Communications

Iodine-Mediated Regioselective C–N and C–I Bonds Formation of Alkenes

Kai Sun, Fengji Ma, Lulu Liu, Jingjing Sun, Xin Liu, Yachao Wang, Zhiguo Zhang* and Guisheng Zhang*†

Iodine-mediated intermolecular C–N and C–I bonds formation of alkenes is described. A series of alkenes could be selectively converted into the corresponding aminioiodination products, which are versatile building blocks in organic synthesis and medicinal chemistry. Wide substrates scope, broad functional groups tolerance and easy scale-up operation make this protocol very practical and attractive in synthetic chemistry.

Alkenes are simple and abundant bulk commodities in organic synthesis, and derivatization of such feedstock materials is thus of great importance. The vicinal difunctionalization of alkenes is a class of significant reactions to rapidly increase molecular complexity with various functional groups. Particularly, the catalytic aminative difunctionalization is highly attractive from the synthetic point of view owing to the remarkable biological activities of the introduced nitrogen atom. In the past decade, transition metal catalyzed dianimation, aminooxygenation, aminoboration and amino-halogenation have been elegantly demonstrated. Organic molecules containing vicinal halogen and amine functional groups have been found not only a basic scaffold of numerous pharmaceutically important molecules and synthetically fine chemicals, but also an important precursor in the synthesis of various useful bioactive molecules. Despite the significances achieved in the amino-halogenation, some challenging issues still exist: (1) A major drawback is the inevitable residual metal in the final products, which greatly restricts their application in pharmaceutical chemistry. (2) Currently, catalytic amino-halogenation dominantly focused on the relatively active alkenes such as styrenes, as well as the less unactivated chain alkenes and sterically hindered internal alkenes (cyclic alkenes) are usually hard to undergo the difunctionalization. (3) The nitrogen sources have been limited to sulfonamides, amidines and carbamates so far, other heterocyclic nitrogen source, such as azoles are rarely used. In terms of green and sustainable chemistry, replacement of these metal catalysts, development of efficient aminative difunctionalization approach with broad substrate scope and functional group tolerance represents a significant fundamental challenge.

Inspired and pioneered by hypervalent iodine chemistry, various bond-formation methods utilizing iodide-catalyzed or mediated coupling reactions have been revealed, including iodide-catalyzed or mediated difunctionalization of alkenes. Aminioiodination of alkenes is an important transformation that most works have focused on intramolecular fashion, while intermolecular aminioiodination of alkenes has rarely been exploited. In connection to our continued interest in C–X (X = C, N, S, I) bond formation reaction, we now disclose an iodine-mediated intermolecular aminioiodination reaction of alkenes by using biological azoles as nitrogen source. In addition, the extension of this method to a gram-scale experiment was also smoothly demonstrated.

At the outset of our studies, styrene (1a) and 1H-benzotriazole (2a) were chosen as the model substrates to optimize the reaction conditions under air. Initially, the reaction was carried out in the presence of I$_2$ (1 equiv) and TBHP (tert-butyl hydroperoxide) (2 equiv) in EtOAc (2mL) at room temperature and afforded a 68% isolated yield of 3a (Table 1, entry 1). Other iodine source, such as KI and nBu$_4$NI were tested, but all of them completely did not work (Table 1, entries 2–3). At this stage, we supposed that I$_2$ might be an active intermediate and the real iodine source. Therefore, IBr was introduced to this system without the addition of TBHP, and to our delight, aminiodination product 3a was isolated in 61% yield (Table 1, entry 4). A slight yield improvement was obtained using I$_2$ instead of IBr (Table 1, entry 5). Moreover, a variety of solvents were subsequently tested (Table 1, entries 6–12). DCE was proved to be the best solvent and gave the desired product 3a in 89% yield (Table 1, entry 10). THF and CH$_2$CN were also good choice for this reaction and afforded 3a in 78% and 71% yields, respectively. Other solvents such as H$_2$O and DMSO were all ineffective and no 3a was detected (Table 1, entries 6 and 7). While an acceptable yield (56%)}
Table 1: Screening of Reaction Conditions. *

