TITLE:

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CITATION:


ISSUE DATE:

2017-09-15

URL:

http://hdl.handle.net/2433/235944

RIGHT:

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Synthesis of Octahydro- and Decahydro-Quinolines by a One-Pot Cascade Reaction of Tetrasubstituted Enecarbamate

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Supporting Information Placeholder

ABSTRACT: A transition metal catalyzed-cyclopropanation followed by ring-opening was investigated for the synthesis of octahydroquinolines 4 and decahydroquinolines 5 having a quaternary carbon center at the angular position, which are core structures of the fawcettimine-type alkaloids. A tandem reaction was also established for the synthesis of decahydroquinolines 5 and the tricyclic compound 6 through an iminium ion intermediate, readily produced by acidic treatment of cyclopropane 2.

Fawcettimine, isolated from Lycopodium fawcetti by Burnell and co-workers in 1959, is one of the representative Lycopodium alkaloids (Figure 1). It is one of more than 80 congeners reported to date, that include fawcettidine,1,2 macleanine,3 and squarrosidine B,5 each of which belong to the fawcettimine class of alkaloids. Recently, new members of this alkaloid class, such as lyconesidines,5 have been found in related species. Among these compounds, a complex tetracyclic skeleton is common, and the structural diversity mainly derives from the oxidation level and substituents on the B and D rings.6 Because of its unique tetracyclic structure, many groups are engaged in synthetic studies of the fawcettimine-type alkaloids.7,8 The main focus of these studies has been the synthesis of thehydrindane skeleton (B and D rings), and they are based on Inubushi and Heathcock’s pioneering work.9,10 As an exceptional strategy, Dake and Kozak reported Pt(II)-catalyzed cyclization to construct an octahydroquinoline skeleton having a quaternary carbon (C and D rings).11a While Dake’s synthesis proposed the possibility of an octahydroquinoline skeleton as a useful intermediate. Additionally, the skeleton has been found in various alkaloids such as fendleridine.9 Therefore, the development of a concise synthetic method for these skeletons would contribute to the synthesis of not only fawcettimine-type alkaloids but also related natural products.

Considering a synthesis of various analogs, we envisioned that an intramolecular cyclopropanation of tetrahydropyrididine 1 followed by ring-opening would give both octa- and decahydroquinolines 4 and 5, respectively (Scheme 1). That is, by introducing an electron-withdrawing group as a substituent (R3 = EWG), a ring-opening of cyclopropane 2 would readily produce an iminium intermediate 3,12 which would be converted to 4 and 5 by a proton transfer and stereoselective reduction, respectively. It was expected that various substituents could be introduced into the obtained compounds 4 and 5 by using ketone functionality for the synthesis of fawcettimine-type alkaloids. Moreover, the iminium intermediate 3, derived from a substrate having a hydroxyethyl group (R2 = CH2CH2OH), would be intramolecularly trapped with an alcohol to give a tricyclic compound 6, which can be found in a fendleridine skeleton. While there are many reports about cyclopropanation of mono-substituted enamides and enecarbamates,11,12 the number of reports decreases as the number of substituents increases. In the case of tetrasubstituted enamides and enecarbamates, pyrolysis of tosylhydrazone13a and formation of carbene from chloroform via treatment of a strong base13b were only employed for cyclopropanation.14 Thus, there is no example of the use of a transition metal-carbene complex. Herein, we report synthesis of octahydroquinolines 4, decahydroquinolines 5, and tricyclic compound 6 having a quaternary carbon center at the angular position via a transition metal-catalyzed cyclopropanation of tetrasubstituted enecarbamate and a ring-opening.

Figure 1. Fawcettimine-type alkaloids and a natural product containing both octa- and decahydroquinoline skeletons.
Initially, cyclization precursors 1a-h were synthesized from 2-piperidone in six to eight steps including Heck or Suzuki-Miyaura coupling, 1,4-reduction and diazotransfer (Scheme 2). We then investigated transition metal-catalyzed cyclopropanation of tetrasubstituted enecarbazate 1a. When compound 1a was treated with Cu(OAc)₂, diketone 10 was obtained in 70% yield via a ring-opening of cyclopropane followed by hydrolysis (Table 1, entry 1). Although Cu(hfacac)₂ could be used for suppressing a ring-opening of cyclopropane, a part of the desired product 2a was converted to octahydroquinoline 4a, which was a mixture of keto- and enol-tautomers owing to the presence of an acidic proton (entry 2). In contrast, the use of rhodium catalysts, including Rho₂(OAc)₃, Rho₂(cap)₃, and Rho₂(esp)₃, was effective for suppressing the undesired side reactions (entries 3–5). Specifically, Rho₂(esp)₃ gave an hexa-substituted cyclopropane 2a in 57% without compounds 4a and 10 (entry 5). For reproducible isolation of the product 2a, addition of triethylamine into an eluent for silica gel column chromatography was important because 2a was not stable on silica gel.

