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Swtiching Electrophile Intermediates to Nucleophiles: Michael and Oxa-Diels-Alder Reactions to Afford Polyoxy-Functionalized Piperidine Derivatives with Tetrosubstituted Carbon

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Supporting Information Placeholder

ABSTRACT: Michael, Michael-annulation, and oxa-Diels-Alder reactions of carbohydrate derivatives that afford polyoxy-functionalized piperidine derivatives bearing tetrosubstituted carbon at the 3-position of the piperidine ring are reported. Iminium ions generated from carbohydrate derivatives with amines were converted to enamines in situ, which acted as nucleophiles. As a result, substituents were introduced at the 3-position or both 2- and 3-positions of the piperidines bearing polyoxy groups. This strategy will be useful in drug discovery efforts.

Piperidines and piperidine-derived bicyclic derivatives bearing polyoxy substituents are found in bioactive natural products and pharmaceuticals and their building blocks.1,2,3 The synthesis of these molecules is of interest in drug discovery efforts and related research.1,2,3 Whereas the synthesis of piperidine derivatives bearing mono- or di-substitutions has been reported,4 these are usually not directly applicable to the synthesis of polyoxy-functionalized versions of piperidines. To access to polyoxy-functionalized piperidine derivatives, reactions of iminium ions derived from carbohydrate derivatives have been used, in which the iminium ions act as electrophiles (Scheme 1a).5 In these reactions, the product polyoxy-functionalized piperidine derivatives have substituents that originate from nucleophiles at the 2-position of the piperidine ring.5 Here, we report a strategy for the synthesis of polyoxy-functionalized piperidines bearing substituents at the 3-position or at both the 2- and the 3-positions of the piperidine ring in one pot from carbohydrate derivatives (Scheme 1b). In the strategy, the reaction mode of the carbohydrate derivative is altered by converting the iminium ion, which acts as an electrophile, to the enamine, which acts as a nucleophile, in situ. The strategy was demonstrated in Michael reactions, Michael-annulation reactions, and oxa-Diels-Alder reactions to synthesize polyoxy-functionalized piperidine derivatives bearing substituents at the 3-position or at both the 2- and the 3-positions of the piperidine ring.

Scheme 1. Reactions Affording Polyoxy-Functionalized Piperidine Derivatives

(a) previous work

TsO

R1

NH2

OP

OP

OP

OP

TsO

R1

H2O

HO

OP

OP

Nu

E

Nu

(b) this study

TsO

R1

OP

OP

OP

OP

TsO

R1

H2O

HO

OP

OP

Nu

Nu

Nu

Nu

E

E

E

E

Nu = nucleophiles

E = electrophiles

R1

R2

R3

R4

R5

R6

R7

R8

R9

R10

R11

R12
It has been recognized that interconversions between iminium ions and enamines occur in situ during reactions catalyzed by amine-based catalysts. However, the formation of enamines from iminium ions in situ under mild conditions for the introduction of substituents at the 3-position of piperidines or related N-heterocycles has been less explored. For functionalization at the 3-position of piperidines, preformed enamines have been used as starting materials or high temperature conditions have been employed to generate the enamines and their precursors.

We hypothesized that the use of conditions suitable for the formation of enamines from the iminium ions and the alteration of the reaction partners from nucleophiles to electrophiles would result in the formation of the products bearing substituents at the 3-position of the piperidine ring. To test this hypothesis, first, the iminium ion generated in situ from D-ribose derivative 1a (1.0 equiv) and benzyl amine (1.2 equiv), which was previously used as an electrophile, was treated with nitrostyrene 2a to afford 3a.

