Unexpected TFA-catalyzed tandem reaction of benzo[d]oxazoles with 2-oxo-2-arylacetic acids: synthesis of 3-aryl-2H-benzo[b][1,4]oxazin-2-ones and cephalandole A

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A convenient and efficient method for the TFA-catalyzed synthesis of 3-aryl-2H-benzo[b][1,4]oxazin-2-ones via a tandem reaction of benzo[d]oxazoles with 2-oxo-2-arylacetic acids was reported for the first time. The efficiency of this transformation was demonstrated by compatibility with a wide range of functional groups. The synthetic utility of this method was confirmed by the synthesis of the natural product cephalandole A. Moreover, a plausible mechanism for the formation of 3-aryl-2H-benzo[b][1,4]oxazin-2-ones involving ring-opening and cyclization steps is proposed. The present synthetic route to 3-aryl-2H-benzo[b][1,4]oxazin-2-ones could be readily scaled up to gram quantity without difficulty.

1,4-Benzoxazines,1 as an important class of heterocycles, have become increasingly important because they have been associated with a wide range of pharmacological and biological activities.2 Among them, 2H-benzo[b][1,4]oxazin-2-one scaffolds have been studied intensively in the past few years because they are synthetic building blocks,3 present in a wide variety of bioactive molecules, as well as photoactive molecules4 which possess fluorescent,5 photophysical and photochemical properties.6 In 2006, the 2H-benzo[b][1,4]oxazin-2-one-based natural product cephalandole A was originally isolated from the Taiwanese orchid Cephalancropsis gracilis (Orchidaceae),7 which had previously been misassigned, and later corrected by Bergman8 and Gross9 (Fig. 1).

The importance of 2H-benzo[b][1,4]oxazin-2-ones has resulted in the development of different synthetic strategies for their preparation. In general, 2H-benzo[b][1,4]oxazin-2-ones are synthesized by the treatment of o-aminophenols with α-ketoesters.10 Nicolaides and co-workers11 reported 3-aryl-2H-benzo[b][1,4]oxazin-2-ones could be obtained by the condensation of O-methyl-o-quinonemonomoximes with arylacetates. In 2006, Yavari and co-workers12 reported that vinylphosphonium salt mediated reaction between o-aminophenols and alkyl propiolic acid leading to the synthesis of 3-aryl-2H-benzo[b][1,4]oxazin-2-ones. In 2008, Kikelj and co-workers13 developed the synthesis of 4-benzyl- and 4-alkyl-3,4-dihydro-1,4-benzoazoxin-2-one derivatives from ethyl 2-(2-hydroxyphenylamino)acetate and aldehydes. Recently, Ballini and co-workers14 reported the preparation of 1,4-benzoazoxin-2-one derivatives via a domino reaction of o-aminophenols with ethyl β-nitroacrylates. As part of the continuing efforts in our laboratory towards the development of new methods for the synthesis of nitrogen-containing heterocycles,15 we herein reported an unexpected TFA-catalyzed tandem reaction of benzo[d]oxazoles with 2-oxo-2-arylacetic acids to access 2H-benzo[b][1,4]oxazin-2-ones under mild conditions (Scheme 1).

Our preliminary studies focused on the model reaction between 2-benzox[d]oxazole (1a) and 2-oxo-2-phenylacetic acid (2a) to obtain 2-phenylbenzo[d]oxazole (4a) via cascade reaction of decarboxylation, decarbonylation and coupling reaction (Scheme 2). Through the screening process, little-to-no target product 4a was detected using silver salts and palladium salts as catalysts with a variety of parameters. To our surprise, a trace amount of unexpected 3-phenyl-2H-benzo[b][1,4]oxazin-2-one (3a) was observed by gas chromatography/mass spectrometry (electron ionization) [GCMS (EI)] analysis using trifluoroacetic acid (TFA) as the Brønsted acid in toluene (Table 1, entry 1). We were
delighted to find that the yield of 3a could be improved to 45% under an air atmosphere after solvent was changed to acetonitrile (Table 1, entry 2). This finding inspired us to examine optimal reaction conditions for the synthesis of 3a in order to obtain more satisfactory results.

Scheme 2 Reaction of 2-benzo[d]oxazole with 2-oxo-2-phenylacetic acid.

Considering solvents always played important roles in organic reactions, we first examined the solvent effect and found that isopropanol was superior to DMSO, DMF, 1,2-dichloroethane, dioxane, CH₃CN, toluene, THF, and EtOH (Table 1, entries 1-9). We also studied influence of the amount of TFA on the reaction yields. The results showed that 0.2 equivalents of TFA was sufficient, and excessive amount of catalyst did not increase the yield (Table 1, entries 9-13). Then various Brønsted acids were screened to examine their effect on the reaction. Replacement of TFA with other acids, including AcOH, PhCO₂H, p-NO₂PhCO₂H, CF₃SO₃H, p-MePhSO₃H, and p-NO₂PhSO₃H, resulted in lower yields (Table 1, entries 14-19). The yield was decreased to some extent when the reaction was carried out at the lowered or elevated temperature (Table 1, entries 20-21). Therefore, the optimal reaction condition was to use 0.2 equiv of TFA in isopropanol at 70 °C under air. As a result, the model reaction was carried out under optimized conditions with 0.2 equiv of TFA in isopropanol at 70 °C under air, which led to 3a in 94% yield (Table 1, entry 12).

