Trace amount of metallic samarium catalysed aroyl substitution reactions of a β-keto ester in air

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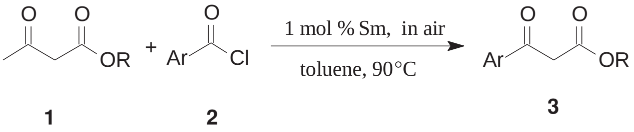
Catalysed by a trace amount of metallic samarium, a β-keto ester can react readily with aroyl chlorides to afford 3-oxo-arylpropionic acid esters in good yields. The reaction proceeds in air with toluene as solvent, which is not purified before use.

Keywords: samarium, β-keto ester, aroyl chlorides, catalysis

Since the time Kagan had shown a simple method for the preparation of samarium diiodide from samarium metal and 1,2-diiodoethane,[1] SmI_2 has been widely used in organic synthetic chemistry.[2] Reports of using SmI_3 as a Lewis acid in organic chemistry have also increased rapidly in these years.[3] Recently, direct use of metallic samarium as a reducing agent in organic transformations has drawn the attention of many organic chemists.[4] However, many of these reactions promoted by samarium reagents must be accomplished in anhydrous conditions and under argon, requiring equivalent or excessive amount of samarium reagents due to their acting as reducing and coupling reagents.[1,2] As far as the reaction directly promoted by metallic samarium is concerned, an equivalent amount of samarium is necessary activated by some reagents, such as iodine, hydrochloric acid, and alkyl halides, *etc*.[4,5,6] Until now, there have been no reports on directly using samarium as a catalyst in organic synthesis, especially using trace amounts of samarium. Moreover, THF or acetonitrile, which always require purifying beforehand in order to adapt the anhydrous condition under argon, are generally used as solvent for samarium reagents.[1,2,3b,3c] Other organic solvents have rarely been seen for samarium reagents, except a few examples such as using ionic liquid[7] and DMF.[8] To the best of our knowledge, toluene, which is much cheaper and more available in chemical industry is never used as solvent for samarium reagents.

Recently, an α-acylated ester was obtained from the reaction of a β-keto ester with acyl or aroyl chloride promoted by magnesium and ethanol in anhydrous toluene.[9] 2-Acetyl-3-hydroxy-3-phenyl-acrylic acid *tert*-butyl ester was also obtained from the reaction of *tert*-butyl acetoacetate and benzoyl chloride induced by magnesium chloride.[10] The reaction of 3-oxo-butyric acid ester and aroyl chloride was studied previously.[11] An equivalent amount of ethyl acetoacetate and benzoyl chloride with a slight excess of NaOH in aqueous solution afforded 3-oxo-arylpropionic acid ester. However, the yield is poor (less than 50%) and the major by-product was 2-benzoyl-3-oxo-3-phenyl-propionic acid ethyl ester. Our group has recently reported that under the promotion of Sm (III) iodide, 2,4-pentanedione can react with aroyl chloride to afford 1-phenyl-butane-1,3-dione or 1,3-diphenyl-propane-1,3-dione.[3d]

Here we wish to report that, catalysed by metallic samarium, β-keto ester **1** can react readily with aroyl chlorides **2** to afford 3-oxo-arylpropionic acid ester **3** in good yields (Scheme 1). The reaction condition is not so rigorous as most of others, which generally require anhydrous conditions and an argon atmosphere. It is carried out in the air with toluene as solvent, which is directly used without further purification. Furthermore, only a trace amount of samarium is necessary for this reaction and its catalytic effect is considerable.



Scheme 1

In the beginning of our study, benzoyl chloride, 3-oxo-butyric acid ethyl ester and equivalent samarium powder were used in anhydrous conditions under a dinitrogen atmosphere, with toluene as solvent (freshly distilled from sodium). We found that the appropriate temperature is 90 °C. A poor yield of 3-oxo-arylpropionic acid esters was obtained when the temperature is lower, while complicated byproducts occurred if the reaction proceeded in refluxing condition. Interestingly, we tried to carry out the reaction in air (90 °C) and got the same results as that seen in anhydrous conditions and under dinitrogen.

