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## 生物活性化合物和有機光學材料的合成方法及應用研究

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# Synthesis of β-Amino and β-Methoxy Ketones by Lewis Acids Promoted β-Substitution Reactions of β,γ-Unsaturated Ketones

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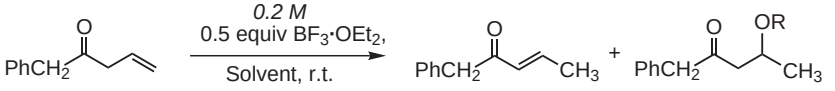
**Abstract:** A reaction mixture of β,γ-unsaturated ketone and $BF_3{\cdot}OEt_2$ in $CH_3OH$ was stirred at room temperature and β-methoxy ketone was produced in high yield. The β-amino ketone was obtained as the major product from a reaction mixture of β,γ-unsaturated ketone, $AlCl_3$ and Ts-$NH_2$ in $CH_2Cl_2$ at room temperature. This Lewis acid promoted β-substitution reaction mechanism was proposed as that the process occurred via in situ isomerization of β,γ-unsaturated ketone to α,β-unsaturated ketone followed by the 1,4-addition reaction.

**Key words:** β,γ-unsaturated ketone, β-amino ketone, β-methoxy ketone, α,β-unsaturated ketone, 1,4-addition reaction

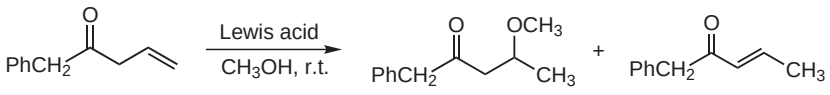
β-Alkoxy and β-amino carbonyl compounds are potentially biologically active molecules and important synthetic intermediates in organic synthesis.[1–4] Specific formation of a new bond on the β-position to the carbonyl functionality is typically produced by Aldol-type reaction,[5,6] organocopper addition reaction[7,8] and 1,4-addition reaction.[9,10] Conjugate addition of organometallic reagent to α,β-unsaturated ketone is the most direct and commonly used method for the preparation of β-substituted ketone.[11] Recently, our laboratory reported a simple and an effective method for the synthesis of β,γ-unsaturated ketone, which is the synthetic precursor of α,β-unsaturated ketone.[12] Thus, we expected that the preparation of α,β-unsaturated ketone may be achieved by the isomerization of β,γ-unsaturated ketone under mild acidic reaction condition. A reaction mixture of 1-phenylpent-4-en-2-one and Lewis acid ($BF_3{\cdot}OEt_2$) in $CH_2Cl_2$ was refluxed for two hours and only 40% yield of isomerized enone, 1-phenyl-pent-3-en-2-one (**I**), was obtained (Scheme 1). When the reaction mixture of 1-phenylpent-4-en-2-one and $BF_3{\cdot}OEt_2$ was stirred in $CH_3OH$ at room temperature for two hours, 4-methoxy-1-phenylpentan-2-one was produced as the major product and isomerized enone **I** as the minor product. The reaction rate for the formation of β-alkoxy ketone decreased when the more sterically hindered ethanol was introduced under the reaction conditions. It should be noted that neither β-substitution reaction nor isomerization reaction occurred in the absence of Lewis acid and more than 98% of β,γ-unsaturated ketone was recovered even if the reaction mixture was stirred in MeOH at room temperature for 48 hours. Both Lewis acid and alcohol are necessary for the formation of β-alkoxy ketone.

