]isoxazole (3k)
Off white solid; mp 42-43 °C; 157 mg, 74% yield; ¹H NMR (400 MHz, CDCl₃): δ 7.70 (d, J = 1.3 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.40 (dd, J = 8.4, 1.3 Hz, 1H), 2.55 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 163.3, 155.0, 127.0, 124.4, 122.1, 121.5, 113.4, 10.0; MS (ESI): m/z 212.35 [M+H]+.

3-Ethylbenzo[d]isoxazole (3l)
Brown oil; 129 mg, 88% yield; ¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, J = 7.9 Hz, 1H), 7.57-7.50 (m, 2H), 7.31-7.27 (m, 1H), 3.02 (q, J = 7.6 Hz, 2H), 1.45 (t, J = 7.6 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 163.0, 159.7, 129.7, 123.1, 121.6, 121.3, 110.0, 19.0, 12.2; MS (ESI): m/z 148.05 [M+H]+.

5-Chloro-3-propylbenzo[d]isoxazole (3m)
Colorless oil; 124 mg, 70% yield; ¹H NMR (400 MHz, CDCl₃): δ 7.62-7.60 (m, 1H), 7.47 (t, J = 1.1 Hz, 2H), 2.92 (t, J = 7.7 Hz, 2H), 1.86 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 161.6, 158.2, 130.2, 128.8, 123.2, 120.8, 111.1, 27.2, 21.2, 14.0; HRMS (ESI): calcd for C₁₀H₁₁ClNO [M+H]+ 196.0512, found 196.0500.

3-Phenylbenzo[d]isoxazole (3n)
Yellow oil; 137 mg, 70% yield; ¹H NMR (400 MHz, CDCl₃): δ 7.98 (dd, J = 7.5, 1.9 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.63-7.54 (m, 4H), 7.39 (t, J = 7.5 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 164.0, 157.4, 130.4, 129.9, 129.3, 129.1, 128.2, 124.0, 122.4, 120.7, 110.3; MS (ESI): m/z 196.12 [M+H]+.

6-Methoxy-3-phenylbenzo[d]isoxazole (3o)
White solid; mp 82-83 °C; 147 mg, 65% yield; ¹H NMR (400 MHz, CDCl₃): δ 7.94 (d, J = 5.9 Hz, 2H), 7.75 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 6.5 Hz, 3H), 7.06 (s, 1H), 6.98 (d, J = 7.8 Hz, 1H), 3.91 (s, 3H); ¹³C
NMR (101 MHz, CDCl₃): δ 165.9, 162.2, 157.1, 130.3, 129.2, 129.1, 128.1, 122.5, 114.9, 114.0, 92.9, 55.9; MS (ESI): m/z 226.19 [M+H]+.

5-Chloro-3-(2-chlorophenyl)benzo[d]isoxazole (3p)²³
White solid; mp 102-103 °C; 219 mg, 83% yield; ¹H NMR (400 MHz, CDCl₃): δ 7.64-7.62 (m, 1H), 7.62-7.55 (m, 4H), 7.50 (dd, J = 7.9, 1.9 Hz, 1H), 7.44 (td, J = 7.5, 1.3 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ 162.0, 156.6, 133.6, 132.0, 131.7, 130.6, 130.5, 129.5, 127.3, 122.8, 122.3, 111.3; MS (ESI): m/z 264.04 [M+H]+.

General Procedure for the Control Experiment Condition A
A solution of BTC (0.148 g, 0.5 mmol) in 5 mL DCM was added to a stirred solution of TPPO (0.417 g, 1.5 mmol) in 5 mL DCM dropwise under ice bath. After addition completed, the mixture was stirred for 30 min at room temperature. Then the ethyl phenyl ketoxime (1 mmol) in 5 mL DCM was added dropwise into the solution. After the addition, the mixture was stirred at room temperature, monitored by TLC until the reaction completed. The reaction mixture was neutralized by the aqueous solution of Na₂CO₃, diluted with DCM (4 × 10 mL), washed with water (2 × 10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄. The combined extracts were dried and the solvent was removed in vacuo. The residue was purified by column chromatography to afford the pure product which was identified as acetanilide in a yield of 80%.

General Procedure for the Control Experiment Condition B
BTC (0.197 g, 0.67 mmol in 5 mL of DCM) was added to a stirred solution of TPPO (0.556 g, 2 mmol in 5 mL of DCM) dropwise under an ice bath. After complete addition, the mixture was stirred for 30 min at room temperature. Then the reaction mixture was dropwise added slowly into a solution of ethyl phenyl ketoxime (1 mmol) and Et₃N (5 mmol, 0.505 g). After the addition, the mixture was stirred at room temperature, monitored (TLC) until completion. The reaction mixture was neutralized by the aqueous solution of Na₂CO₃, diluted with DCM (4 × 10 mL), washed with water (2 × 10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄. The combined extracts were dried and the solvent was removed in vacuo. The residue was purified by a silica gel column chromatography to afford the pure product which was identified as acetanilide in a yield of 10%.

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REFERENCES