Versatile and Direct Transformation of Secondary Amides into Ketones by Deaminative Alkylation with Organocerium Reagents

Kai-Jiong Xiao, Ai-E Wang, Ying-Hong Huang, and Pei-Qiang Huang[a]

Amides are a class of easily available and highly stable compounds. Secondary amides[1] also serve as powerful directing groups in C–H activation.[2] Ketones are also a class of extremely versatile molecules that enable a number of fundamental transformations in organic synthesis.[3] Hence the transformation of amides into ketones[4] is of high relevance in organic synthesis. However, because of the high stability of amides, their direct transformation into more reactive ketones presents a formidable challenge. Although a limited number of specially designed amides, such as Weinreb amides (N-methoxy-N-methylamides), have been prepared as intermediates for the conversion of carboxylic acids/esters into ketones,[5] such methods cannot be used for the transformation of simple amides into ketones. Herein, we report a general one-pot method for the direct conversion of secondary amides into ketones[6] by using organocerium species as the alkylating reagents.

On the basis of carbonyl activation with trifluoromethanesulfonic anhydride (Tf₂O),[6] we have recently reported the direct conversion of tertiary lactams/amides into tertiary alkyl amines by sequential reductive alkylation with Grignard and organolithium reagents.[7] As a continuation of this study, and in connection with our general interest in the development of step-economical synthesis,[7a,k,9] we investigated the Tf₂O-activated reductive alkylation of secondary amides. We discovered that cerium complexes generated in situ from RLi and CeCl₃ and cerium complexes generated in situ from RMgX and CeCl₃, and organocerium reagents (RCeCl₂) generated in situ from RLi and CeCl₃ were effective for the direct conversion of secondary amides into ketones by activation with Tf₂O and 2-fluoropyridine (Scheme 1).

The conversion of N-butylbenzamide (1a) into ketone 2a was selected as a model reaction. An investigation of the influence of the base revealed that the use of a base was necessary, and 2-fluoropyridine[10] gave the best results. The influence of the organometallic reagent was then explored in combination with 2-fluoropyridine (1.2 equiv) as the base. Organocerium reagents (RCeCl₂) [12] generated in situ from RLi and CeCl₃ and cerium complexes generated in situ from RMgX and CeCl₃[13] are more efficient than organomagnesium, organolithium, and organozinc species for this reaction. Optimal yields were achieved by using the cerium complex nBuMgBr/CeCl₃ (3.0 equiv). The optimal protocol for one-pot transformation of secondary amides into ketones was identified as successive treatment of a solute of the amide in dichloromethane and 2-fluoropyridine (1.2 equiv) with Tf₂O (1.1 equiv, −78°C, then 0°C), and RM/CeCl₃ (3.0 equiv, −78°C), then hydrolysis with aqueous HCl.

Under the optimized conditions, the scope of the transformation was studied. As shown in Table 1, this method of converting secondary amides into ketones by deaminative alkylation with organocerium reagents has a wide scope and broad functional group tolerance.

A wide array of arylox (Table 1, entries 1–16), alkanoyl (Table 1, entries 17–25), and alkenoyl amides (Table 1, entry 26) were converted into the corresponding ketones in high yields. The substituents on the N atom of the secondary amides, regardless of whether they are N-n-alkyl (Table 1, entries 1–9, 15–18, 24–26), N-s-alkyl (Table 1, entries 10–14, 21–23) or N-aryl (Table 1, entry 19), do not have much influence on the reactivity. The reaction also went smoothly with hindered amides, such as 1o (Table 1, entry 24).

The reaction is compatible with many functional groups on the amides, including ethers (Table 1, entry 12), aromatic bromides (Table 1, entry 13), tertiary aromatic amines (Table 1, entry 14), thiophene (Table 1, entry 16), terminal C=C bonds (Table 1, entry 25), and even conjugated C=C bonds (Table 1, entry 26). For α,β-unsaturated amide 1q, only the 1,2-addition product 2u was obtained, which provides an alternative approach to enones[14] (Table 1, entry 26).

