

Stereo- and regiospecific four-molecule reaction of aroyl chlorides with *iso*-pentylene: direct formation of (*E*)- β,γ -unsaturated carbonyl compounds promoted by samarium metal in DMF

Yongjun Liu^a and Yongmin Zhang^{a,b,*}

^aDepartment of Chemistry, Zhejiang University (Campus Xixi), Hangzhou 310028, PR China

^bState Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, PR China

Received 9 July 2003; revised 18 November 2003; accepted 21 November 2003

Abstract—Promoted by samarium metal in DMF, aroyl chlorides react readily with *iso*-pentylene in a four-molecule manner, which offers an efficient stereo- and regiospecific synthesis of (*E*)- β,γ -unsaturated carbonyl compounds and also provides a facile method for the construction of monoterpene skeleton. The reaction is an additional example of organic reactions mediated by direct use of unactivated metallic samarium.

© 2003 Elsevier Ltd. All rights reserved.

Though SmI_2 is a useful reducing reagent,¹ however, its application in organic synthesis is limited to some extent. For example, Sm^{2+} has only one electron to give, which seriously restricts its application in large scale. Therefore, the direct use of metallic samarium as a reducing agent in organic transformations has attracted the attention of many organic chemists.² In most cases, the reactions promoted by samarium were carried out in THF,³ and metallic samarium had to be activated or pretreated by various methods so as to ensure the reactions proceeding smoothly.^{3,4} Until now, only a few reports were found concerning organic reactions promoted efficiently by metallic samarium without activation or pretreatment.⁵ In our investigations on the applications of metallic samarium in organic synthesis, we have recently found that metallic samarium, in the absence of any activator, exhibited some extraordinary capabilities when *N,N*-dimethylformamide (DMF) was used as reaction medium instead of THF.⁶

β,γ -Unsaturated carbonyl moieties, known to exist in natural products, serve as versatile intermediates in organic transformations⁷ and have wide application in natural product synthesis.^{7a,b} A number of synthetic

methodologies have appeared,⁸ however, few general preparative methods are available and the synthesis is usually complicated mainly due to a proclivity toward prototropic rearrangement producing conjugated α,β -unsaturated isomers. To develop a more convenient and efficient method for the preparation of β,γ -unsaturated carbonyl compounds is of practical importance and still in demand.

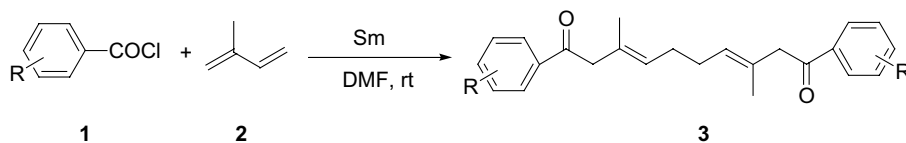
We now report a novel and facile synthesis of (*E*)- β,γ -unsaturated ketone compounds promoted by metallic samarium. As shown in Scheme 1, samarium, without any activation or pretreatment, can promote a four-molecule reaction of aroyl chlorides **1** and *iso*-pentylene **2** to afford (*E*)- β,γ -unsaturated ketones **3** when DMF is used as a solvent.

The reaction proceeds smoothly and efficiently in both stereo- and regiospecific manner, and resulting a variety of the corresponding (*E,E*)-3,8-dimethyl-1,10-diaryl-deca-3,7-diene-1,10-diones **3** in good yields (Table 1).⁹

The results show that the substituents on the aromatic rings does not have notable effects on the yields of product **3**, though a relative longer time was required to complete the reaction when R are electron-donating groups. Attempts to extend the reaction to aliphatic acid chlorides were not successful and lead to a complex mixture (entries 9 and 10). Although the physical data

Keywords: Samarium; DMF; Aroyl chloride; *iso*-Pentylene; (*E*)- β,γ -Unsaturated ketone; Terpenoid; Stereo- and regiospecific reaction.

* Corresponding author. E-mail: yminzhang@mail.hz.zj.cn



Scheme 1.

Table 1. Sm-promoted four-molecule reaction of aryl chlorides with *iso*-pentylene to afford (*E*)- β,γ -unsaturated ketones in DMF¹⁰

| Entry | Substrate 1 | Time (h) | Yield of product 3 ^a |
|-------|--|----------|---------------------------------|
| 1 | C ₆ H ₅ COCl (1a) | 3 | 92 (3a) |
| 2 | 4-F-C ₆ H ₄ COCl (1b) | 3 | 94 (3b) |
| 3 | 4-CH ₃ -C ₆ H ₄ COCl (1c) | 3 | 87 (3c) |
| 4 | 4-Cl-C ₆ H ₄ COCl (1d) | 3 | 82 (3d) |
| 5 | 4-CH ₃ O-C ₆ H ₄ COCl (1e) | 5 | 90 (3e) |
| 6 | 3-CH ₃ -C ₆ H ₄ COCl (1f) | 2 | 76 (3f) |
| 7 | 3-Cl-C ₆ H ₄ COCl (1g) | 1 | 65 (3g) |
| 8 | (1h) | 5 | 61 (3h) |
| 9 | PhCH ₂ COCl | 5 | — ^b |
| 10 | CH ₃ CH ₂ COCl | 5 | — ^b |

^a Isolated yields based on aryl chlorides.^b A complex mixture was obtained.

(¹H NMR, ¹³C NMR, IR, MS, and elemental analysis) of product **3** shows that it must be a four-molecule coupling product, the coupling of some protons is weak

as indicated in ¹H NMR.¹⁰ To further ascertain the structure, a single-crystal X-ray diffraction study of **3b** was done and it was determined unambiguously that product **3** is in *E,E*-configuration (Fig. 1). The chain elongation was realized regioselectively by combining two isoprene units in a 'head-to-head' direction with two aryl groups attaching, respectively, on the 'tail' of each of the isoprene unit. The fact that all the products share the same NMR patterns suggests the stereochemistry of these compounds should be identical.

According to the experimental results, we suggested that the mechanism may involve a radical procedure (Scheme 2). Firstly, an aryl radical is formed with the reduction of samarium and the 1-position of *iso*-pentylene is attacked intermediately to give the intermediate **A**, which is more stable than **A'**. In an equilibrium **A** rearranges to intermediate **B**, which then dimerizes to afford product **3** in a sterically more favored *E,E*-configuration.¹¹

The adoption of DMF as the reaction medium is crucial. If THF is used as a solvent instead, this reaction did not

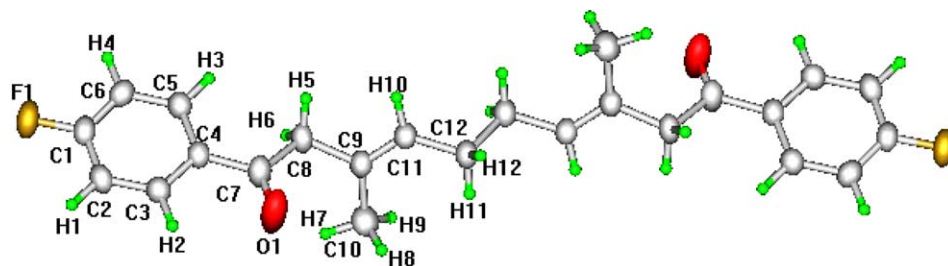
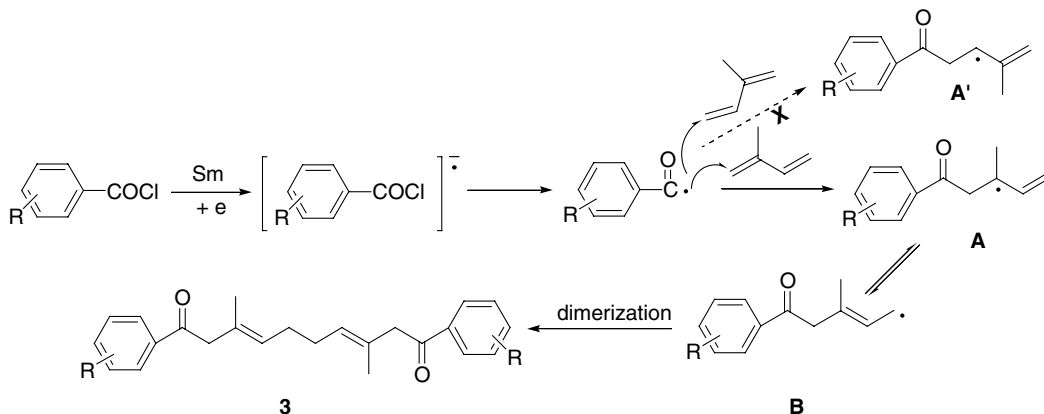


Figure 1.



Scheme 2.

occur, even the self-coupling products of aroyl chloride can hardly be achieved.¹² As a solvent with strong polarity and excellent dissolubility, DMF may play an important role in stabilizing the intermediates and dissolving samarium salt, thus ensuring the reaction to proceed smoothly.

Products **3** containing 1,5-diene moieties are in fact isoprenoid compounds. Most of the isoprenoids are biosynthesized from the universal precursors such as isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP),^{13a–d} A variety of artificial methods were also developed for their syntheses.^{13e,f,g}

In conclusion, the samarium-promoted four-molecule reaction of aroyl chlorides with *iso*-pentylene afforded an unprecedentedly efficient, highly selective protocol for the synthesis of stereo- and regiodefined β,γ -unsaturated ketones, it provides an extremely facile method for the construction of monoterpene skeleton, which is useful in the natural products syntheses. As a result of direct use of metallic samarium without activator, simple equipment and material, short reaction time, facile operation procedure, mild reaction conditions, as well as high potential for large-scale preparation, this innovating reaction would offer one of the most promising method for the synthesis of such compounds.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (Project No. 20072033) and Specialized Research Fund for the Doctoral Program of Higher Education of China.

References and notes

- (a) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698; (b) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745–777; (c) Molander, G. A. *Acc. Chem. Res.* **1998**, *31*, 603–609; (d) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321–3354; (e) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338; (f) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68.
- Reviews: Banik, B. K. *Eur. J. Org. Chem.* **2002**, 2431–2444.
- (a) Ogawa, A.; Nanke, T.; Takami, N.; Sumino, Y.; Ryu, I.; Sonoda, N. *Chem. Lett.* **1994**, 379–380; (b) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778–1786; (c) Imamoto, T.; Takeyama, T.; Koto, H. *Tetrahedron Lett.* **1986**, *27*, 3243–3246; (d) Yanada, R.; Negoro, N.; Okaniwa, M.; Miwa, Y.; Taga, T.; Yanada, K.; Fujita, T. *Synlett* **1999**, 537–540; (e) Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729–8730; (f) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942–3944.
- (a) Wang, L.; Zhang, Y. *Tetrahedron* **1998**, *54*, 11129–11140; (b) Banik, B. K.; Mukhopadhyay, C.; Venkatraman, M. S.; Becker, F. F. *Tetrahedron Lett.* **1998**, *39*, 7243–7246; (c) Yanada, R.; Negoro, N.; Yanada, K.; Fujita, T. *Tetrahedron Lett.* **1997**, *38*, 3271–3274; (d) Yanada, R.; Bessho, K.; Yanada, K. *Chem. Lett.* **1994**, 1279–1282; (e) Komachi, Y.; Kudo, T. *Chem. Pharm. Bull.* **1994**, *42*, 402–404; (f) Komachi, Y.; Kudo, T. *Chem. Pharm. Bull.* **1995**, *43*, 1422–1424; (g) Ghatak, A.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2000**, *41*, 3793–3796; (h) Talukdar, S.; Fang, J.-M. *J. Org. Chem.* **2001**, *66*, 330–333.
- (a) Hou, Z.; Fujiwara, Y.; Taniguchi, H. *J. Org. Chem.* **1988**, *53*, 3118–3120; (b) Yanada, R.; Negoro, N. *Tetrahedron Lett.* **1996**, *37*, 9313–9316; (c) Wang, L.; Li, P.; Zhou, L. *Tetrahedron Lett.* **2002**, *43*, 8103–8105.
- (a) Liu, Y. J.; Liu, X.; Zhang, Y. M. *Tetrahedron Lett.* **2003**, *44*, 1667–1670; (b) Liu, Y. J.; Zhang, Y. M. *Tetrahedron Lett.* **2003**, *44*, 4291–4294.
