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Reductive Coupling of Carbonyl Compounds Using Lanthanum Metal

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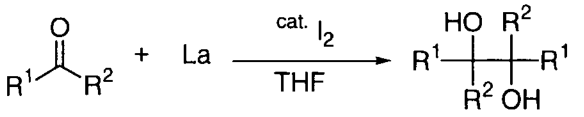
ABSTRACT: *We found that lanthanum metal was an excellent agent for the reduction of carbonyl compounds in the presence of a catalytic amount of iodine. When carbonyl compounds were treated with lanthanum metal in the presence of a catalytic amount of iodine, the reductive coupling of the carbonyl compounds proceeded efficiently to afford the corresponding vic-diols in moderate to good yields.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:81–85, 2000

INTRODUCTION

The use of lanthanoid salts and organolanthanoid compounds in organic synthesis has been steadily increasing in recent years. In particular, low valent, trivalent, and tetravalent lanthanoid compounds have been widely used as versatile reagents in organic synthesis [1]. On the other hand, the direct use of lanthanoid metals as reagents in organic synthesis has been limited, in spite of the disadvantages of elemental lanthanoid metals due to their low solubility in an organic solvent or to their instability under aerobic conditions. Recently the direct utilization of cerium [2], samarium [3], and ytterbium [4] metals in organic reactions has been developed; however, these metals do suffer from some disadvantages. Samarium and ytterbium metals are relatively stable metals under aerobic conditions but are expensive [5]. Cerium metal can be purchased at a low price; however, cerium powder easily catches fire with friction [5]. On the other hand, lanthanum metal is a relatively stable metal under aerobic conditions and can be purchased at a moderate price; in addition, lanthanum metal has the largest redox potential (2.522 V) [6] among the lanthanoid metals. However, there are only a limited number of reports on the direct use of lanthanum metal in organic reactions [2,7]. We then examined the utilization of lanthanum metal in organic synthesis and found that carbonyl compounds underwent pinacol coupling with lanthanum metal in the presence of a catalytic amount of iodine (Equation 1) [8–10].



(1)

RESULTS AND DISCUSSION

The results of the reaction of acetophenone (**1a**) with lanthanum metal under various reaction conditions are shown in Table 1. When **1a** was treated with one equivalent of lanthanum metal in the presence of a catalytic amount of iodine (0.2 equiv.) in tetrahydrofuran (THF) solution at 25°C, the color of the solution (red) gradually darkened. After the solution was

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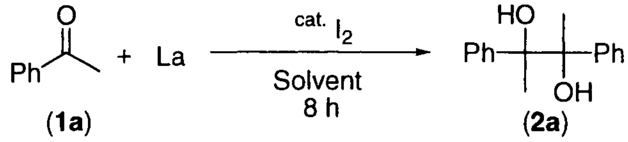
TABLE 1 Reaction of Acetophenone (**1a**) with Lanthanum Metal under Various Reaction Conditions[a]



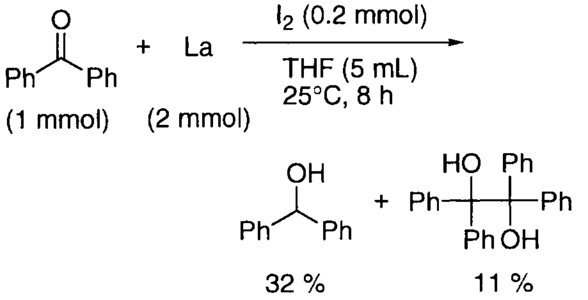
(**1a**) (**2a**)

Entry	*Solvent*	*Temp. (°C)*	*Yield/%*[b] *(dl/meso)*[c]
1	THF	25	77 (75:25)
2[d]	THF	25	0
3[e]	THF	25	78
4	THF	0	21
5	THF	67	56
6	CH_3OH	25	0
7	DME	25	44
8	1,4-dioxane	25	trace
9	CH_3CN	25	40
10	benzene	25	4
11	*n*-hexane	25	trace

[a] Reaction conditions: acetophenone (**1a**) (1.0 mmol), La (1.0 mmol), I_2 (0.2 mmol) and solvent (5 mL).
[b] GC yield based on **1a** used.
[c] Determined by ^{1}H NMR.
[d] In the absence of I_2.
[e] HMPA (1 mL) was added.

