Regioselective Annulation of Aryl Sulfonamides with Allenes through Cobalt-Promoted C−H Functionalization

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Supporting Information

ABSTRACT: The development of an efficient method for the construction of biologically relevant sultams is described, which represents the first case of cobalt-promoted C−H/N−H functionalization of sulfonamides with allenes. This newly developed annulation reaction demonstrated good functional group tolerance and excellent regioselectivity. Both terminal monosubstituted allenes and internal disubstituted allenes can be employed to give the desired sultams in good yields. This strategy can be successfully used to build a unique sultam library with novel structural diversity.

Cyclic sulfonamides (sultams) are an important class of chemicals that serve as structural motifs in different drugs and bioactive compounds (Figure 1).1 For example, the attractive

Figure 1. Drugs containing sultam motifs.

biological activities of sultams have been found in a wide range of fields including anti-inflammatory,2 antibacterial,3 anti-HIV,4 and antimalarial,5 etc.6 Because of its significance in pharmaceutical development, a number of strategies have been developed for the synthesis of sultams.7 However, most of the reported methods rely on intramolecular cyclization of elaborate precursors or intermolecular reactions starting from prefunctionalized starting materials. These methods usually suffer from multistep synthesis of precursors, tedious procedures, and low yields. Thus, further development of new, efficient, and general methods toward the synthesis of cyclic sulfonamides using readily available precursors is quite appealing.

In recent years, transition-metal-catalyzed annulation reactions through C−H bond functionalization have gradually emerged as a powerful tool for the synthesis of various heterocyclic compounds.8 The straightforward synthesis of sultam scaffolds from simple starting materials through C−H functionalization reactions would be very attractive. To date, several annulation reactions generating sultams through transition-metal-catalyzed ortho C−H activation of aryl sulfonamides with alkynes and allenes have been developed.9 For example, in 2012, the Cramer group reported the synthesis of sultam scaffolds through Rh-catalyzed C−H functionalization of acylated aryl sulfonamides with alkynes. In 2014, Li and co-workers9b described the synthesis of five-membered sultams via Rh-catalyzed annulation reaction between acylated aryl sulfonamides and alkenes. More recently, the groups of Ribas9c and Sundararaju9d independently introduced the annulation reactions of aryl sulfonamides with alkynes through cobalt10,11c catalysis. It should be noted that these methods generally employ alkynes and allenes as coupling partners. In contrast, the practice of using allenes as annulation partners in C−H functionalization is still rare.12 Different from alkynes and alkynes, the complexity of two orthogonal carbon−carbon double bonds of allenes can provide chances to access structurally unique products.

Because of the special reactivity of the 1,2-diene functionality, allenes have demonstrated great potential in organic chemistry.13 In particular, the carbometalation reaction of allenes recently is one of the most interesting research field and has exhibited high potential for the preparation of novel and diverse scaffolds.14 However, to the best of our knowledge, there are no reported examples of cobalt-promoted C(sp3)−H functionalization of sulfonamides with allenes. We envisioned that the cobalt-promoted ortho C(sp3)−H activation of sulfonamides might undergo an annulation reaction with allenes to produce corresponding sultams. Herein, we report the first example of regioselective sultam synthesis through cobalt-promoted C−H/N−H annulation of aryl sulfonamides with allenes (Scheme 1).

Initially, we began our investigations by screening different cobalt reagents in the reaction system, which consists of sulfonamide 1a, allene partner 2a, Mn(OAc)2, KOAc, and 

Received: November 23, 2016
Published: February 23, 2017
trifluoroethanol (TFE) under air at 100 °C for 16 h. We found that Co(OAc)2·4H2O was the optimal promoter among the four cobalt sources tested (Table 1, entries 1−5). When Co(OAc)2·4H2O was used, the desired sultam product 3a was observed in 13% NMR yield (entry 5; for the X-ray crystal structure, see the Supporting Information). Changing the oxidant from Mn(OAc)2 to Mn(OAc)3·2H2O resulted in an improved 35% NMR yield (entry 6). To our delight, we found that O2 could promote the reaction significantly (entries 5, 7, and 12). Furthermore, a higher isolated yield (70%) can be obtained by replacing KOAc with NaOPiv·H2O (entry 10). For all of the conditions examined in Table 1, no obvious regioisomers can be observed. The control experiment showed that the omission of cobalt source resulted in the complete inactivity of the reaction (entry 14).

With the optimal conditions in hand, we next attempted to explore the substrate scope for this new reaction. A variety of substituted sulfonamides bearing 8-aminoquinoline directing groups were tested under the optimal conditions (Scheme 2). Electron-rich substrates (3a−e) could proceed smoothly to furnish the desired products in good isolated yields, whereas electron-deficient substrates (3h−k) only gave low to moderate isolated yields under the standard conditions with almost half of the starting material remaining. That may attribute to the increased difficulty of the C−H activation step caused by electron-withdrawing groups. To our satisfaction, these electron-deficient substrates could provide products in good yields when the Co(OAc)2·4H2O loading was increased from 20 to 50 mol %.

