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Sm/TiCl$_4$ (cat.) system-mediated intermolecular and intramolecular reductive coupling reactions of ketones with esters*

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Abstract: Sm/TiCl$_4$ system could well integrate the high reactivity of samarium(II) and high deoxygenation capacity of low valent titanium within one system. In this paper, the intermolecular and intramolecular reductive coupling reactions of ketones with esters mediated by metallic samarium (Sm) and a catalytic amount of titanium tetrachloride (TiCl$_4$) were successfully developed. A series of substituted ketones and cyclic β-keto-esters were prepared in moderate to good yields under reflux and neutral conditions.

Key words: Samarium (Sm), Titanium tetrachloride (TiCl$_4$), Ketone, Ester, Reductive coupling reaction
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INTRODUCTION

Samarium diiodide (SmI$_2$) (Girard *et al.*, 1980) as a powerful one-electron transfer reductant has been extensively applied in organic synthesis in the last decades. Because of its mild and neutral reaction conditions as well as excellent selectivity, the novel transformations induced by SmI$_2$ are daily on the increase (Krief and Laval, 1999; Molander and Harris, 1996; Molander, 1992). Although SmI$_2$ is a useful reductive reagent, its application in organic synthesis is limited to some extent. For example, it is expensive and needs delicate treatment and careful storage because it is very sensitive to air oxidation. In addition, it only gives one electron in the reaction, which seriously restricts its large scale application.

However, metallic samarium is stable in air, and has strong reducing power ($Sm^{3+}/Sm=-2.41$ V) which is comparable with that of magnesium ($Mg^{2+}/Mg=-2.37$ V), and superior to that of zinc ($Zn^{2+}/Zn=-0.71$ V). Moreover, it has more electrons to be transferred than SmI$_2$ in reactions. These properties prompted us to use the more convenient and cheaper samarium metal directly as a reductant instead of SmI$_2$. As part of our efforts in this area (Zhang and Liu, 2001; Liu *et al.*, 2002; 2006), we found that Sm/TiCl$_4$ system could well integrate the high reactivity of samarium(II) and high deoxygenation capacity of low valent titanium (McMurry, 1974; 1983; 1989; Lenoir, 1989; Fürstner and Bogdanović, 1996) within one system, which could replace SmI$_2$ to promote some reactions and afford the same products, such as the cross-coupling reaction of nitriles with nitro compounds (Zhou and Zhang, 1998a; 1998b) and reductive coupling of ketones with imines (Ma and Zhang, 2000; Ma *et al.*, 2000), etc. However, in some cases, different products were obtained when Sm/TiCl$_4$ system was used as the reductive reagent instead of SmI$_2$. For examples, SmI$_2$-mediated intermolecular and intramolecular reductive coupling reactions of ketones with nitriles afforded α-hydroxy ketones and monocyclic α-amino alcohols (Zhou and Zhang, 1998c), whereas the reaction mediated by

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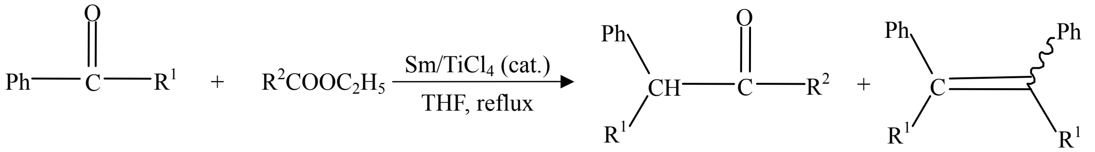
Sm/$TiCl_4$ system gave deoxygenated products (Zhou and Zhang, 2000); SmI_2-mediated coupling of aroyl chlorides gave α,α′-stilbenediol dibenzoates as main product (Li and Zhang, 2001) while tetraarylfurans were observed from aroyl chlorides with the Sm/$TiCl_4$ system (Li *et al.*, 2002). We recently reported SmI_2-mediated intermolecular and intramolecular reductive coupling reactions of ketones with esters (Liu and Zhang, 2001). In this paper we wish to describe an Sm/$TiCl_4$ (cat.) system-mediated intermolecular and intramolecular reductive coupling reactions of ketones with esters.

RESULTS AND DISCUSSIONS

Initially, the intermolecular cross-coupling reaction of ketone with ester was investigated (Fig.1) with the results being summarized in Table 1. Our initial attempts focused on using Sm/$TiCl_4$ system as coupling reagent. When 1 equiv. of benzophenone (**1**) was treated with 1.2 equiv. of ester (**2**), 1 equiv. of samarium powder and 1 equiv. of $TiCl_4$ for 2 h at reflux, substituted ketone (**3**) was obtained as main product along with 1,1,2,2-tetraaryl-ethene (**4**) as a by-product (Entry 1) (Shi *et al.*, 1993). To our surprise, when $TiCl_4$ was reduced to a catalytic amount (10 mol% based on samarium), the formation of 1,1,2,2-tetraaryl-ethene (**4**) was suppressed obviously although prolonged time was needed for the reaction (Entry 1). Thus we decided to carry out the reaction with the Sm/$TiCl_4$ (cat.) system. To our delight, both aliphatic acid esters and aromatic acid esters were coupled efficiently. However, it needed longer time in the reaction of the former together with lower yields in comparison with the latter. Attempts to carry out the reaction at room temperature gave unsatisfactory results (Entry 1).

Under the optical conditions, the intramolecular reductive coupling reactions of ketones with esters were also successful (Fig.2 and Table 2). Substrates **5** (keto-diesters) bearing a carbonyl group and two ethoxy carbonyl groups could undergo intramolecular ketone-ester reductive coupling reaction at reflux under a nitrogen atmosphere to give the reductive cyclization products cyclic β-keto-esters **6** in moderate to good yields. The reaction is highly chemoselective, only cyclization products were obtained. Furthermore, substituents such as chloro and alkoxy groups could be tolerated under the reaction conditions. It is noteworthy that in the present reaction no hydroxy-remaining products as obtained in the SmI_2-mediated reaction (Liu and Zhang, 2001) were formed at room temperature.



1 **2** **3** **4** (trace)

Fig.1 Intermolecular reductive coupling reaction of ketones with esters mediated by Sm/$TiCl_4$ (cat.) system

Table 1 Intermolecular cross-coupling reaction of ketones with esters promoted by Sm/$TiCl_4$ (cat.) system[a]

Entry	R^1	R^2	Time (h)	Product	Yield (%)[b]
1	C_6H_5	C_6H_5	7 (2[c])	**3a**	84 (62[c], 35[d])
2	C_6H_5	4-ClC_6H_4	5	**3b**	82
3	C_6H_5	4-$CH_3C_6H_4$	7	**3c**	70
4	C_6H_5	$C_6H_5CH_2$	9	**3d**	71
5	C_6H_5	*n*-C_3H_7	12	**3e**	65
6	4-$CH_3C_6H_4$	C_6H_5	9	**3f**	73
7	4-$CH_3OC_6H_4$	C_6H_5	9	**3g**	72
8	4-ClC_6H_4	C_6H_5	9	**3h**	77

[a] Reaction conditions: ketone (1.0 mmol), ester (1.2 mmol), Sm (1.0 mmol), $TiCl_4$ (0.1 mmol), THF (15 ml), 65 °C; [b] Isolated yield; [c] The reaction was carried out with 1.0 mmol of Sm and 1.0 mmol of $TiCl_4$, 1,1,2,2-tetraphenyl-ethene was obtained in 25% yield; [d] The reaction was carried out at room temperature

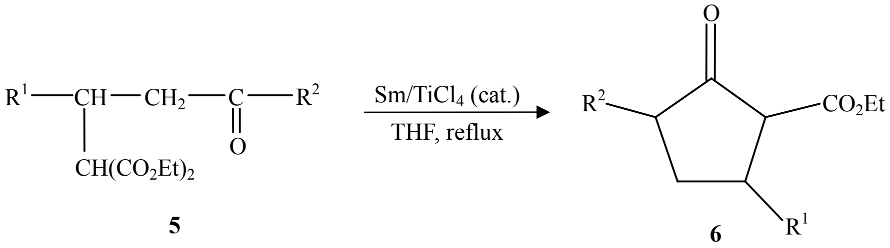


Fig.2 Intramolecular reductive coupling reaction of ketones with esters mediated by Sm/TiCl$_4$ (cat.) system

Table 2 Intramolecular ketone-ester cross-coupling reaction of keto-diesters 5 promoted by Sm/TiCl$_4$ (cat.) system[a]

Entry	R^1	R^2	Time (h)	Product	Yield (%)[b]
1	C_6H_5	C_6H_5	6	**6a**	82
2	4-$CH_3C_6H_4$	C_6H_5	8	**6b**	80
3	4-$CH_3C_6H_4$	4-ClC_6H_4	6	**6c**	78
4	4-ClC_6H_4	C_6H_5	7	**6d**	83
5	3,4-$OCH_2OC_6H_3$	C_6H_5	8	**6e**	76

[a] Reaction conditions: **5** (1.0 mmol), Sm (1.0 mmol), TiCl$_4$ (0.1 mmol), THF (15 ml), 65 °C; [b] Isolated yield

EXPERIMENTAL DETAILS AND CONCLUSION

In summary, we have demonstrated that the Sm/TiCl$_4$ (cat.) system is an effective reagent for the intermolecular and intramolecular cross-coupling reactions of ketone with ester to give substituted ketones and cyclic β-keto-esters in moderate to good yields under neutral conditions. Further studies of this reagent on other chemical transformations are in progress.