We next focused on the selective transformation of the hexa-substituted cyclopropane 2a into octahydroquinoline 4a and decahydroquinoline 5a. When compound 2a was treated with trifluoroacetic acid (TFA) or BF₃·OEt₂, ring-opening of cyclopropane was followed by a proton transfer to give compound 4a in excellent yields (Table 2, entries 1 and 2). These results indicated that cyclopropane 2a was readily cleaved to

Scheme 2. Synthesis of tetrasubstituted enecarbazate 1a.

<table>
<thead>
<tr>
<th>entry</th>
<th>cat.</th>
<th>time</th>
<th>yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)₂</td>
<td>10 h</td>
<td>0 0 70</td>
</tr>
<tr>
<td>2</td>
<td>Cu(hfacac)₂b</td>
<td>24 h</td>
<td>13 33 0</td>
</tr>
<tr>
<td>3</td>
<td>Rho₂(cap)₃</td>
<td>2.5 h</td>
<td>42 0 0</td>
</tr>
<tr>
<td>4</td>
<td>Rho₂(OAc)₃</td>
<td>30 min</td>
<td>52 0 0</td>
</tr>
<tr>
<td>5</td>
<td>Rho₂(esp)₃</td>
<td>15 min</td>
<td>57 0 0</td>
</tr>
</tbody>
</table>

a. Isolated yield. b. 60 mol%/c. 0.1 mol%. Tf = triflate, hfacac = hexafluoroacetylacetionato, cap = caprolactamate, esp = a,a,a′,a′-tetramethyl-1,3-benzenediropionic acid.

produce an iminium ion such as 3. Thus, reduction of the iminium ion was examined for obtaining decahydroquinoline 5a. When compound 2a was treated with Et₃SiH, Ph₃SiH, or NaBH₄CN under acidic conditions (TFA), these reductions did not proceed (entries 3–5). In sharp contrast, use of NaBH₄(OAc) was effective, and the reaction gave the desired product 5a in 72% yield along with a small amount of 4a (entry 6). Several Lewis acids were also examined instead of TFA. In the case of BF₃·OEt₂, the reaction gave 5a, but the yield was low (31%, entry 7). In contrast, a combination of NaBH₄(OAc) and other Lewis acids, including Ti(OiPr)₄, AlCl₃, Sc(OTf)₃, and MgBr₂·OEt₂, gave only octahydroquinoline 4a in low to moderate yields (entries 8–11). Therefore, BF₃·OEt₂ was employed for opening the cyclopropane ring to access compound 4a, and a combination of TFA and NaBH₄(OAc) was determined to provide the best conditions for the synthesis of compound 5a. Reduction of the iminium intermediate 3a proceeded with excellent stereoselectivity because the reductant chemistry of the trans-fused ring system was determined by NOESY experiments after formation of tert-butyl(dimethyl)silyl (TBS) enol ether 13a (Scheme 3). For the synthesis of compound 5a, compound 4a was also treated under the optimized reduction conditions (TFA and NaBH₄(OAc), rt). However, the reaction did not proceed to give 5a. This result indicated that the iminium ion 3a was not produced from compound 4a under these mild conditions.

Table 1. Transition metal-catalyzed cyclopropanation of tetrasubstituted enecarbazate 1a.

Table 2. Selective formation of octahydroquinoline 4a and decahydroquinoline 5a.
To determine the scope and limitations, the optimized conditions were applied for the synthesis of several octahydroquinolines 4b-4h (Table 3). Cyclopropanation of substrates 1b and 1c having CO₂Me and Boc group as protecting groups gave compounds 2b and 2c in moderate yields, respectively (entries 1 and 2). Compound 2b readily converted to octahydroquinoline 4b when treated with BF₃·OEt₂. In the case of 2c, MgBr₂·OEt₂ was used instead of BF₃·OEt₂ for suppressing the undesired deprotection of the Boc group. Compound 4c was obtained in excellent yield. Interestingly, the reaction of 1d with its tosyl group gave 4d in 76% yield without acidic treatment, as the corresponding cyclopropane 2d was easily cleaved (entry 3). The reaction of β-keto-α-diazoester 1e did not give compound 2e. Thus a nitrile group is essential for this cyclopropanation (entry 4). The reaction of 1f did not give cyclopropane 2f because C–H insertion was competitive (entry 5). Benzyl (Bn) and TBS groups were compatible under these reactions, and octahydroquinolines 4g and 4h were obtained in 80% and quantitative yields, respectively (entries 6 and 7).

Table 3. Scope and limitations of synthesis of octahydroquinoline 4.