- (a) Wilsey, S.; Bearpark, M. J.; Bernardi, F.; Olivucci, M.; Robb, M. *J. Am. Chem. Soc.* **1996**, *118*, 176–184; (b) Ohtsuka, Y.; Sasahara, T.; Oishi, T. *Chem. Pharm. Bull.* **1982**, *30*, 1106; (c) Zaidlewicz, M. *Synthesis* **1988**, 701; (d) Mathew, J. J. *J. Org. Chem.* **1991**, *56*, 713–716; (e) Smith, A. B., III, Toder, B. H.; Branca, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 3995–4001; (f) Houk, K. N. *Chem. Rev.* **1976**, *76*, 1; (g) Demuth, M. *Org. Photochem.* **1991**, *11*, 37; (h) Armesto, D.; Ortiz, M. J.; Romano, S. *Tetrahedron Lett.* **1995**, *36*, 965–968; (i) Eckersley, T. J.; Parker, S. D.; Rogers, N. A. J. *Tetrahedron* **1984**, *40*, 3749–3758.
- (a) Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645–2646; (b) Ferré, K.; Mignot, P. L.; Sinbandhit, S.; Toupet, L.; Guerschais, V. *Chem. Commun.* **2000**, 1405–1406; (c) Lee, C.-W.; Hong, J. E.; Oh, D. Y. *J. Org. Chem.* **1995**, *60*, 7027–7029; (d) Hirao, T.; Masunaga, T.; Hayashi, K.-I. *Tetrahedron Lett.* **1983**, *24*, 399–400; (e) Ohtsuka, Y.; Sasahara, T.; Oishi, T. *Chem. Pharm. Bull.* **1982**, *30*, 1106–1109; (f) Baruah, B.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **1996**, *37*, 9087–9088; (g) Kachinsky, J. L. C.; Salomon, R. G. *J. Org. Chem.* **1986**, *51*, 1393–1401; (h) Suzuki, K.; Katayama, E.; Tsuchihashi, G. *Tetrahedron Lett.* **1984**, *25*, 1817–1820; (i) Marceau, P.; Gautreau, L.; Béguin, F. *J. Organomet. Chem.* **1991**, *403*, 21–27; (j) Hegde, S. G.; Wolinsky, J. *Tetrahedron Lett.* **1981**, *22*, 5019–5022; (k) Jun, C.-H. *J. Organomet. Chem.* **1990**, *390*, 361–370; (l) Salamon, R. G.; Kachinsky, J. L. C. *J. Org. Chem.* **1986**, *51*, 1393–1401.
- A typical procedure is as follows: To a mixture of Sm powder (1 mmol), *iso*-pentylene (4 mmol) in freshly distilled *N,N*-dimethylformamide (DMF, 10 mL), benzoyl chloride (2 mmol, freshly distilled) was added at room temperature with magnetic stirring under a nitrogen atmosphere. The resulting solution turned yellow-green within 30 min. After the completion of the reaction (about 3 h), a routine workup of the reaction mixture followed by column chromatography afforded (*E,E*)-3,8-dimethyl-1,10-diphenyl-deca-3,7-diene-1,10-dione in 92% yield.
- All of the products obtained in this study were characterized (¹H NMR, ¹³C NMR, MS, IR, EA). For example, (*E,E*)-1,10-bis-(4-fluoro-phenyl)-3,8-dimethyl-deca-3,7-diene-1,10-dione (**3b**): White solid. Mp: 102–104 °C. ν_{\max} (KBr)/cm⁻¹: 2973, 1688, 1596, 1504, 1457. δ_{H} (CDCl₃): 8.00–8.03 (4H, m, *ArH*), 7.11–7.15 (4H, m, *ArH*), 5.29 (2H, s, -(Me)C=CH-CH₂-), 3.61 (4H, s, *ArCOCH*₂-(Me)C=CH-), 2.12 (4H, t, -(Me)C=CH-CH₂-), 1.68 (6H, s, -CH₃). ¹³C NMR δ (CDCl₃): 197.8, 167.1, 164.6, 134.2, 134.1, 132.1, 132.0, 130.6, 129.1, 116.6, 116.4, 49.4, 28.4, 17.3. *m/z* (%): 383 (M⁺+1, 0.89), 382 (M⁺, 3.16), 259 (0.66), 244 (0.99), 191 (6.35), 123 (100.00), 95 (34.70). Anal. Calcd for C₂₄H₂₄F₂O₂: C, 75.37; H, 6.32. Found: C, 75.44; H, 6.30.
- Tanko, J. M.; Drumright, R. E.; Suleman, N. K.; Brammer, L. E., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 1785–1791.
- Liu, Y. S.; Jiang, T.; Bei, M. Z. *Chem. J. Chin. Univer.* **1993**, *14*, 54–55.

13. (a) Sacchetti, J. C.; Poulter, C. D. *Science* **1997**, *277*, 1788–1789; (b) Amslinger, S.; Kis, K.; Hecht, S.; Adam, P.; Rohdich, F.; Arigoni, D.; Bacher, A.; Eisenreich, W. *J. Org. Chem.* **2002**, *67*, 4590–4594; (c) Bohlmann, J.; Meyer-Gauen, G.; Croteau, R. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 4126–4133; (d) Jackson, B. E.; Hart-Wells, E. A.; Matsuda, S. P. T. *Org. Lett.* **2003**, *5*, 1629–1632; (e) Negishi, E.-i.; Liou, S.-Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, *4*, 261–264; (f) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955–8956; (g) McMurry, J. E.; Bosch, G. K. *J. Org. Chem.* **1987**, *52*, 4885–4893.