Synthesis of Chiral 1,3-Diketones from the Coupling Reaction of (+)-3z-Bromocamphor with Acyl Chlorides in the Presence of Samarium Diodide

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Some hindered chiral 1,3-diketones were successfully synthesized from the reaction of (+)-3z-bromocamphor with acyl chlorides in the presence of samarium diiodide (SmI₂) under mild reaction conditions in high yields.

Key words chiral 1,3-diketones, samarium diiodide, (+)-3z-bromocamphor.

Chiral 1,3-diketones have wide applications in stereochemical research. For example, they can be used as chiral ligands in asymmetric reactions, chiral stationary phase on GC and HPLC for the determination of enantiomeric excess, and separation of enantiomers. Furthermore, their lanthanide complexes can be used as optically active nuclear magnetic resonance chemical shift reagents for the direct determination of enantiomeric compositions. Until now, the main synthetic method used for the preparation of chiral 1,3-diketones has been the condensation of enolates with acyl chlorides or esters (Chart 1). However, in this approach, in addition to the chiral 1,3-diketones the O-acyl derivatives are also obtained as by-products in many cases. Especially for hindered 1,3-diketones, the compounds 2 could be the major products even when using modified reaction procedures, for example, using LDA or bromomagnesium disopropylamide (BrMgDA) as a base. Herein we wish to report an alternative and very useful synthetic method for the chiral 1,3-diketones promoted by samarium diiodide (SmI₂) in tetrahydrofuran (THF).

As a superior one-electron transfer reducing agent and coupling agent, samarium (II) diiodide has been widely utilized in organic synthesis in the past decade. The well-known coupling reactions promoted by SmI₂ are the Pinaocol coupling reaction and Wurtz-type coupling reaction. Moreover, recently Zhang and co-workers have reported that 3z-haloketones can reductively form samarium enolates which readily further react with acyl chlorides and esters to produce the 1,3-diketones. Based on those results, we used this new synthetic method to prepare chiral 1,3-diketones derived from (+)-3z-bromocamphor (3) (endo-form) in the presence of samarium (II) diiodide. First we examined this coupling reaction by carrying out the reaction of 3 (2 mmol) and heptafluorobutyryl chloride (2 mmol) in the presence of SmI₂ (4 mmol) in anhydrous THF for 2 h. The desired 1,3-diketone 4b was obtained as the sole product in 87% yield with specific rotation \([\alpha]_D^{20} +123 \; (c \; 2.6, \; CHCl_3)\), which is very similar to that of the authentic sample (purchased from Aldrich). Thus we can conclude that the chiral 1,3-diketone 4b could be obtained by this new synthetic method in very high yields under mild reaction conditions and its stereogenic center on C3 is the exo-form, which is the same as that prepared from the sodium enolate of camphor. This result strongly suggests that this coupling reaction proceeds

![Chart 1](image)

Table 1. Yields and Reaction Time for the Preparation of Chiral 1,3-Diketones 4a-h in the Presence of Samarium Diodide in THF

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>Reaction time</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Me</td>
<td>2.5</td>
<td>92</td>
</tr>
<tr>
<td>4b</td>
<td>C₆F₅</td>
<td>2.0</td>
<td>87</td>
</tr>
<tr>
<td>4c</td>
<td>Ph</td>
<td>2.3</td>
<td>86</td>
</tr>
<tr>
<td>4d</td>
<td>PhNO₂Ph</td>
<td>2.0</td>
<td>86</td>
</tr>
<tr>
<td>4e</td>
<td>PhMePh</td>
<td>3.0</td>
<td>90</td>
</tr>
<tr>
<td>4f</td>
<td></td>
<td>2.5</td>
<td>80</td>
</tr>
<tr>
<td>4g</td>
<td></td>
<td>2.5</td>
<td>90</td>
</tr>
<tr>
<td>4h</td>
<td></td>
<td>3.0</td>
<td>80</td>
</tr>
</tbody>
</table>

* Isolated yields.

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through a samarium enolate. Variousexo-form chiral 1,3-diketones were prepared by this reaction in high yields under mild reaction conditions (Chart 2, Table 1). It is noteworthy that many hindered chiral 1,3-diketones such as 4f—h(1) could be smoothly synthesized by this coupling reaction promoted by SmI₂. This indicates significant progress because using the classic synthetic methods or even the Whiteside modified procedure for hindered acyl chloride, the 1,3-diketones 4 are only obtained in 5—10% yield and the major products are O-acyl derivatives 2, 3a, 5). Moreover, another type of chiral 1,3-diketones 8a and 8b from the more hindered (+)3a-bromocamphor 7 can also be easily synthesized using this new synthetic method (Chart 3). The compound 5 was prepared from (+)-10-camphorsulfonic acid according to the method reported in the literature, which was then transferred to the compound 6 by treatment with thionyl chloride. The amide 7 was then obtained from the reaction of 6 with dicyclohexylamine in the presence of triethylamine in dichloromethane at room temperature. The coupling reaction of 7 with trifluoroacetyl chloride or heptafluorobutyril chloride in the presence of SmI₂ was carried out in the same manner as that described above to give 8a or 8b in good yield. We also examined the reaction of 7 with heptafluorobutyril chloride using LDA or BrMgDA as a base. We verified that 8b could not be formed using the classic synthetic method.

In conclusion, two types of hindered chiral 1,3-diketones 4g—h and 8a—b were successfully synthesized by the coupling reaction of (+)-3a-bromocamphor with the hindered acyl chloride or the hindered (+)-3a-bromocamphor with acyl chloride in the presence of SmI₂ in good yield. Those sterically bulky chiral 1,3-diketones are very attractive chiral sources in asymmetric reactions. The preparation of their various metal complexes (Co, V, Mn, Ni) is underway in order to begin studies of the asymmetric reaction using the novel chiral metal complexes.

Acknowledgments We thank the National Natural Sciences Foundation of China for financial support.

References and Notes


11) Typical reaction procedure for the preparation of chiral 1,3-diketone 4g. To a solution of SmI₂ (4 mmol) in anhydrous THF (40 ml) prepared from Sm and CH₂Cl₂ (+)-3a-bromocamphor (3) (462 mg, 2 mmol) was added and the reaction mixture was stirred for 0.5 h at 0°C. 9-Anthracencarboxyl chloride (460 mg, 2 mmol) was added to the mixture and further stirred for 2 h. The solvent was removed under reduced pressure and 5% HCl aqueous solution 10 ml was added to the residue. Then the mixture was extracted with ether and dried over MgSO₄. The solvent was again removed under reduced pressure and the residue was purified by flash chromatography to give 4g as a white solid. Yield: 641 mg, 90%; mp: 146—147°C; [α]D₂₀ = 12.4 (c = 0.14, CH₂Cl₂); IR (KBr) v: 1747 (C=O) cm⁻¹; 1H-NMR (300 MHz, CDCl₃) δ: 6.05 (3H, s, Me), 1.04 (3H, s, Me), 1.12 (3H, s, Me), 1.25—1.40 (1H, m), 1.42—1.62 (1H, m), 1.67—1.80 (1H, m), 1.96—2.10 (1H, m), 2.55 (1H, t, J = 3.6 Hz), 6.07 (1H, d, J = 3.6 Hz), 7.50—7.65 (4H, m, Ar), 8.05 (2H, d, J = 9.2 Hz, Ar), 8.14 (2H, d, J = 9.2 Hz, Ar), 8.58 (1H, s, Ar); MS (El) m/z 356 (M⁺); Anal. calcd. for C₂₅H₂₃O₂: C, 84.24; H, 6.79. Found: C, 84.32; H, 6.74%.