Table 1. Conditions for the Reaction of 1a with Benzylamine and with Nitrostyrene 2a to Afford 3a

<table>
<thead>
<tr>
<th>entry</th>
<th>additive (equiv)</th>
<th>time (h)</th>
<th>yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td>18</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>Et3N (1.0)</td>
<td>15</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>DIPEA (1.0)</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>pyridine (0.5)</td>
<td>15</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>pyridine (1.0)</td>
<td>15</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>DMAP (0.1)</td>
<td>16</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>DMAP (0.2)</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>DABCO (1.0)</td>
<td>15</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>DBU (0.2)</td>
<td>15</td>
<td>20</td>
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Conditions: D-Ribose tosylate 1a (1.0 mmol, 1.0 equiv) and benzylamine (1.2 equiv) in CH2Cl2 (3.0 mL) at rt (25 °C) for 3 h, then addition of nitrostyrene 2a (1.5 equiv) and additive, and the mixture was stirred at rt (25 °C) for the indicated time. Product 3a was isolated as a single diastereomer. DIPEA = N,N-diisopropylethylamine; DMAP = 4-(N,N-dimethylamino)pyridine; DABCO = 1,4-diazabicyclo[2.2.2]octane; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Using the optimal conditions identified to afford 3a (i.e., conditions of Table 1, entry 7), reactions of 1a with various nitrostyrenes 2 were performed (Scheme 2). Various oxabridged piperidine derivatives 3 bearing tetra-substituted carbon centers at the 3-position of the piperidine were synthesized from 1a in one pot. The structure of 3e was confirmed by X-ray crystal structural analysis (see Supporting Information). Although enamines may also be formed via the deprotonation from the benzylic position of the benzylamine moiety of the iminium ion intermediates generated during the reactions, the products from such pathways were not detected in the reactions shown in Scheme 2.

Scheme 2. Reactions of 1a with Benzylamine and with Nitroolefins 2 to Afford 3a

When iminium ions were derived from 1a with amines other than benzylamine, the reactions with nitrostyrenes afforded corresponding oxabridged products 4 (Scheme 3).

When reactions of 1a were performed with nitrostyrenes bearing hydroxymethyl groups 5 or 6, pyran-fused piperidine derivatives 7 or 8, respectively, were obtained (Scheme 4). The structure of 7a was determined by the X-ray crystal
The reaction strategy was also applicable to the starting material other than 1a. The use of D-lyxose derivative 1b instead of D-ribose derivative 1a in the reaction afforded corresponding product 7d.

Scheme 3. Reactions of 1a with Various Amines and with Nitrostyrene

![Reaction Scheme 3](image)

Scheme 4. Reactions of 1 with Benzylamine and with Hydroxymethyl Nitrosoyrenes

![Reaction Scheme 4](image)

The electrophiles that reacted with the enamine generated in situ from 1a or 1b were not limited to nitroolefin derivatives. Reactions of 1a and of 1b with α,β-unsaturated carbonyl compounds also afforded the corresponding products (Scheme 5). The reaction of 1a with vinyl phenyl ketone afforded Michael addition product 9 (Scheme 5a). The reactions of 1a and of 1b with substituted enone 10 afforded Michael-annulation products 11 and 12, respectively (Scheme 5b and c). The reactions with unsaturated pyrazolone derivative 13 also afforded Michael-annulation reaction or [4+2] cycloaddition reaction products 14 and 15, respectively (Scheme 5d and e). Products 9, 11, 12, 14, and 15 were all isolated as single diastereomers.

Scheme 5. Reactions of 1 with Benzylamine and with Enone Derivatives

![Reaction Scheme 5](image)

Addition of non-oxa-substituents at the 2-position of the piperidine ring was achieved with the Michael addition at the 3-position. When the reactions with nitrostyrene 2a were performed with the use of 2.0 equiv of benzylamine (instead of 1.2 equiv) at the initial iminium ion formation stage, products 16 and 17 were obtained as single diastereomers (after purification) from 1a and 1b, respectively. The amine was introduced at the 2-position of the piperidine with the Michael addition at the 3-position (Scheme 6). Note that treatment of 3a with benzylamine and DMAP did not form 16.
Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data of compounds, additional results of the reactions of less-oxy-functionalized substrates, additional discussions about the reaction pathways and the stereoselectivities, and NMR spectra (PDF)

CCDC 1974279 (compound 3e) and CCDC 1974281 (compound 7a) contain the supplementary crystallographic data of this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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Notes
The authors declare no competing financial interest.

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