Table 1 Screening for optimal reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Equiv (x)</th>
<th>Solvent</th>
<th>Yield (%) b</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA</td>
<td>1.0</td>
<td>toluene</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>1.0</td>
<td>CH₃CN</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>TFA</td>
<td>1.0</td>
<td>DMF</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>TFA</td>
<td>1.0</td>
<td>dichloroethane</td>
<td>trace</td>
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<td>5</td>
<td>TFA</td>
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<td>dioxane</td>
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<td>THF</td>
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<tr>
<td>10</td>
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<td>0.3</td>
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<td>11</td>
<td>TFA</td>
<td>0.2</td>
<td>PrOH</td>
<td>94</td>
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</table>

b Reaction conditions: 1a (0.2 mmol), 2a (0.3 mmol), TFA (x mmol), PrOH (2 mL), air, 70 °C, 18 h. b Isolated yield. b At 60 °C. b At 80 °C.

With the optimized reaction conditions in hand, we next explored the scope and generality of the reaction using various 2-benzo[d]oxazoles with 2-oxo-2-arylacetic acids (Table 2). First, the reaction between benzo[d]oxazole (1a) and various 2-oxo-2-arylacetic acids (2a-2k) was investigated under the standard reaction conditions. The electronic properties of the substituents on the phenyl ring of the 2-oxo-2-arylacetic acids had an obvious impact on the yield of the reaction. The 2-oxo-2-arylacetic acids bearing an electron-withdrawing substituent (e.g., –F, –Cl, –Br, –I, –CN, and –NO₂) produced higher yields of products than those analogues bearing an electron-donating substituent (e.g., –Me, and –OMe) (Table 2, entries 2-9). Substrate 2-(naphthalene-
2-(yl)-2-oxoacetic acid (2) reacted with 1a to give the desired product 3j in 88% yield (Table 2, entry 10), but a lower yield was observed when substrate 2-(furann-2-yl)-2-oxoacetic acid (2k) bearing a heteroaril group was used as a substrate (Table 2, entry 11).

Table 3 Reaction of different benzo[d]oxazoles with 2-oxo-2-phenylacetic acid

To demonstrate the synthetic utility of this method, it was applied to the synthesis of the natural product cephalandole A (Scheme 4). TFA-catalyzed tandem reaction of benzo[d]oxazoles (1a) with 2-(1H-indol-3-yl)-2-oxoacetic acid (2m) afforded the desired natural product cephalandole A in 86% yield through single-step operation under the standard reaction conditions.

Scheme 4. Applications in the synthesis of the natural product.

To elucidate the mechanism, some control experiments were carried out under the standard reaction conditions as shown in Scheme 5. If only benzo[d]oxazole (1a) was applied under the standard reaction conditions, α-aminophenol (4) was isolated in 67% yield (Scheme 5a). However, no reaction happened and almost 90% of reactant 2a was recovered when only 2-oxo-2-phenylacetic acid (2a) was applied under the standard reaction conditions (Scheme 5b). Under the standard reaction conditions, when α-aminophenol reacted with 2a, afforded the desired product 3a in 89% yield (Scheme 5c), suggesting that α-aminophenol is a key intermediate. This result revealed that a ring-opening pathway was taken in the reaction.

Scheme 5. Control experiments.

On the basis of the above experimental results, we proposed a possible reaction pathway for the formation of 3-aryl-2H-benzo[b][1,4]oxazin-2-ones. The first step may involve the ring-opening of benzo[d]oxazoles leading to α-aminophenol. Then cyclization reaction of α-aminophenol with 2-oxo-2-arylacetic acid in the presence of TFA delivers the corresponding 3-aryl-2H-benzo[b][1,4]oxazin-2-ones as the products.

Finally, it is noteworthy that the present synthetic route to 3-aryl-2H-benzo[b][1,4]oxazin-2-ones could be readily scaled up to gram quantity without difficulty. For instance, the reaction at the 20 mmol scale afforded the corresponding product 3-phenyl-2H-benzo[b][1,4]oxazin-2-one (3a) in 87% yield (Scheme 6).


In summary, we have developed a new strategy for constructing 3-aryl-2H-benzo[b][1,4]oxazin-2-ones from TFA-catalyzed tandem reaction of benzo[d]oxazoles with 2-oxo-2-
arylacetic acids. In addition, the method provides an efficient access to the natural product cephalandole A. Further efforts to extend this catalytic system to the preparation of other useful nitrogen-containing heterocycles are currently underway in our laboratories. Financial support was provided by the National Natural Science Foundation of China (Nos. 21272176 and 21102105) and Natural Science Foundation of Zhejiang Province (No. LY12B02011).

Notes and references


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highlighting the novelty of the work:


Colour graphic: