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Metal-free aminoamidiniumation employing N-iodosuccinimide: facile syntheses of bicyclic imidazolidininiums and cyclic vicinal diamines

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NIS-mediated aminoamidiniumation have been developed for the syntheses of bicyclic imidazolidinium salts, which could be readily converted into cyclic vicinal diamines.

Vicinal diamines have attracted much attention for their occurrence in a variety of bioactive molecules and natural products, and for their use as building blocks in organic transformation, and chiral ligands for stereoselective synthesis. For example, chiral cyclic vicinal diamines A are well-known efficient chiral catalytic source for the enantioselective borane reduction of prochiral ketones (Figure 1). Imidazolidin-2-ylidene carbene are among the most important vicinal diamine derivatives due to their widespread and spectacular applications as organocatalysts and as ligands for organometallic catalysis. Elaborately tuning the structural parameters of N-heterocyclic carbene (NHC) scaffold could directly and precisely influence their catalytic performance. Recently, several types of NHCs having a fused ring in their scaffolds, such as B, C, and D, have been developed for organocatalysts and as ligands for organometallic catalysis. The fused ring could twist the framework, and hamper rotation of the N-substituent, thereby rendering decomposition pathway unfavorable, increasing the stability of catalysts, and/or create a tunable chiral environment.

Direct difunctionalization of alkenes is clearly an attractive route to generate vicinal diamines, and, since 2005, much resurgent attention have been paid to the development of efficient catalytic procedures for Pd(II), Cu(II), Au(I), and Ni(II)-mediated intramolecular diamination of alkenes.

**Figure 1.** Selected cyclic vicinal diamines and NHC carbenes

Metal-free systems, such as IPy2BF4 (Py = pyridine), N-iodosuccinimide (NIS), KBr/NaClO3, ArI(OAc)2 (or PhI=O)/acid, and PhI(OAc)2/halide reagent systems have been also established for this process to circumvent the toxicity and cost issue associated with metal catalysts. Recently, we have developed several synthetic strategies for the facile preparation of various NHC carbene precursor azolium salts starting from formamidines. Unsymmetric formamidines could be prepared readily from one pot condensation reaction of two primary amines and orthoformate [eqn (1)]. Therefore, we envisioned that the N,N-disubstituted amidines could be used as efficient nitrogen sources. Herein, we report an NIS-mediated aminoamidiniumation of amidines for the synthesis of bicyclic imidazolidinium salts [eqn (2)], which could be readily converted into corresponding cyclic vicinal diamines A, including a chiral vicinal diamine (Figure 1).

Bromine and Iodine reagents are often used to activate and oxidize alkenes through the formation of halonium ions. We started our investigation with reacting halogen reagents with formamide 1a, which was synthesized through one pot condensation reaction of 2,4,6-trimethylaniline, allylamidine, and triethylorthoformate in 49 % yield. NIS (1 equiv) was proven to be efficient to promote this process to bicyclic imidazolidinium salts 2a, while NCS and NBS led to disappointing results (entries 1–3, Table 1).iodine showed less reactive towards the process than NIS (entries 4, Table 1).

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† Electronic Supplementary Information (ESI) available: Experimental and spectroscopic data for all compounds. CCDC 1017139 (2a), CCDC 1017140 (2c), CCDC 1016877 (2i), CCDC 1017141 (2b), and CCDC 1017397 ((S)-S)-S). For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/b000000x/
Lower yields were obtained when using CH₂Cl₂ and THF as solvents (entries 5 and 6, Table 1). Increasing either reaction temperature or the amount of NIS led to lower yields (entries 7–9, Table 1), and addition of NaHCO₃ as base disfavoured the formation of 2a (entry 10, Table 1).

Table 1. Intramolecular amidiniumation of formamidine 1a[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>Solvent</th>
<th>Additive</th>
<th>Yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NCS (1.0)</td>
<td>toluene</td>
<td>-</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>NBS (1.0)</td>
<td>toluene</td>
<td>-</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>NIS (1.0)</td>
<td>toluene</td>
<td>-</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>I₂ (1.0)</td>
<td>toluene</td>
<td>-</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>NIS (1.0)</td>
<td>DCM</td>
<td>-</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>NIS (1.0)</td>
<td>THF</td>
<td>-</td>
<td>53</td>
</tr>
<tr>
<td>7</td>
<td>NIS (1.0)</td>
<td>toluene</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>NIS (1.5)</td>
<td>toluene</td>
<td>-</td>
<td>66</td>
</tr>
<tr>
<td>9</td>
<td>NIS (2.0)</td>
<td>toluene</td>
<td>-</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>NIS (1.0)</td>
<td>toluene</td>
<td>NaHCO₃</td>
<td>55</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: Solvent (0.1 M), 25 °C, 1 h. [b] Isolated yields. [c] 120 °C. Mes = mesityl.