The amount of Lewis acid used was investigated and the results are shown in Scheme 2. The ratio of 0.7 to 1.0




| | | | |
|---|---|---|---|
| $CH_2Cl_2$, 2 h, reflux | **I** 40% | + | Unknowns |
| MeOH, 2 h | **I** 16% | + | 72% (R=Me) |
| EtOH, 22 h | **I** 20% | + | 75% (R=Et) |

**Scheme 1**




| | | | |
|---|---|---|---|
| * 0.3 $BF_3{\cdot}OEt_2$, $CH_3OH$, 26 h | 2% | + | 17% + 59% **S.M.** |
| * 0.7 $BF_3{\cdot}OEt_2$, $CH_3OH$, 2 h | 86% | + | 10% |
| * 1.0 $BF_3{\cdot}OEt_2$, $CH_3OH$, 2 h | 89% | + | 7% |
| * 1.5 $BF_3{\cdot}OEt_2$, $CH_3OH$, 2 h | 70% | + | 6% |

**Scheme 2**

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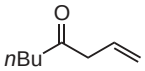
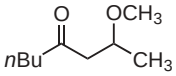
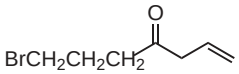
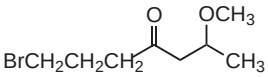
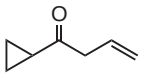
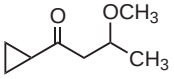
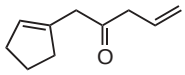
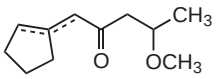
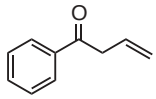
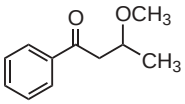
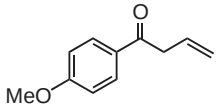
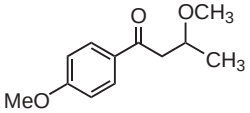
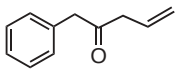
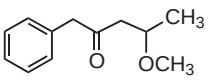
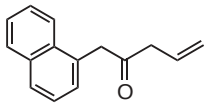
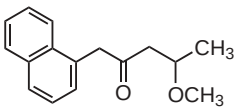
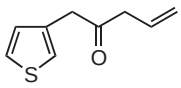
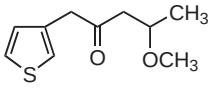
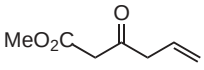
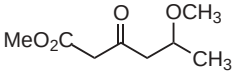
molar equivalents of Lewis acid to substrate afforded the highest yield of β-methoxy ketone. Interestingly, higher or lower ratios than this molar range led to a dramatic decrease in the yield of β-methoxy ketone obtained. The $BF_3{\cdot}OEt_2$ amount was determined to be in equal molar ratio to the substrate and it was introduced to provide the β-substitution reaction conditions. Other Lewis acids such as $AlCl_3$, $ZrCl_4$ and $Me_3SiOTf$ also can behave as promoters for the β-substitution reactions of β,γ-unsaturated ketones. The experimental results showed that $BF_3{\cdot}OEt_2$ is the best choice of Lewis acid for the synthesis of β-methoxy ketone.

β-Methoxy of ketones are extensively observed in many naturally occurring compounds and exhibit a wide range of biological activities.[13–17] A series of β,γ-unsaturated ketones was investigated under the typical reaction conditions and the results are shown in Table 1.

All β,γ-unsaturated ketones were transformed into their corresponding β-methoxy ketones in moderate to high yields and α,β-unsaturated ketones also were generated under the reaction conditions. The β-methoxy ketones were obtained in reasonable yields even if relatively acidic α-protons existed on β,γ-unsaturated ketones (Table 1, entries 1–4, 7–10). β-Amino carbonyl compounds exhibit as an important structure in many natural products and a useful synthetic intermediate in organic synthesis.[18–23] β-Amino ketone is typically produced by the addition reaction of nucleophilic amine to α,β-unsaturated ketone in the absence of acidic α-protons. According to the results β,γ-unsaturated ketones were transformed into their corresponding β-methoxy ketones by Lewis acid promoted β-substitution reactions. This new Lewis acid promoted β-substitution reaction may provide a useful method for the synthesis of β-amino ketone under mild reaction conditions. Thus, we expected and that the relatively acidic 4-

