Synthesis of Heterocycles Based on Rhodium-Catalyzed C–H Amination

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Abstract: A new stereoselective approach to substituted pyrrolidines and piperidines is described that involves Du Bois’ C–H amination reaction, Boc-activation of a cyclic sulfamate group, and base-promoted intramolecular cyclization. This methodology can be utilized for the synthesis of tetrahydrofuran and tetrahydrothiophene derivatives.

Key word: C–H amination, heterocycle synthesis, rhodium-catalyzed reaction, cyclization

Developing new methodologies for the synthesis of heterocyclic compounds is of great importance in drug discovery, material science, and natural product synthesis.1,2 Recently, we reported the total synthesis of kaitocephalin,3 in which we devised a new methodology to construct the highly substituted pyrrolidine core through a rhodium-catalyzed C–H amination4,5 followed by an intramolecular nucleophilic attack of a nitrogen atom on a sulfamate group (Scheme 1). Since, to our knowledge, such an approach to heterocyclic compounds has not been reported,6,7 we became interested in probing the scope and limitations of this particular pyrrolidine synthesis.

Scheme 1 The key pyrrolidine synthesis

To assess the feasibility of our pyrrolidine synthesis, we first conducted experiments using cyclic N-Boc-sulfamate 7a as a substrate, which was prepared from 4 via 5 and 6a according to Du Bois’ protocol (Scheme 2).4b Initially, the cyclization was examined by using NaH (2 equiv) in tetrahydrofuran (THF) according to the conditions employed for the synthesis of 3 (Table 1). In this case, the cyclized compound 8a was not observed on TLC even after ten hours.

Scheme 2 Preparation of cyclic N-Boc-sulfamate 7a

However, when water was added to the mixture, the cyclization occurred instantaneously to give 8a in 59% yield (Table 1, entry 1). Interestingly, after treatment of 7a with NaH at 0 °C for 5 min, addition of water (10 equiv) was found to effectively promote the cyclization to afford 8a in good yield (entry 2). When the reaction was carried out in DMF, 8a was obtained in high yield8 and the use of a large excess of water gave comparable results (entries 3 and 4). It turned out that performing the reaction with 3 M NaOH (2 equiv) in place of NaH and H2O also brought about the cyclization effectively, although the reaction became sluggish (entry 5). However, when a large excess of aqueous NaOH was used, the yield of 8a decreased markedly (entry 6). MeOH could also be employed in place of water (entry 7), although the use of NaOMe diminished the yield of 8a (entries 7 and 8). It was also found that no reaction occurred by using K2CO3 in MeOH at room temp-

Scheme 3 Confirmation of the stereochemistry of 8a

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temperature (entry 9). Although the role of the water is not clear, hydrogen bonding interactions are possibly one of the main factors that influence the reactivity of the process.\textsuperscript{9} The NOESY spectrum of 9 prepared from 8a confirmed the stereostructure of 8a (Scheme 3), thus proving that the cyclization took place in an SN2 fashion with complete inversion of the stereochemistry.

We next explored the effect of various protecting groups of the primary amine using the optimized NaH and H\textsubscript{2}O conditions (Table 2). As a result, in addition to Cbz, Moc, and Alloc groups, even the sterically demanding Boc group was found to be suitable for this cyclization (entries 1–4). Similarly, benzamide 7e and acetamide 7f afforded the corresponding cyclized products 8e and 8f, respectively, in comparable yields (entries 5 and 6).

Based on the optimized reaction conditions, we then evaluated the substrate scope (Table 3). First, five substituted Boc-protected sulfamates 7g–k were prepared from 6g–k and subjected to cyclization (Method A). It should be stressed that pyrroldines 8g–j as well as piperidine 8k could be synthesized in moderate overall yields regardless of the substitution pattern, even in the case where a quaternary center is present near the reaction site (entries 2–5). Next, step-economical one-pot preparation\textsuperscript{10} of 8a and 8f–k from 6a and 6f–k was also investigated (Method B).\textsuperscript{11} Thus, after confirming the formation of 7a and 7g–k on TLC, their cyclizations were conducted by adding NaH (3 equiv) followed by water (10 equiv). We were pleased to find that this one-pot procedure worked effectively and, except for 8i, afforded the corresponding products in good yields (entries 7 and 8).

\begin{table}[h]
\centering
\caption{Base-Promoted Cyclization of 7a–f}
\begin{tabular}{llc}
\hline
Entry & Sulfamate & X & Yield of 8 (%)\textsuperscript{a} \\
\hline
1 & 7a & Cbz & 99 \\
2 & 7b & Moc & 89 \\
3 & 7c & Alloc & 77 \\
4 & 7d & Boc & 75 \\
5 & 7e & Bz & 71 \\
6 & 7f & Ac & 80 \\
\hline
\end{tabular}
\end{table}
cyclized products in good yields. In the case of 6i, butoxy-carbonylation did not proceed selectively on the sulfamate nitrogen and the reaction produced several Boc-protected products.