Further investigation indicated that most of the samarium remained when the reaction was completed. However, the yield was very poor (less than 20%) if the reaction proceeded in the absence of samarium. In view of this, we presumed that samarium might have a catalytic effect and its amount could be reduced. After doing a series of reactions using ethyl acetoacetate and benzoyl chloride as substrates catalysed by different amount of metallic samarium, we found that the appropriate amount of samarium was 1 mol%. The results of these trials are listed in Table 1. We can neither reduce the reaction time nor improve the yields if we increase the amount of samarium above 1 mol%.

In air, using toluene as solvent without further purification and 1 mol% of samarium as catalyst, a variety of aroyl chlorides and 3-oxo-butyric acid ester reacted to afford 3-oxo-arylpropionic acid esters in moderate to good yields. The results are listed in Table 2.

The influence of the substituting group attached on the benzene ring of the aroyl chloride is manifest. When aroyl chlorides contain electron-withdrawing groups, the yields of corresponding products are higher (Entries 1, 2, and 3) while

Table 1 The yields of reaction under different amounts of samarium at different times.

Entry	The amount of Sm/mol%[a]	Reaction time/h	Yield/%
1	100	8	15
2	100	20	50
3	100	30	75
4	10	30	75
5	1	8	15
6	1	20	50
7	1	30	75
8	0.5	45	25
9	0	45	12

[a]The reaction proceed at 90 °C using toluene as solvent.

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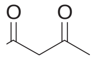
Table 2 Trace amount of samarium catalysed acyl substitution reaction of 3-oxo-butyric acid ester in air

Entry	Ar	R	Isolated yield (%) of **3**[a]	Reaction time/h
1	4-$\mathrm{FC_6H_4}$	$\mathrm{CH_2CH_3}$	(**3a**) 90 [b] (0) [c]	44
2	4-$\mathrm{BrC_6H_4}$	$\mathrm{CH_3}$	(**3b**) 85 (0)	44
3	2-$\mathrm{ClC_6H_4}$	$\mathrm{CH_3}$	(**3c**) 80 (0)	36
4	2-furyl	$\mathrm{CH_3}$	(**3d**) 78 (10)	36
5	2-furyl	$\mathrm{CH_2CH_3}$	(**3e**) 77 (10)	30
6	$\mathrm{C_6H_5}$	$\mathrm{CH_3}$	(**3f**) 75 (14)	30
7	$\mathrm{C_6H_5}$	$\mathrm{CH_2CH_3}$	(**3g**) 75 (15)	30
8	2-$\mathrm{CH_3OC_6H_4}$	$\mathrm{CH_2CH_3}$	(**3h**) 75 (5)	42
9	4-$\mathrm{CH_3OC_6H_4}$	$\mathrm{CH_2CH_3}$	(**3i**) 65 (10)	33
10	2-$\mathrm{IC_6H_4}$	$\mathrm{CH_3}$	(**3j**) 65 (0)	30
11	$\mathrm{C_6H_5CH_2}$	$\mathrm{CH_3}$	(**3k**)— (0)	32
12	*p*-toluene-sulfonyl	$\mathrm{CH_2CH_3}$	(**3l**) 0 (0)	96
13	$\mathrm{C_6H_5}$		(**3m**) 20 (0)[d]	48
14	$\mathrm{C_6H_5}$	$\mathrm{CH_2CH_3}$	(**3g**) 25[e]	30
15	$\mathrm{C_6H_5}$	$\mathrm{CH_2CH_3}$	(**3g**) 77[f]	36
16	4-$\mathrm{BrC_6H_4}$	$\mathrm{CH_2CH_3}$	(**3b**) 85[f]	36

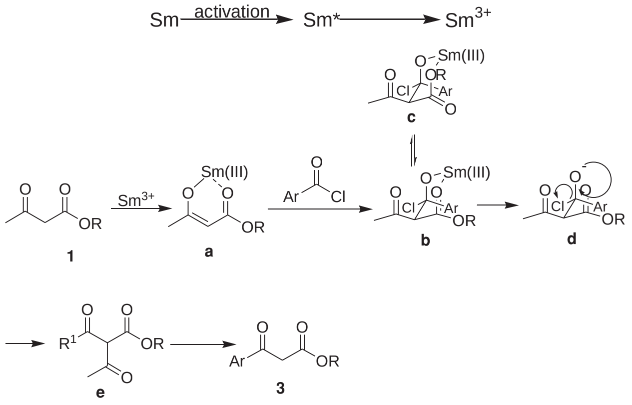
[a] Isolated yields based on β-keto ester. [b] The reaction proceeded with 1 mol % samarium. [c] The reaction proceeded in the absence of samarium. [d] 2,4-Pentanedione was subjected to the same reaction conditions. [e] The reaction proceeded in anhydrous acetonitrile under dinitrogen with 1 mol % samarium. [f] The reaction proceeded with 1mol % samarium(III) iodide instead of 1 mol% samarium under the same conditions.

the yields are comparatively lower if electron-donating groups substitute the aryl chlorides (Entries 8, 9). However, 2-iodobenzoyl chloride, which contains a electron-withdrawing group also gives a poor yield, probably due to the steric hindrance (Entry 10). In this reaction, 3-oxo-arylpropionic acid ester is the exclusive product. As far as some reactions of low yields (for example: Entry 9) are concerned, prolonging the reaction time can not convert the unreacted β-keto esters to corresponding products.

Only aroyl chloride was good for this kind of reaction. When phenyl-acetyl chloride reacts with 3-oxo-butyric acid methyl ester it gives complex products (Entry 11). *p*-Toluenesulfonyl chloride was also used as a substrate, however, it did not react at all (Entry 12).

We thought that, catalysed by samarium, 2,4-pentanedione which contains two acetyl groups, may also react with aroyl chloride. Therefore, 1 mol 2,4-pentanedione and 2.2 mol benzoyl chloride were subjected to the same reaction conditions, however, only a small amount of 1,3-diphenyl-propane-1, 3-dione was obtained (Entry 13). This might be attributed to the fact that 1,3-diphenyl-propane-1,3-dione cannot form an intermediate such as **c** (Scheme 2) compared with the β-keto ester. This reaction was also conducted in refluxing acetonitrile and anhydrous conditions with the protection of dinitrogen, however, the yield of **3** is poor (Entry 14).

The mechanism of this reaction is not clear. Our group has recently reported the reaction of pentane-2,4-dione and aroyl chloride mediated by Sm (III) iodide, which acts as Lewis acid.[3d] We also used 1 mol% $\mathrm{SmI_3}$ instead of samarium under the same conditions to promote this reaction and obtained the corresponding products of almost same yields (Entries 15, 16). In the report on the reaction of magnesium chloride and 3-oxo-butyric acid ester, magnesium enolate was referred to.[10] Due to the similarity of samarium to magnesium in oxophilicity,[12] we presume that it may undergo the following process (Scheme 2). The reaction of a trace amount of aroyl acid in aroyl chloride with metallic samarium afford activated samarium, which is then converted to Sm (III). β-Keto ester reacts with samarium (III) to form the samarium enolate **a** and it attacks the carbonyl group of aroyl chloride to afford the intermediate **b**. Then chloride ion leaves and an intermediate **e** containing three acyl group on one carbon is formed. The most strongly acidic one of these acyl groups in **e** is then cleaved[13] and the corresponding 3-oxo-arylpropionic acid ester **3** is obtained.



Scheme 2

As a result of directly using a trace amount of metallic samarium, this reaction will surely be economical in practical use. Its operation is convenient since the reaction can proceed in the air and its solvent needs no further purification. All these data indicate that it may be a good way to substitute the acyl group of 3-oxo-butyric acid ester by an aroyl group.

Experimental

General: Infrared spectra were recorded on an IR-408 spectrometer in film with absorption in cm^{-1}. ^{1}H NMR spectra were determined in a Bruker AC–400 spectrometer as $\mathrm{CDCl_3}$ solutions. *J* values are in Hertz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on a HP 5989B MS spectrometer. Microanalysis was carried out on a EA 1110 instrument. The reaction was monitored by TLC, and the products were isolated by silica gel column chromatography using ethyl acetate and cyclohexane (1 : 15) as eluant.

Typical procedure for the synthesis of product **3f**: Samarium powder (0.003 g, 0.02 mol) and toluene (20 ml) were added to a three-neck flask and the temperature was raised to 90 °C. Then benzoyl chloride (0.28 ml, 2.4 mmol freshly distilled) and 3-oxo-butyric acid methyl ester (0.216 ml, 2 mmol) were injected. After being stirred for a given time (Table 1, the reaction was monitored by TLC), the reaction was quenched with dilute HCl (0.1 mol/l, 5 ml) and extracted with ether (3 × 30 ml). The organic phase was washed with water (20 ml), saturated brine (15 ml), and dried over anhydrous $\mathrm{Na_2SO_4}$. The solvents were removed under reduced pressure to give the crude product, which was purified to afford in 75% yield.

3-(4-Fluoro-phenyl)-3-oxo-propionic acid ethyl ester (**3a**): Oil. ν_{max}(film)/cm^{-1}: 3112, 3077, 1741, 1688, 1598, 1508. δ_H($\mathrm{CDCl_3}$): 7.92–8.00 (2H, m), 7.13–7.71 (2H, m), 4.21 (2H, q, *J*=7.2), 3.98 (2H, s), 1.26 (3H, t, *J*=7.2). *m/z*(%): 210 (M^+, 4.75), 123 (100), 165 (4.41), 95 (36.10). Anal. $\mathrm{C_{11}H_{11}FO_3}$. C, 62.85; H, 5.27. Found C, 62.76; H, 5.24%

3-(4-Bromo-phenyl)-3-oxo-propionic acid methyl ester (**3b**): Oil. ν_{max}(film)/cm^{-1}: 3092, 3064, 2922, 2851, 1743, 1686. δ_H($\mathrm{CDCl_3}$): 7.80–7.83 (2H, m), 7.63–7.66 (2H, m), 3.98 (2H, s), 3.76 (3H, s). *m/z*(%): 258 (M^++2, 23.68), 257 (M^++1, 35.05), 256 (M^+, 20.76), 241 (5.67), 225 (4.38), 185 (94.73), 183 (100), 155 (2.69), 157 (2.55), 105 (5.34). Anal. $\mathrm{C_{10}H_9BrO_3}$. C, 46.72; H, 3.53. Found C, 46.59; H, 3.55%

3-(2-Chloro-phenyl)-3-oxo-propionic acid methyl ester (**3c**): Oil. ν_{max}(film)/cm^{-1}: 2924, 2851, 1746, 1702. δ_H($\mathrm{CDCl_3}$): 7.31–7.62 (4H, m), 4.06 (2H, s), 3.74 (3H, s). *m/z*(%): 215 (M^++3, 1.81), 213 (M^++1, 5.63), 212 (M^+, 1.09), 177 (47.77), 139 (100), 141 (34.29), 111 (28.26), 113 (10.00). Anal. $\mathrm{C_{10}H_9ClO_3}$. C, 56.49; H, 4.27. Found C, 56.29; H, 4.25%

3-Furan-2-yl-3-oxo-propionic acid methyl ester (**3d**): Oil. ν_{max}(film)/cm^{-1}: 2922, 2852, 1741, 1672, 1569. δ_H($\mathrm{CDCl_3}$): 7.616–7.620 (1H, m), 7.27–7.29 (1H, m), 6.57–6.59 (1H, m), 3.87 (2H, s), 3.75 (3H, s). *m/z*(%): 168 (M^+, 12.67), 95 (100), 137 (4.48). Anal. $\mathrm{C_8H_8O_4}$. C, 57.14; H, 4.80. Found C, 57.23; H, 4.78%.

3-Furan-2-yl-3-oxo-propionic acid ethyl ester **(3e)**: Oil. ν_{max}(film)/cm^{-1}: 3135, 2927, 1741, 1679. δH(CDCl$_3$): 7.626–7.628 (1H, m), 7.28–7.29 (1H, m), 6.57–6.59 (1H, m), 4.21 (2H, q, J = 7.2 Hz), 3.86 (2H, s), 1.26 (3H, t, J = 7.2 Hz). ^{13}C NMR δ(CDCl$_3$): 181.4, 167.4, 152.4, 147.4, 118.7, 113.1, 61.9, 45.9, 14.4. *m/z*(%): 183 (M$^+$ + 1, 8.76), 182 (M$^+$, 13.62), 137 (9.85), 95 (100.00). Anal. $C_9H_{10}O_4$. C, 59.34; H, 5.53. Found C, 59.39; H, 5.51 %.

3-Oxo-3-phenyl-propionic acid methyl ester **(3f)**: Oil. ν_{max}(film)/cm^{-1}: 3063, 2954, 1745, 1686. δ$_H$(CDCl$_3$): 7.49–7.93 (5H, m), 3.99 (2H, s), 3.77 (3H, s). *m/z*(%): 178 (M$^+$, 4.35), 105 (100), 59 (9.43). Anal. $C_{10}H_{10}O_3$. C, 67.41; H, 5.66. Found C, 67.37; H, 5.63%

3-Oxo-3-phenyl-propionic acid ethyl ester **(3g)**: Oil. ν_{max}(film)/cm^{-1}: 3064, 2982, 2928, 1741, 1687. δ$_H$(CDCl$_3$): 7.60–7.98 (5H, m), 4.23 (2H, q, J=7.2), 4.01 (2H, s), 1.27 (3H, t, J=7.2). *m/z*(%): 193 (M$^+$+1, 25.16), 192 (M$^+$, 5.16), 105 (100), 147 (3.96), 77 (6.70). Anal. $C_{11}H_{12}O_3$. C, 68.74; H, 6.29. Found C, 68.85; H, 6.23%

3-(2-Methoxy-phenyl)-3-oxo-propionic acid ethyl ester **(3h)**: Oil. ν_{max}(film)/cm^{-1}: 2937, 2840, 1725, 1681. δ$_H$(CDCl$_3$): 7.31–7.85 (4H, m), 4.35 (2H, q, J=7.2), 3.886 (2H, s), 3.880 (3H, s), 1.37 (3H, t, J=7.2). *m/z*(%): 222 (M$^+$, 10.15), 135 (100), 105 (21.07), 77 (58.59). Anal. $C_{12}H_{14}O_4$. C, 64.85; H, 6.35. Found C, 64.71; H, 6.37%

3-(4-Methoxy-phenyl)-3-oxo-propionic acid ethyl ester **(3i)**: Oil. ν_{max}(film)/cm^{-1}: 2828, 2850, 1741, 1678. δ$_H$(CDCl$_3$): 7.92–7.97 (2H, m), 6.91–6.99 (2H, m), 4.22 (2H, q, J=7.2), 3.96 (2H, s), 3.87 (3H, s), 1.28 (3H, J=7.2). *m/z*(%): 223 (M$^+$+1, 17.60), 222 (M$^+$, 12.25), 177 (.11), 135 (100). Anal. $C_{12}H_{14}O_4$. C, 64.85; H, 6.35. Found C, 64.77; H, 6.32%

3-(2-Iodo-phenyl)-3-oxo-propionic acid ethyl ester **(3j)**: Oil. ν_{max}(film)/cm^{-1}: 2924, 2852, 1727, 1656. δ$_H$(CDCl$_3$): 7.31–8.11 (4H, m), 4.00 (2H, s), 3.75 (3H, s). *m/z*(%): 304 (M$^+$, 2.33), 231 (100), 203 (30.30), 177 (72.82). Anal. $C_{10}H_9IO_3$. C, 39.50; H, 2.98. Found C, 39.64; H, 2.97%