**Table 1** Synthesis of β-Methoxy Ketones

| Entry | Substrate | Product | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  |  | 2 | 76 + 8[b] |
| 2 |  |  | 2 | 58 + 13[b] |
| 3 |  |  | 1 | 60 |
| 4 |  |  | 3 | 50 + 12[c] |
| 5 |  |  | 3 | 73 + 8[b] |
| 6 |  |  | 1.5 | 80 + 12[b] |
| 7 |  |  | 2 | 89 + 7[b] |
| 8 |  |  | 4 | 82 + 8[b] |
| 9 |  |  | 4 | 77 + 7[b] |
| 10 |  |  | 8 | 64 + 8[b] |

[a] The yields were determined after chromatographic purification.
[b] The yield of isomerized enone after chromatographic purification.
[c] The yield of *endo* double bond isomer.

toluenesulfonamide (Ts-$NH_2$, $pK_a$ = 16)[24,25] may possibly react as a nuclephile rather than a base under this Lewis acid promoted β-substitution reaction conditions and investigated this reaction. A reaction mixture of 1-phenylpent-4-en-2-one, $BF_3{\cdot}OEt_2$, and Ts-$NH_2$ in $CH_2Cl_2$ was stirred at room temperature for 20 hours and a very low yield (<3%) of the expected product was formed with many undetermined side products. The 47% yield of the expected β-amino ketone **A** and 28% of 1-phenylpent-3-en-2-one (**I**) were obtained when the amount of $BF_3{\cdot}OEt_2$ was decreased to 0.5 molar equivalents with respect to the substrate (Scheme 3). Other Lewis acids such as $AlCl_3$, $ZrCl_4$ and $Me_3SiOTf$ were also investigated and $AlCl_3$ proved to be the best choice for β-amination reaction of β,γ-unsaturated ketone. The yield of β-amino ketone **A** was improved dramatically to 79% when 1.5 equivalents of Ts-$NH_2$ were introduced. It should be noted that the yield of β-amino ketone decreased when more than 0.5 equivalents of the amine were introduced. The best β-amination reaction conditions were determined to be 0.5 equivalents of $AlCl_3$ and 1.5 equivalents of Ts-$NH_2$ to 1 equivalent of substrate in $CH_2Cl_2$ solvent. Other more basic amines such as *n*-Bu-$NH_2$, Ph-$NH_2$, pyrrolidine and $Et_2NH$ were investigated and none of the expected β-amino ketones were produced. Only low yields of α,β-unsaturated ketone and some unidentified side products were obtained under these reaction conditions.

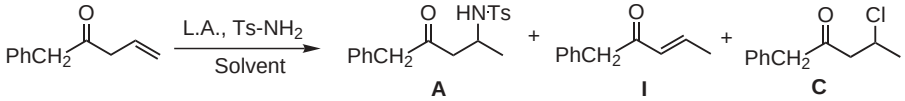
A series of β,γ-unsaturated ketones was investigated under the typical reaction conditions and the results are shown in Table 2. All β,γ-unsaturated ketones were transformed into their corresponding β-amino ketones as the major product and β-chloro ketones and α,β-unsaturated ketones as the minor products. The β-amino ketones were obtained in moderate to high yields even if relatively acidic α-protons exist on β,γ-unsaturated ketones (Table 2, entries 1–4, 7–9).