We also examined the synthesis of tetrahydrofuran 12 and tetrahydrothiophene 13 from 10 and 11, based on the methodology detailed above (Scheme 4). As a result, a one-pot procedure involving butoxycarbonylation of a sulfamate and methanolytic removal of the acetyl group turned out to be operative in these cases, and the cyclized compounds 12 and 13, respectively, were obtained in good yields. The stereochemistries of 12 and 13 were un-

Table 3 Synthesis of 8a,g–k

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfamate</th>
<th>Yield of 7 (%)(^a)</th>
<th>Product</th>
<th>Yield of 8 (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>80</td>
<td>8a</td>
<td>99(^b) (81)(^c)</td>
</tr>
<tr>
<td>2</td>
<td>7g</td>
<td>70</td>
<td>8g</td>
<td>84(^b) (80)(^c)</td>
</tr>
<tr>
<td>3</td>
<td>7h</td>
<td>80</td>
<td>8h</td>
<td>79(^b) (77)(^c)</td>
</tr>
<tr>
<td>4</td>
<td>7i</td>
<td>39</td>
<td>8i</td>
<td>74(^b) (complex mixture)(^c)</td>
</tr>
<tr>
<td>5</td>
<td>7j</td>
<td>65</td>
<td>8j</td>
<td>88(^b) (77)(^c)</td>
</tr>
<tr>
<td>6</td>
<td>7k</td>
<td>72</td>
<td>8k</td>
<td>85(^b) (80)(^c)</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield.
\(^b\) Method A: (1) Boc\(_2\)O, Et\(_3\)N-DMAP, CH\(_2\)Cl\(_2\); (2) NaH (2 equiv), DMF, 0 °C, 5 min, then H\(_2\)O (10 equiv), r.t., 5 min.
\(^c\) Method B (one-pot): Boc\(_2\)O, Et\(_3\)N-DMAP, DMF, then NaH (3 equiv), 0 °C, 5 min, then H\(_2\)O (10 equiv), r.t., 5 min.
ambiguously determined by X-ray crystallographic analysis of their derivatives 14 and 15.

In conclusion, the present work provides a new methodology for the stereoselective construction of substituted heterocycles such as pyrrolidines, piperidines, tetrahydrofurans, and tetrahydrothiophenes utilizing rhodium-catalyzed C–H amination.

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References and Notes


Preparation of 8a from 4 via 5, 6a, and 7a


Representative One-Pot Preparation (Method B): Et3N (0.05 mL, 0.38 mmol), DMAP (3 mg, 0.025 mmol), and Boc2O (72 mg, 0.33 mmol) were added to a solution of 6a (100 mg, 0.25 mol) in DMF (2 mL) at r.t. The mixture was stirred at r.t. for 5 h, then NaH (60% in mineral oil, 16 mg, 0.40 mmol) was added and the mixture was stirred at r.t. for 5 min. The mixture was neutralized with 1 M HCl, extracted with EtOAc, washed with sat. NaHCO3, and concentrated in vacuo. Purification of the residue by column chromatography (SiO2 5 g, hexane–EtOAc, 4:1) gave 7a (1.176 g, 99%) as a colorless amorphous solid.

the mixture was stirred at r.t. for 5 min. The mixture was neutralized with 1 M HCl, extracted with EtOAc, washed with saturated NaHCO₃ and brine, dried over MgSO₄, and concentrated in vacuo. Purification of the residue by column chromatography (SiO₂, 5 g; hexane-EtOAc, 5:1) gave 8a (85 mg, 81%) as a colorless solid.

(12) The crystallographic data (CCDC 943270) can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) The crystallographic data (CCDC 943271) can be obtained free of charge from the Cambridge Crystallographic Data centre via www.ccdc.cam.ac.uk/data_request/cif.