General procedure for the intermolecular cross-coupling reaction of ketones with esters

TiCl$_4$ (11 μl, 0.1 mmol) was added to a suspension of Sm powder (0.15 g, 1 mmol) in freshly distilled THF (15 ml) at room temperature under an N$_2$ atmosphere. The mixture was refluxed for 20 min. Then a dilution of diarylketones **1** (1 mmol) and esters **2** (1.2 mmol) in THF (3 ml) was added dropwise. The mixture was stirred at reflux temperature for the time indicated in Table 1. Then dilute HCl (5%, 4 ml) solution was added and the mixture was extracted with ether (3×30 ml). After usual work-up, the crude product was then purified by preparative thin layer chromatography of silica gel with dichloromethane-petroleum ether (30~60 °C) (2:3) as the eluent to yield the products.

3a. m.p. 135~137 °C (138~138.5 °C (Henze and Leslie, 1950)); ^{1}H NMR (CDCl$_3$, 80 MHz) δ: 6.02 (s, 1H), 7.12~8.12 (m, 15H, ArH); IR (KBr) ν: 1690 cm^{-1} (C=O); MS (70 eV) m/z (%): 272 (M$^+$).

3b. m.p. 106~108 °C (108~110 °C (Zhou and Zhang, 2000)); ^{1}H NMR (CDCl$_3$, 80 MHz) δ: 5.92 (s, 1H), 7.14~7.94 (m, 14H, ArH); IR (KBr) ν: 1690 cm^{-1} (C=O); MS (70 eV) m/z (%): 308 (M$^+$+2), 306 (M$^+$).

3c. m.p. 98~100 °C (100~101 °C (Koelsch, 1932)); ^{1}H NMR (CDCl$_3$, 80 MHz) δ: 2.32 (s, 3H), 5.96 (s, 1H), 7.04~7.60 (m, 12H, ArH), 7.83~7.96 (d, *J*=7.2 Hz, 2H, ArH); IR (KBr) ν: 1690 cm^{-1} (C=O); MS (70 eV) m/z (%): 286 (M$^+$).

3d. m.p. 82~83 °C (82~83 °C (Zhou and Zhang, 2000)); ^{1}H NMR (CDCl$_3$, 80 MHz) δ: 3.66 (s, 2H), 5.12 (s, 1H), 6.94~7.40 (m, 15H, ArH); IR (KBr) ν: 1680 cm^{-1} (C=O); MS (70 eV) m/z (%): 286 (M$^+$).

3e. m.p. 208~209 °C; ^{1}H NMR (CDCl$_3$, 80 MHz) δ: 0.80 (t, *J*=6.0 Hz, 3H), 1.14~1.70 (m, 2H), 2.30 (t, *J*=6.0 Hz, 2H), 4.94 (s, 1H), 7.18~7.40 (m, 10H, ArH); ^{13}C NMR (CDCl$_3$, 100 MHz) δ: 17.33, 22.63, 44.74, 64.03, 127.06, 128.57, 128.88, 138.45, 208.45; IR (KBr) ν: 1695 cm^{-1} (C=O); MS (70 eV) m/z (%): 238 (M$^+$); Anal. calcd. for $C_{17}H_{18}O$: C 85.67, H 7.61; Found: C 85.36, H 7.70.

3f. m.p. 96~97 °C (97.5~98.5 °C (Koelsch, 1932)); ^{1}H NMR (CDCl$_3$, 80 MHz) δ: 2.28 (s, 3H), 6.02 (s, 1H), 7.12~8.21 (m, 14H, ArH); IR (KBr) ν:

1695 cm^{-1} (C=O); MS (70 eV) m/z (%): 286 (M$^+$).

3g. m.p. 127~128 °C (128~130 °C (Nagano, 1955)); ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 3.66 (s, 3H), 5.90 (s, 1H), 6.86 (d, *J*=9.0 Hz, 2H), 7.20~7.41 (m, 10H, ArH), 8.00 (d, *J*=9.0 Hz, 2H, ArH); IR (KBr) ν: 1685 cm^{-1} (C=O); MS (70 eV) m/z (%): 302 (M$^+$).

3h. m.p. 104~105 °C (105~106 °C (Zhou and Zhang, 2000)); ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 6.14 (s, 1H), 7.30~7.72 (m, 12H, ArH), 8.12 (d, 2H, *J*=8.0 Hz, ArH); IR (KBr) ν: 1690 cm^{-1} (C=O); MS (70 eV) m/z (%): 308 (M$^+$+2), 306 (M$^+$).

General procedure for the intramolecular cross-coupling reaction of ketones with esters

After the suspension of samarium (0.15 g, 1 mmol) and $TiCl_4$ (11 μl, 0.1 mmol) in THF (15 ml) was refluxed under N_2 atmosphere for 20 min, a solution of keto-diesters **5** (1 mmol) in anhydrous THF (3 ml) was added at room temperature under a nitrogen atmosphere. The reaction mixture was then reacted at reflux for the time given in Table 2 and quenched with dilute HCl (5%, 2 ml). After usual work-up, the crude product was purified by preparative thin layer chromatography on silica gel using ethyl acetate-cyclohexane (1:5) as the eluent.

6a (diastereoisomers). ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 1.16 (t, 3H, *J*=6.8 Hz, CH_3), 2.13~2.78 (m, 2H, ring CH_2), 3.39~3.96 (m, 3H, ring CH), 4.16 (q, 2H, *J*=6.8 Hz, OCH_2), 7.16~7.45 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.03, 36.96, 43.52, 55.96, 61.49, 62.54, 126.81, 127.23, 128.04, 128.60, 128.79, 136.88, 140.55, 168.57, 208.47; IR (KBr) ν: 1750 cm^{-1} (C=O), 1716 cm^{-1} (C=O); MS (70 eV) m/z (%): 308 (M$^+$); Anal. calcd. for $C_{20}H_{20}O_3$: C 77.90, H 6.54; Found: C 77.58, H 6.43.

6b (diastereoisomers). ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 1.17 (t, 3H, *J*=6.8 Hz, CH_3), 2.00~2.92 (m, 5H, ring CH_2, CH_3), 3.38~3.96 (m, 3H, ring CH), 4.17 (m, 2H, *J*=6.8 Hz, OCH_2), 7.02~7.62 (m, 9H, ArH); IR (KBr) ν: 1755 cm^{-1} (C=O), 1720 cm^{-1} (C=O); MS (70 eV) m/z (%): 322 (M$^+$); Anal. calcd. for $C_{21}H_{22}O_3$: C 78.23, H 6.88; Found: C 77.80, H 6.76.

6c (diastereoisomers). ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 1.17 (t, 3H, *J*=6.8 Hz, CH_3), 2.02~2.90 (m, 5H, ring CH_2, CH_3), 3.32~3.94 (m, 3H, ring CH), 4.14 (q, 2H, *J*=6.8 Hz, OCH_2), 6.98~7.60 (m, 8H, ArH); IR (KBr) ν: 1755 cm^{-1} (C=O), 1722 cm^{-1} (C=O); MS (70 eV) m/z (%): 358 (M$^+$+2), 356 (M$^+$); Anal. calcd. for $C_{21}H_{21}ClO_3$: C 70.68, H 5.93; Found: C 70.98, H 5.85.

6d (diastereoisomers). ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 1.18 (t, 3H, *J*=6.8 Hz, CH_3), 2.04~2.88 (m, 2H, ring CH_2), 3.32~3.96 (m, 3H, ring CH), 4.15 (q, 2H, *J*=6.8 Hz, OCH_2), 7.06~7.55 (m, 9H, ArH); IR (KBr) ν: 1756 cm^{-1} (C=O), 1724 cm^{-1} (C=O); MS (70 eV) m/z (%): 344 (M$^+$+2), 342 (M$^+$); Anal. calcd. for $C_{20}H_{19}ClO_3$: C 70.07, H 5.59; Found: C 70.58, H 5.48.

6e (diastereoisomers). ^{1}H NMR ($CDCl_3$, 80 MHz) δ: 1.16 (t, 3H, *J*=6.8 Hz, CH_3), 1.98~2.90 (m, 2H, ring CH_2), 3.26~3.96 (m, 3H, ring CH), 4.13 (q, 2H, *J*=6.8 Hz, OCH_2), 5.80 (s, 2H, O-CH_2-O), 6.64~7.26 (m, 8H, ArH); IR (KBr) ν: 1752 cm^{-1} (C=O), 1722 cm^{-1} (C=O); MS (70 eV) m/z (%): 352 (M$^+$); Anal. calcd. for $C_{21}H_{20}O_5$: C 71.58, H 5.72; Found: C 71.17, H 5.79.

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