The mechanism for Lewis acid promoted formation of β-amino ketone and β-methoxy ketone from β,γ-unsaturated ketone was investigated. A reaction mixture of 1-phenylpent-3-en-2-one (**I**) and $BF_3{\cdot}OEt_2$ in MeOH was stirred at room temperature for 2 hours yielding 80% of β-methoxy ketone while 9% of the starting material was recovered (Scheme 4). The reaction mixture of 1-phenylpent-3-en-2-one (**I**), Ts-$NH_2$ and $AlCl_3$ in $CH_2Cl_2$ was stirred at room temperature for 96 hours and 65% of β-amino ketone **A** and 10% β-chloro ketone **C** were obtained. It is interesting to note that a higher yield of β-amino ketone or β-methoxy ketone was obtained by reaction with β,γ-unsaturated ketone instead of α,β-unsaturated ketone under this Lewis acid promoted β-substitution reaction conditions. The β-substitution reaction did not occur when the carbon-carbon double bond isomerization process of β,γ-unsaturated ketone was inhibited. When a reaction mixture of 1-phenyl-pent-4-en-2-one and $BF_3{\cdot}OEt_2$ in THF was refluxed for 14 hours only 21% of 1-phenyl-pent-3-en-2-one (**I**) and 66% of starting material were obtained. These results showed that the isomerization rate is much faster in MeOH than in THF. Thus, we believed that the formation of β-substituted ketone proceeded firstly by the in situ isomerization of β,γ-unsaturated ketone to α,β-unsaturated ketone followed by the 1,4-addition reaction.

In conclusion, this Lewis acid promoted β-substitution reaction of β,γ-unsaturated ketone provides a simple and highly efficient method for synthesis of β-amino and β-alkoxy ketones. The C–N and C–O bonds are selectively formed on the β-position to the carbonyl group even if the acidic α-protons exist. The extension of this reaction to differently β-substituted β,γ-unsaturated ketones and α,β-unsatured ketones using this Lewis acid promoted β-substitution reactions is underway.

**Typical Procedure for the Synthesis of β-Methoxy Ketone**

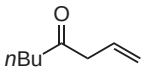
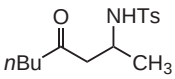
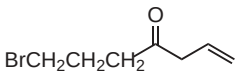
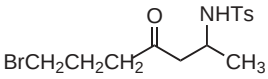
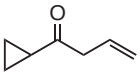
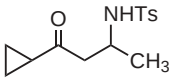
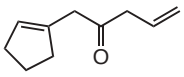
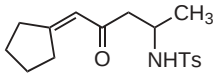
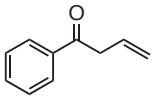
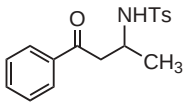
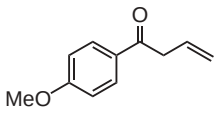
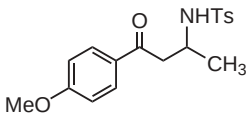
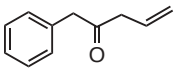
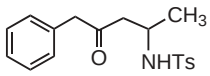
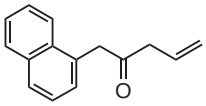
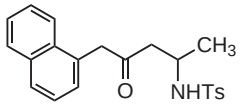
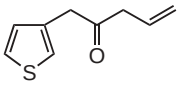
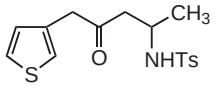
A reaction mixture of β,γ-unsaturated ketone (1.0 mmol) and $BF_3{\cdot}OEt_2$ (1.0 mmol) in anhyd $CH_3OH$ (5 mL) was stirred at r.t. After the reaction was completed (monitored by TLC), the organic solvent was removed directly under reduced pressure. Further purification was achieved by flash chromatography with EtOAc/hexane as eluant.