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iodine source</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂</td>
<td>TBHP</td>
<td>EtOAc</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>KI</td>
<td>TBHP</td>
<td>EtOAc</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>nBuNI</td>
<td>TBHP</td>
<td>EtOAc</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>IBr</td>
<td>no</td>
<td>EtOAc</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>I₂</td>
<td>no</td>
<td>H₂O</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>I₂</td>
<td>no</td>
<td>DMSO</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>I₂</td>
<td>no</td>
<td>THF</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>I₂</td>
<td>no</td>
<td>CH₃CN</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>I₂</td>
<td>no</td>
<td>DCE</td>
<td>89</td>
</tr>
<tr>
<td>10</td>
<td>I₂</td>
<td>no</td>
<td>DCE</td>
<td>43</td>
</tr>
<tr>
<td>11</td>
<td>I₂</td>
<td>no</td>
<td>EtOH</td>
<td>56</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a (0.5 mmol), 2a (1.0 mmol), iodine source (0.5 mmol) and solvent (2.0 mL) at 20 °C for 6 h. * Yield of isolated product. * Reaction was performed at 40 °C.

of 3a was obtained using EtOH as the solvent. After optimization of the reaction conditions, we established a highly efficient route for the aminiodination of styrene (Table 1, entry 10).

With the optimum conditions in hand, we next explored the scope of terminal styrenes under air at room temperature. The results were summarized in Scheme 1. As expected, various substituents on the benzene ring of styrene were well tolerated, electron-donating groups (Me, MeO and t-Bu) and electron-withdrawing groups (F, Cl and Br) were all furnished the transformation and gave the aminiodination products in high efficiencies (Scheme 1). Some of these functional groups are useful for further synthetic diversification. Styrene with substitutes on different position, such as 1-chloro-2-vinylbenzene 1b, 1-methyl-3-vinylbenzene 1c and 1-methyl-4-vinylbenzene 1d, could also produced the desired products in high yields (92-96%). It is noteworthy that during this aminative difunctionalization, besides 2a, other biological azoles, imidazole 2b, 5-phenyltetrazole 2c and 1H-benzod[de]1,2,3-triazol-4-ol 2d can offered the corresponding products 3j, 3k and 3l in 82%, 85% and 69% yields, respectively.

Furthermore, the unactivated alkenes which were of chemical inertness in previously reported olefin difunctionalizations, performed well under the standard conditions (Scheme 1). Cyclopentene 1m, cyclohexene 1n, and cyclooctene 1o delivered the products 3m, 3n and 3o from 82% to 93% yields. 2,5-Dihydrofuran 1p was also compatible with this system and offered the

Table 2: Scope of Alkenes. *, *

<table>
<thead>
<tr>
<th>R</th>
<th>X, Y = C or N</th>
<th>I₂</th>
<th>DCE, 6 h, rt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Reaction conditions: 1 (0.5 mmol), 2 (1.0 mmol), I₂ (0.5 mmol), and DCE (2 mL) at 20 °C for 6 h. * Yield of isolated product.
were obtained in 82% and 83% yields, respectively. When methyl acrylate was tested as substrates, products 3s and 3t were obtained in 82% and 83% yields, respectively.

According to the aforementioned information and based on previous reports, a proposed mechanism for this I$_2$-mediated difunctionalization of alkenes is outlined in Scheme 1. Initially, the substrate alkene reacts with I$_2$ to afford the iodonium ion intermediate 1, which undergoes regioselective ring opening with azoles giving the the desired iodo products 3. The iodiode ion is then reoxidized with TBHP to regenerate I$_2$ for the next catalytic cycle.

Scheme 1: Proposed reaction mechanism.

In order to prove the practicality of this approach, a gram-scale aminooiodination experiment using styrene 1a as the substrate was performed under the optimized conditions. After 6 hours later, the desired product 3a can be isolated in 79% yield, which suggests that it can be potentially applied in chemical industry (equiv 1). In addition, further conversion from the C–I bond to C–O, C–N and C–S bond was also easily carried out (equiv 2, equiv 3 and equiv 4).

Conclusions

In summary, we have developed an efficient iodine mediated intermolecular aminooiodination of alkenes under mild reaction conditions. This protocol provides a valuable synthetic tool for simultaneously introduction biological azoles and iodine to a wide range of alkenes, which are expected to be useful intermediates for the preparation of pharmaceutically and biologically active compounds as well as functional materials. Easy scale-up operation make this protocol very practical and attractive in synthetic chemistry.

Acknowledgements

Financial support from the China Postdoctoral Science Foundation funded project (2015M572110) and Science and Technology Plan Projects of Henan Province (15A150030) is greatly acknowledged.

Notes and references

An efficient iodine mediated intermolecular C–N and C–I bonds formation of alkenes was realized under mild reaction conditions. A series of alkenes could be selectively converted into the corresponding aminoiiodination products, which are versatile building blocks in organic synthesis and medicinal chemistry.