Under optimized condition, the generality and scope of this new synthetic protocol was investigated (Chart 1). Besides aryl groups (for 2a and 2b, Chart 1), alkyl groups at nitrogen atom were also tolerated (for 2c–2e, Chart 1). Yields were generally moderate to good. Formamidines with sterically demanding aryl N-substituents, such as 2,6-diisopropylphenyl group, were also reactive under reaction condition (for 2b). Further study exhibited, besides formamidines, benzamidines were tolerated towards the process as well (for 2f–2k, Chart 1). This method allowed for cyclization of benzamidines with a variety of N-substituents, even those with sterically demanding mesityl group (for 2f, 2i, and 2k, Chart 1). Notably, N-5-hexenyl benzamidines could also be cyclized to form the 6-membered ring imidazolium salt 2k. Single crystals of 2a, 2c, and 2i suitable for X-ray diffraction analysis were obtained (Figure S1 for 2a, Figure S2 for 2c, and Figure S3 for 2i, see Supporting Information), and their structures confirm the formation of the desired imidazolium salts.

Two experiments were carried out to investigate the mechanism of the two C-N bond-forming steps. Treatment of (E)-11 with NIS offered anti-configured 2l as single diastereoisomer, indicating that the process is stereospecific regarding the double bond geometry and also proving our new methodology to be compatible with internal alkenes (Scheme 1). The X-ray crystal structure of 2l confirmed its constitution and relative anti configuration (Figure S4 for 2l, see Supporting Information). Selectively deuterated formamidines 1m was also submitted to the NIS-mediated process, and the expected cis-configured 2m were obtained (Scheme 1). Based on the amidiniumation products and the observed results of control experiments, we propose a plausible reaction mechanism (Scheme 2). Formamidine 1 reacts with NIS to afford an N-iodinated formamidine A, the N-I group of which further oxidizes the double bond of the alkene to form cyclic iodonium ion B. Intermediate B is subsequently underwent a nucleophilic backside attack of nitrogen atom to give cyclic formamidine C. It suggests that the first C-N bond formation proceeds through a trans-amino-iodination. Intermediate C undergoes an S₅₋₂ amidiniumation under an inversion of configuration to form second C-N bond and closes the second ring to generate amidiniumation product 2.

Using the resulting amidine salts 2, we finally explored transformation of them into corresponding vicinal diamines (Scheme 3). Treatment formamidine salt 2a with KOtBu in THF resulted in a ring-opening process, and subsequently hydrolysis led to form 2-substituted indoline 3. In the case of benzamidine salt 2h, ring-opening reaction proceeded in the presence of KOH, and subsequently hydrolysis gave free products.
transformed into chiral free diamine (synthesis of chiral 2) substituted indolines, and other chiral auxiliary methodology affords an efficient method for amidines. The methods proceed under very practical and clean imidazolidinium salts, starting from readily available reaction conditions without the need for any additive. The vicinal diamines. 

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afforded the diastereomeric products (enantiopure cyclic vicinal diamine). Inspired by the successful results mentioned above, we attempted to obtain enantiopure cyclic vicinal diamine converted into 2) substituted pyrrolidine and indoline diamines. The resultant bicyclic imidazolidinium salts could be readily separated by recrystallization. The absolute configuration of (S)-5 was confirmed by the X-ray diffraction analysis of its single crystals (Figure S5 for (S)-5). Treatment of (R)-5 could be further converted into chiral free diamine (S,S)-6 in diastereo- and enantiopure form by the aforementioned method. The chiral auxiliary methodology affords an efficient method for synthesis of chiral 2-substituted indolines, and other chiral vicinal diamines.

In conclusion, we present an NIS-mediated aminoaamidiniumation for the synthesis of bicyclic imidazolidinium salts, starting from readily available amidines. The methods proceed under very practical and clean reaction conditions without the need for any additive. The resultant bicyclic imidazolidinium salts could be readily converted into 2-substituted pyrrolidine and indoline diamines. Our methodologies provide efficient methods for the concise syntheses of bicyclic imidazolidinium salts and cyclic vicinal diamines.

Notes and references