Table 1. Optimization of Cobalt-Promoted C−H Activation and Annulation with Allene

<table>
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<tr>
<th>entry</th>
<th>cobalt source</th>
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<th>base</th>
<th>yield of 3a (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Co(acac)2</td>
<td>Mn(OAc)2</td>
<td>KOAc</td>
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<td>KOAc</td>
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<td>CoF3</td>
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<td>KOAc</td>
<td>&lt;5</td>
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<td>Mn(OAc)2</td>
<td>KOAc</td>
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<td>Mn(OAc)3</td>
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<td>Mn(OAc)3</td>
<td>KOAc</td>
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</tr>
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<td>9</td>
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<td>69</td>
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*Reaction conditions: aryI sulfonamide (0.1 mmol), 2a (3.0 equiv), Co(OAc)2·4H2O (20−50 mol %; in some cases Co(NO3)2·6H2O was used instead of Co(OAc)2·4H2O), Mn(OAc)3·2H2O (2.0 equiv), NaOPiv·H2O (2.0 equiv), 1.5 mL of TFE, 100 °C, O2.

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desired sultam (3l), which could be regarded as an analogue of brinzolamide. It is worth noting that in our case the 2-pyrolesulfonamide substrate is well tolerated, even though the substrate contains the free N–H group.

Utilizing this annulation reaction, we then turned our attention to explore the scope and reactivity pattern of the allene partners. As shown in Scheme 3, both electron-poor and electron-rich allenes (2b–g) were examined in the reaction system. It was found that the electrochemical properties of the allenes do not change the fashion of the annulation reaction. The new C–C bond formed preferentially between the ortho carbon of the aryl sulfonamides and the less hindered terminal carbon of the allenes. Under these conditions, all tested allenes could be regioselectively incorporated to generate the desired sultams in good isolated yields. For the internal disubstituted allene 2b, the small steric hindrance difference between the methyl group and the ester group can be accurately recognized. It was interesting that when 2e was used as the allene partner, 1,3-diene derivatives 4ae–je formed as the final products. When 2g was used as the allene partner, partial elimination led to a mixture of product (4ag and 4ag′) in a ratio of 3:1. This sequential reaction enriches the diversity of products derived from the annulation reaction. Satisfyingly, the nine-membered cyclic allene 2f is also compatible with the reaction system to furnish the three-ring-fused heterocycle products 4af–lf, which are difficult to obtain through known methods of sultam synthesis. This new reaction demonstrates excellent regioselectivity. Compared with rhodium- or cobalt-catalyzed annulation of aryl sulfonamides with alkenes, which may provide two regioisomers with terminal aliphatic alkenes, only one regioisomer can be observed from this reaction in all cases. It should be mentioned that all of the alkenes used can be easily accessed on large scale through inexpensive and simple starting materials in one or two steps, except 2e, which takes three steps for preparation. To further evaluate the practical utility of this new reaction, a larger scale reaction was performed by using 1a (2 mmol, 600 mg) and allene partner 2h, which gave 4ah in 70.5% yield (see Scheme 4).

As illustrated in Scheme 5, a plausible reaction mechanism was proposed. The first step involves the oxidation of Co(II) to give Co(III) by Mn(OAc)3. Next, chelation of Co(III) to the quinoline directing group and subsequent C–H functionalization12g,15 and cobalt-catalyzed alkyne annulation14f,16 in which vinylmetal intermediates were proposed, the next step might be the insertion of the less hindered double bond of the allene into the carbon–cobalt bond to form intermediate C in this case. Following this step, the reductive elimination of intermediate C gives Co(I) and intermediate D. Intermediate D could be isolated and identified (for details, see Supporting Information). Finally, intermediate D undergoes 1,3-H shift to provide the desired product 3a.17 The Co(I) can be further oxidized to Co(III) for the next turnover. O2 is likely to play a role as the terminal oxidant in the entire process. In conclusion, we have established a new, effective method for the construction of biologically relevant sultam scaffolds that represents the first example of cobalt-promoted C–H/N–H functionalization of aryl sulfonamides with allenes. A broad range of aryl sulfonamides can be exploited to react with both terminal monosubstituted allenes and internal disubstituted allenes to give the desired sultams in good yields with excellent regioselectivity.
有机化合物在不同条件下表现出不同的表征。例如，在酸性条件下，化合物（1）的光谱表现出特征吸收，而碱性条件下则没有。此外，化合物（2）在不同温度下表现出显著的热稳定性。这些结果为后续的结构研究提供了重要的信息。

**REFERENCES**


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T.L. and L.W. contributed equally.

**Notes**

The authors declare no competing financial interest.

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