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

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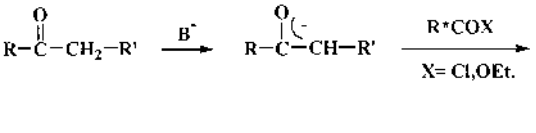
Some hindered chiral 1,3-diketones were successfully synthesized from the reaction of (+)-3α-bromocamphor with acyl chlorides in the presence of samarium diiodide (SmI_2) under mild reaction conditions in high yields.

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

Chiral 1,3-diketones **1** have wide applications in stereochemical research. For example, they can be used as chiral ligands in asymmetric reactions,[1] chiral stationary phase on GC and HPLC for the determination of enantiomeric excess, and separation of enantiomer.[2] Furthermore, their lanthanide complexes can be used as optically active nuclear magnetic resonance chemical shift reagents for the direct determination of enantiomeric compositions.[3] 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).[4] However, in this approach, in addition to the chiral 1,3-diketones **1** the O-acyl derivatives **2** 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 diisopropylamide (BrMgDA) as a base.[4c,5] Herein we wish to report an alternative and very useful synthetic method for the chiral 1,3-diketones promoted by samarium diiodide (SmI_2) 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.[6] The well-known coupling reactions promoted by SmI_2 are the Pinacolic coupling reaction[7] and Wurtz-type coupling reaction.[8] Moreover, recently Zhang and co-workers have reported that α-haloketones can reductively form samarium enolates which readily further react with acyl chlorides and esters to produce the 1,3-diketones.[9] Based on those results, we used this new synthetic method to prepare chiral 1,3-diketones derived from (+)-3α-bromocamphor (**3**) (endo-form)[10] 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 SmI_2 (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.[3a] This result strongly suggests that this coupling reaction proceeds



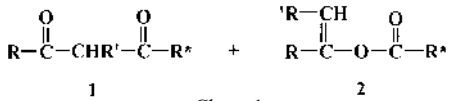


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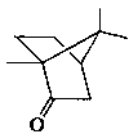
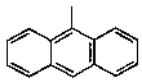
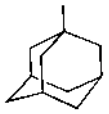
Chart 1

Table 1. Yields and Reaction Time for the Preparation of Chiral 1,3-Diketones **4a**—**h** in the Presence of Samaium Diiodide in THF

No.	R	Reaction time [h]	Yield[a] [%]
4a	Me	2.5	92
4b	C_3F_7	2.0	87
4c	Ph	2.3	86
4d	*p*-NO_2Ph	2.0	86
4e	*p*-MePh	3.0	90
4f		2.5	80
4g		2.5	90
4h		3.0	80

a) Isolated yields.

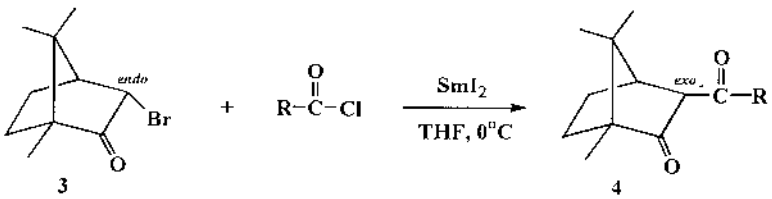


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Chart 2

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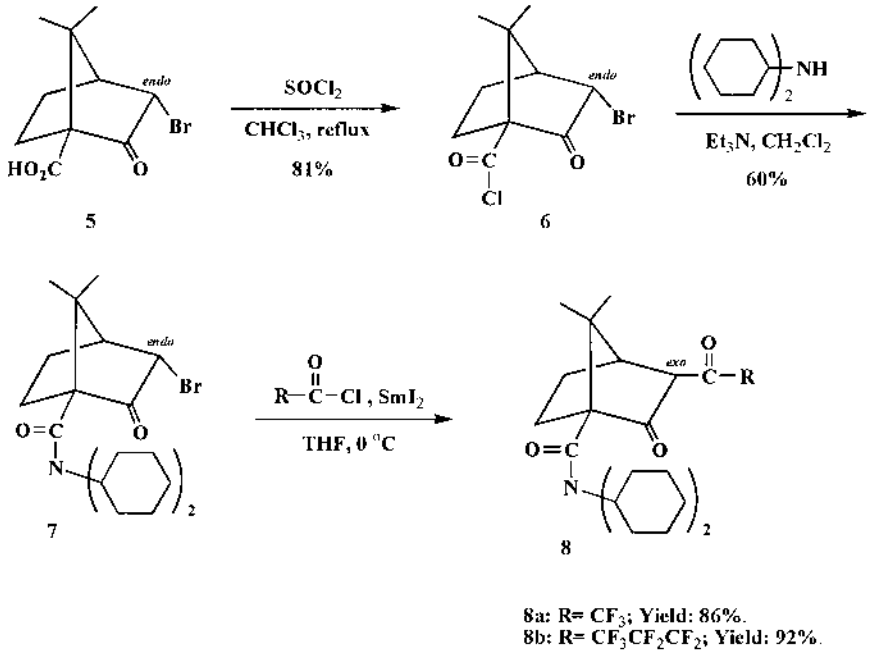

Chart 3

through a samarium enolate. Various exo-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**[11] could be smoothly synthesized by this coupling reaction promoted by SmI_2. 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**.[4a,5] Moreover, another type of chiral 1,3-diketones **8a** and **8b** from the more hindered (+)-3α-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,[10,12] 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 heptafluorobutyryl chloride in the presence of SmI_2 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 heptafluorobutyryl 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 (+)-3α-bromocamphor with the hindered acyl chloride or the hindered (+)-3α-bromocamphor with acyl chloride in the presence of SmI_2 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.

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11) Typical reaction procedure for the preparation of chiral 1,3-diketone **4g**. To a solution of SmI_2 (4 mmol) in anhydrous THF (40 ml) prepared from Sm and CH_2I_2 (+)-3α-bromocamphor (**3**) (462 mg, 2 mmol) was added and the reaction mixture was stirred for 0.5 h at 0 °C. 9-Anthracenecarbonyl 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 $MgSO_4$. 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; $[\alpha]_D$ −12.4 (*c* 0.14, CH_2Cl_2); IR (KBr) *v*: 1747 (C=O) cm^{-1}; ^{1}H-NMR (300 M, $CDCl_3$) δ: 0.85 (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 (EI) *m/z* 356 (M^+); *Anal*. calcd. for $C_{25}H_{24}O_2$: C, 84.24; H, 6.79. Found: C, 84.32; H, 6.74%.
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