With regard to the organocerium complexes, alkyl (Table 1, entries 1–4, 9–17, 19, 22, 24, 26), benzyl (Table 1, entries 20, 21, 23, 25), aryl (Table 1, entries 6 and 7), and alkenyl cerium complexes (Table 1, entry 18) generated from

Scheme 1. Direct transformation of secondary amides into ketones. Tf₂O = trifluoromethanesulfonic anhydride; 2-F-Py = 2-fluoropyridine.
Table 1. Direct transformation of secondary amides 1 into ketones 2.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate RM</th>
<th>Product (Yield [%])</th>
<th>Entry</th>
<th>Substrate RM</th>
<th>Product (Yield [%])</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhOCONHnBuMgBr</td>
<td>1a (80)</td>
<td>14</td>
<td>4-Me2NC6H4OCH3H</td>
<td>1g (85)</td>
</tr>
<tr>
<td>2</td>
<td>nBuMgBr</td>
<td>2a (87)</td>
<td>15</td>
<td>nBuMgBr</td>
<td>2k (83)</td>
</tr>
<tr>
<td>3</td>
<td>iPrMgBr</td>
<td>2b (82)</td>
<td>16</td>
<td>nBuMgBr</td>
<td>2l (85)</td>
</tr>
<tr>
<td>4</td>
<td>PhMgBr</td>
<td>2c (78)</td>
<td>17</td>
<td>nC11H23CH3OCH3H</td>
<td>2m (79)</td>
</tr>
<tr>
<td>5</td>
<td>BnMgBr</td>
<td>2d (78)</td>
<td>18</td>
<td>nC11H23CH3OCH3H</td>
<td>2n (86)</td>
</tr>
<tr>
<td>6</td>
<td>PhMgBr</td>
<td>2e (84)</td>
<td>19</td>
<td>nC11H23CH3OCH3H</td>
<td>2o (70)</td>
</tr>
<tr>
<td>7</td>
<td>BnMgBr</td>
<td>2f (69)</td>
<td>20</td>
<td>BnMgBr</td>
<td>2p (68)</td>
</tr>
<tr>
<td>8</td>
<td>PhOCONenBuLi</td>
<td>2g (75)</td>
<td>21</td>
<td>BnMgBr</td>
<td>2q (84)</td>
</tr>
<tr>
<td>9</td>
<td>nBuMgBr</td>
<td>2a (83)</td>
<td>22</td>
<td>nBuLi</td>
<td>2r (85)</td>
</tr>
<tr>
<td>10</td>
<td>PhOCONHex</td>
<td>2a (87)</td>
<td>23</td>
<td>BnMgBr</td>
<td>2s (77)</td>
</tr>
<tr>
<td>11</td>
<td>4-MeC6H4OCH3H</td>
<td>nBuLi</td>
<td>24</td>
<td>4-MeC6H4OCH3H</td>
<td>nBuLi</td>
</tr>
<tr>
<td>12</td>
<td>4-MeOC6H4OCH3H</td>
<td>nBuLi</td>
<td>25</td>
<td>4-MeOC6H4OCH3H</td>
<td>nBuLi</td>
</tr>
<tr>
<td>13</td>
<td>4-BrC6H4OCH3H</td>
<td>nBuLi</td>
<td>26</td>
<td>PhOCONHex</td>
<td>nBuLi</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1) Amide (1.0 mmol), 2-fluoropyridine (1.2 mmol), TiO2 (1.1 mmol), CH2Cl2 (4 mL), –78°C, then 0°C, 10 min; 2) RM/CeCl3 (3.0 mmol), –78°C, 1 h; 3) aq. HCl (2 M, 5 mL), RT, 2 h. [b] Yield of isolated product. Bn = benzyl; Hex = hexyl; Pent = pentyl.