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References

1 P. Girard, J.L. Namy and H.B. Kagan, *J. Am. Chem. Soc.*, 1980, **102**, 2693.
2 For review to see: (a) A. Krief and A.M. Laval, *Chem Rev.*, 1999, **99**, 745-777; (b) G.A. Molander, *Acc. Chem. Res.*, 1998, **31**, 603; (c) G.A. Molander and C.R. Harris, *Tetrahedron* 1998, **54**, 3321; (d) G.A. Molander and C.R. Harris. *Chem Rev.* ,1996, **96**, 307; (e) G.A. Molander, *Chem Rev*., 1992, **92**, 29; (f) T. Imamoto, *Lanthanides in Organic Synthesis*; Academic Press: London, 1994, Chap. 4.
3 (a) F. Akiko, S.S. Sato and I. Yasutaka, *J. Org. Chem.*, 2000, **65**, 6209; (b) X.Y. Chen, W.L. Bao and Y.M. Zhang, *Synth. Commun.*, 1996, **26**, 2905; (c) Y.P. Yu, R.H. Lin and Y.M. Zhang, *Tetrahedron Lett*., 1993, **34**, 4547; (d) W.Y. Hao, Y.M. Zhang, T.K. Ying and P. Lu, *Synth. Commun.*, 1996, **26**, 2421.
4 For Review see: B.K. Banik, *Eur. J. Org. Chem.*, 2002, **67**, 2431.
5 (a) A. Ogawa, T. Nanke, N. Takami, Y. Sumino, I. Ryu and N. Sonoda, *Chem. Lett*., 1994, 379; (b) G.A. Molander and J.B. Etter, *J. Org. Chem*., 1986, **51**, 1778; (c) T. Imamoto, T. Takeyam and H. Koto, *Tetrahedron Lett*., 1986, **27**, 3243.
6 (a) B.K. Banik, C. Mukhopadhyay, M.S. Venkatraman and F.F. Becker, *Tetrahedron Lett.*, 1998, **39**, 7243; (b) R. Yanada, N. Negora. K. Yanada and T. Fujita, *Tetrahedron Lett.*, 1997, **38**, 3271; (c) A. Ogawa, N. Takami, M. Sckiguchi, I. Ryu, N. Kambe and N. Sonoda, *J. Am. Chem. Soc*., 1992, **114**,8729; (d) L. Wang and Y. Zhang, *Tetrahedron* 1998. **54**, 11129; (e) A. Ghatak, F.F. Becker and B.K. Banik, *Tetrahedron Lett*., 2000, **41**, 3793; (f) S. Talukdar and J. -M. Fang, *J. Org. Chem*., 2001, **66**, 330.
7 X.L. Zheng and Y.M. Zhang, *Synth. Commun.*, 2003, **33**, 161.
8 (a) Y.J. Liu, X. Liu and Y.M. Zhang, *Tetrahedron Lett*., 2003, **44**, 1667; (b) Y.J. Liu and Y.M. Zhang, *Tetrahedron Lett.*, 2003, **44**, 4291.
9 J.J. Jung, E.B. Watkins and M.A. Avery, *Tetrahedron*, 2002, **58**, 3639.
10 R.D. Little and A. Wade, *Russ. J. Org. Chem.*, 2000, **65**, 8096.
11 S.N. Khitrik, *J.Gen. Chem* (U.S.S.R) 1940, **10**, 2095.
12 (a) G.A. Molander, J.B. Etter and P.W. Zinke, *J. Am. Chem. Soc.*, 1987**, 109**, 453; (b) T. Gillmann, *Tetrahedron Lett*., 1993, **34**, 607; (c) E.J. Enholm and H. Satici, *Tetrahedron Lett*., 1991, **32**, 2433; (d) G.A. Molander and J.A. Mckie, *J. Am. Chem. Soc.* 1993**, 115**, 5821.
13 (a) H. Stetter, *Angew. Chem*., 1955, **67**, 769; (b) S. Hunig and M. Salzwedel, *Chem. Ber*., 1966, **99**, 823; (c) S. Hunig and W. Lendle, *Chem. Ber*., 1960, **93**, 913.