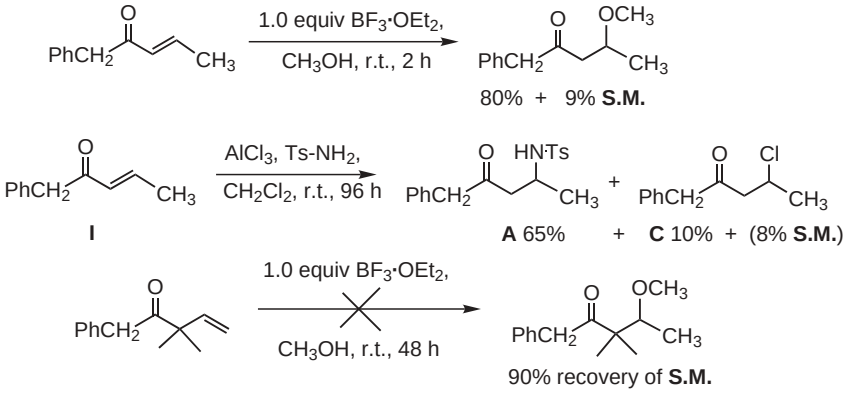

| | |
|---|---|
| * 1.0 $BF_3{\cdot}OEt_2$, 1.0 Ts-$NH_2$, $CH_2Cl_2$, r.t., 20 h | **A** (<3%) + Unknowns |
| * 0.5 $BF_3{\cdot}OEt_2$, 1.0 Ts-$NH_2$, $CH_2Cl_2$, r.t., 96 h | **A** (47%) + **I** (28%) |
| * 0.5 $AlCl_3$, 1.0 Ts-$NH_2$, $CH_2Cl_2$, r.t., 96 h | **A** (57%) + **I** (5%) + **C** (22%) |
| * 0.5 $ZrCl_4$, 1.0 Ts-$NH_2$,$CH_2Cl_2$, r.t., 96 h | **A** (46%) + **C** (9%) |
| * 0.5 $Me_3SiOTf$, 1.0 Ts-$NH_2$, $CH_2Cl_2$, r.t., 96 h | **A** (28%) |
| * 0.7 $AlCl_3$, 1.0 Ts-$NH_2$, $CH_2Cl_2$, r.t., 96 h | **A** (55%) + **I** (6%) + **C** (14%) |
| * 0.5 $AlCl_3$, 1.5 Ts-$NH_2$, $CH_2Cl_2$, r.t., 96 h | **A** (79%) + **I** (4%) + **C** (12%) |
| * 0.5 $AlCl_3$, 2.0 Ts-$NH_2$, $CH_2Cl_2$, r.t., 96 h | **A** (60%) + **I** (3%) + **C** (16%) |
| * 0.5 $ZrCl_4$, 1.5 Ts-$NH_2$, $CH_2Cl_2$, r.t., 96 h | **A** (57%) + **I** (4%) + **C** (8%) |

**Scheme 3**

**Table 2** Synthesis of β-Amino Ketones

| Entry | Substrate | Product | Time (h) | Yield[a] |
|---|---|---|---|---|
| 1 |  |  | 78 | 68% (0%, 4%)[b] |
| 2 |  |  | 61 | 51% (0%, 17%)[b] |
| 3 |  |  | 48 | 34% (0%, 20%)[b] |
| 4 |  |  | 50 | 39% (4%, 11%)[b] |
| 5 |  |  | 50 | 40% (6%, 23%)[b] |
| 6 |  |  | 96 | 69% (0%, 7%)[b] |
| 7 |  |  | 96 | 79% (4%, 12%)[b] |
| 8 |  |  | 96 | 66% (0%, 14%)[b] |
| 9 |  |  | 50 | 57% (4%, 19%)[b] |

[a] Yields were determined after chromatographic purification.
[b] Yields of α,β-unsaturated ketone and β-chloroketone.




**Scheme 4**

**Typical Procedure for the Synthesis of β-Amino Ketone**

The reaction mixture of β,γ-unsaturated ketone (1.0 mmol), $AlCl_3$ (0.5 mmol) and Ts-$NH_2$ (1.5 mmol) in anhyd $CH_2Cl_2$ (5 mL) was stirred at r.t. After the reaction was completed (monitored by TLC), the organic solvent was removed directly under reduced pressure. Further purification was achieved by flash chromatography with EtOAc/hexane as eluant.

## Acknowledgment

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