<table>
<thead>
<tr>
<th>entry</th>
<th>first step</th>
<th>yielda</th>
<th>second step</th>
<th>yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>60%</td>
<td>2b:</td>
<td>96%</td>
</tr>
<tr>
<td>2</td>
<td>2c:</td>
<td>50%</td>
<td>4c:</td>
<td>quantb</td>
</tr>
<tr>
<td>3</td>
<td>2d:</td>
<td>(-)</td>
<td>4d:</td>
<td>76%c,d</td>
</tr>
<tr>
<td>4</td>
<td>2e:</td>
<td>0%</td>
<td>4e:</td>
<td>(-)</td>
</tr>
<tr>
<td>5</td>
<td>2f:</td>
<td>0%</td>
<td>4f:</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>2g:</td>
<td>49%</td>
<td>4g:</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2h:</td>
<td>52%</td>
<td>4h:</td>
<td>quantb</td>
</tr>
</tbody>
</table>

a. Isolated yield. b. MgBr₂·OEt₂ was used instead of BF₃·OEt₂. c. Without acidic treatment. d. The reaction time was 35 min. Bn = benzyl, TBS = tert-butyldimethylsilyl.

Because compound 2 was not stable as described above, a one-pot cyclopropanation/reductive ring-opening was attempted for the synthesis of decahydroquinolines 5. Treatment of 1a with Rh₂(esp); was followed by reductive ring-opening using TFA and NaBH(OAc)₃ to give decahydroquinolines 5a in 48% yield, which was comparable to the yield of the stepwise procedure (Table 4, entry 1). Methoxy carbonyl and Boc groups were compatible under these conditions (entries 2 and 3). In the case of substrates having Bn and TBS groups, the desired decahydroquinolines 5g and 5h were obtained as major products, respectively, while the reductive ring-opening competed with formation of octahydroquinolines 4g and 4h.

Table 4. One-pot cyclopropanation and reductive ring-opening for synthesis of decahydroquinoline 5.

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
<th>R₂</th>
<th>time</th>
<th>product</th>
<th>yield (%)ab</th>
<th>ratiobc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Cbz</td>
<td>Et</td>
<td>2 h</td>
<td>5a</td>
<td>48%</td>
<td>4.0:1</td>
</tr>
<tr>
<td>2d</td>
<td>CO₂Me</td>
<td>Et</td>
<td>50 min</td>
<td>5b</td>
<td>64%</td>
<td>7.3:1</td>
</tr>
<tr>
<td>3d</td>
<td>Boc</td>
<td>Et</td>
<td>45 min</td>
<td>5c</td>
<td>77%</td>
<td>6.5:1</td>
</tr>
<tr>
<td>4</td>
<td>Cbz</td>
<td>CH₃CH₂OBn</td>
<td>8 h</td>
<td>5g</td>
<td>47%</td>
<td>3.3:1</td>
</tr>
<tr>
<td>5d</td>
<td>Cbz</td>
<td>CH₃CH₂OTBS</td>
<td>2 h</td>
<td>5h</td>
<td>43%</td>
<td>3.8:1</td>
</tr>
</tbody>
</table>

a. Isolated yield. b. The ratio was calculated by ¹H NMR. c. 0.1 mol% of Rh₂(esp) was used. d. Rh(OAc)₃ was used instead of Rh(esp).²

This one-pot procedure for decahydroquinolines 5 was extended to a one-pot synthesis of tricyclic compound 6 (Scheme...
4). Treatment of β-keto-α-diazonitrile 1i with Rh2(esp)2 followed by BF3·OEt2 gave compound 6 via cyclopropanation in 66% yield. It is interesting that the cyclopropanation was the preferable process rather than O–H insertion in the first step, and an iminium ion could be trapped without formation of enecarbamate in the second step. It was difficult to obtain compound 6 from octahydroquinoline 4i under mild conditions including treatment with BF3·OEt2 or CSA.

Scheme 4. One-pot synthesis of tricyclic compound 6.

In summary, we have investigated a concise synthesis of octahydroquinolines 4 and decahydroquinolines 5 having a quaternary carbon center at the angular position via a one-pot reaction involving cyclopropanation and ring-opening. The use of Ts-protected ene-sulfonamide 1d was found to be effective for direct access to 4. One-pot procedures for the synthesis of decahydroquinolines 5 and tricyclic compound 6 were also established. These methods would be powerful because a quaternary carbon center and a six-membered carbocycle were constructed at once. Synthesis of related alkaloids based on the developed strategy for decahydroquinolines 5 is now underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectra data (1H and 13C NMR, IR, and HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by the JSPS KAKENHI (GrantNo. JP17H05051), the Platform Project for Supporting Drug Discovery and Life Science Research from Japan Agency for Medical Research and Development (AMED).

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