These are not the final page numbers!
either organolithium or Grignard reagents can be used for the one-pot synthesis of ketones. The reaction of amide 1a with the allyl cerium complex generated from allylmagnesium bromide proceeded with migration of the C=C bond to produce the conjugated enone 2d in 78% yield (Table 1, entry 5). The use of alkynyl cerium complexes can also lead to enones, such as 2g (Table 1, entry 8). The reaction of amide 1a with aryl cerium complexes gave diaryl ketones[15] (Table 1, entries 6 and 7). It should be noted that functionalyzed aryl magnesium reagents that were reported by Knochel et al.[16] can also be applied in this procedure (Table 1, entry 7).

It is interesting that use of alkyl cerium reagents generated from lithium acetylides yielded β-chloroenones, such as 2g (Table 1, entry 8), which are versatile building blocks for the synthesis of heterocycles.[17] It seems that the addition of a chlorine ion occurred in situ after ynone formation.

In conclusion, we have developed a simple, efficient, and general method for the direct transformation of secondary amides into ketones. Considering the central role played by amides into ketones. The reaction of amide 1a with either organolithium or Grignard reagents can be used for the one-pot synthesis of ketones. The reaction of amide 1a with the allyl cerium complex generated from allylmagnesium bromide proceeded with migration of the C=C bond to produce the conjugated enone 2d in 78% yield (Table 1, entry 5). The use of alkynyl cerium complexes can also lead to enones, such as 2g (Table 1, entry 8). The reaction of amide 1a with aryl cerium complexes gave diaryl ketones[15] (Table 1, entries 6 and 7). It should be noted that functionalyzed aryl magnesium reagents that were reported by Knochel et al.[16] can also be applied in this procedure (Table 1, entry 7).

Experimental Section

**General procedure for the direct transformation of secondary amides 1 into ketones 2**

Trifluoromethanesulfonic anhydride (185 μL, 1.1 mmol, 1.1 equiv) was added dropwise to a cooled (−78°C) solution of amide 1 (1.0 mmol, 1.0 equiv) and 2-fluoropyridine (103 μL, 1.2 mmol, 1.2 equiv) in dichloromethane (4 mL). The reaction was warmed to 0°C in an ice bath and stirred for 10 min. The mixture was then cannulated into a freshly prepared solution of the organocerium complex (3.0 mmol, 3.0 equiv) in diethyl ether (3/C14810 mL). The combined organic layers were washed with aq. NaHCO3, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column to afford the desired ketone 2.

Acknowledgements

We are grateful for financial support from the National Basic Research Program (973 Program) of China (Grant No. 2010CB833200), the NSF of China (21072160 and 20832005), the Fundamental Research Funds for the Central Universities of China (Grant No. 201112G0001), and a Scholarship Award for Excellent Doctoral Student granted by Ministry of Education of China (2010). We are grateful to Prof. Dr. G. M. Blackburn for valuable discussions.

**Keywords:** amides · C=C bond formation · ketones · organocerium reagents · synthetic methods


[5] W. S. Bechara, G. Pelletier, A. B. Charette, Nat. Chem. 2012, 4, 228–234. This work appeared while we were submitting our own manuscript. The two methods are complementary as a general method for the transformation of secondary amides to ketones in terms of the scope, reaction conditions, and nucleophiles used.


Received: July 17, 2012
Published online: 0 0 0 0
These are not the final page numbers!
Versatile and Direct Transformation of Secondary Amides into Ketones by Deaminative Alkylation with Organocerium Reagents

Cerium makes it simple: A simple, efficient, and versatile C–C bond-forming method for the direct transformation of secondary amides into ketones by Tf₂O-mediated deaminative alkylation with organocerium reagents is described. A wide variety of ketones, including α,β-unsaturated ketones, β-chloroenones, diaryl ketones, and yrones were synthesized by using this method.