stirred at 25°C for 8 hours, the reaction mixture was hydrolyzed with aqueous HCl (3 M) and extracted with diisopropyl ether. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography on silica gel to afford 2,3-diphenyl-2,3-butanediol (**2a**), the pinacol coupling product of **1a**, in 77% yield (*dl:meso* = 75:25) along with a small amount of 1-phenylethanol (7%) (Entry 1 in Table 1). In the absence of iodine, 92% of acetophenone was recovered (Entry 2 in Table 1). Under reflux conditions, unfortunately, undesired side reactions are induced (Entry 5 in Table 1). In these reactions, the yield of **2a** was drastically affected by the solvent used. THF gave the best result and the use of acetonitrile and 1,2-dimethoxyethane (DME) as the solvent led to the formation of pinacol in moderate yields (Entries 1, 7, and 9 in Table 1). On the other hand, methanol, which is reported to be the best solvent in the reductive coupling of carbonyl compounds with the Sm-I_2 system [11], did not give **2a** at all (Entry 6 in Table 1). Addition of hexamethylphosphoramide (HMPA), which often gave good results in the reaction with SmI_2, did not reveal a positive effect in the present case (Entry 3 in Table 1) [23].

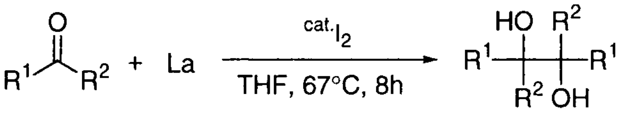
Various carbonyl compounds were allowed to react with lanthanum metal in the presence of a catalytic amount of iodine (0.2 equiv.), and the results are shown in Table 2. 4-Methylacetophenone and 2-acetylnaphthalene were treated with lanthanum metal under the same reaction conditions as Entry 1 in Table 1 to give the corresponding *vic*-diols in slightly lower yield. The yields of products were improved when the reaction was carried out at a somewhat higher reaction temperature (67°C) (Entries 1 and 6 in Table 2). 2-Methylacetophenone was also converted into the corresponding pinacol coupling product in 56% yield (Entry 5 in Table 2). In the reaction of 4-methoxy-, 4-chloro-, and 4-bromoacetophenone, the yields of reductive coupling products were 43, 44, and 49% due to the production of various by-products (Entries 2–4 in Table 2). In the case of aromatic ketones bearing hydroxy and nitro groups on the aromatic ring, the starting ketones were recovered (96 and 92%). Aliphatic ketones as well as aromatic ketones gave the pinacol coupling products in moderate yields along with the formation of alcohols (Entries 7 and 8 in Table 2). In contrast to ketones, in the case of aldehydes, the yields of pinacol coupling products decreased due to various side reactions (Entries 9 and 10 in Table 2). The pinacol coupling of 1,3-dibenzoylpropane also took place intramolecularly, giving the corresponding diol in 68% yield (Entry 11 in Table 2). On the other hand, when benzophenone was treated with lanthanum metal, the reductive coupling reaction was suppressed, and reduction to benzhydrol mainly occurred (Equation 2).

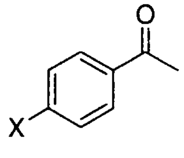
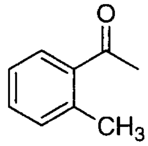
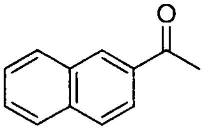
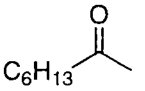
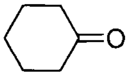
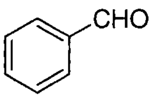
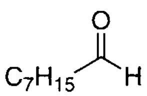
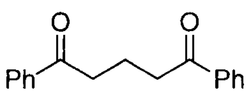


(2)

Although a detailed study of the reaction pathway has not yet been completed, one of the possible reaction pathways is shown in Scheme 1. We suggest that the reductive coupling products are formed by the coupling of ketyl radical (**3**) generated in situ by the single-electron-transfer reaction of carbonyl compounds with lanthanum metal. Fujiwara and coworkers have already reported that the reaction of benzophenone with Yb metal in the presence of a catalytic amount of MeI gave benzhydrol in good yield [20]. In this work, they proposed that benzhydrol was formed by the hydrolysis of intermediate (**5**). In fact, more recently, Hou and coworkers suc-

TABLE 2 Reductive Coupling of Various Carbonyl Compounds with Lanthanum Metal[a]



Entry	Substrate	La (equiv.)	Yield / %[b] (*dl* / *meso*)[c]
			
1	X = CH_3	1	65 (70 / 30)
2	X = OCH_3	2	43 (71 / 29)
3	X = Cl	1	44 (63 / 37)
4	X = Br	2	49 (61 / 39)
5		2	56 (>99 / <1)
6		1	68 (66 / 34)
7		3	49[d] (54 / 46)
8		2	49[e]
9		1	28 (60 / 40)
10		3	27 (60 / 40)
11		1	68[f] (<1 / >99)

[a] Reaction conditions: substrate (1.0 mmol), I_2 (0.2 equiv.) and THF (5 mL) at 67°C for 8 hours.

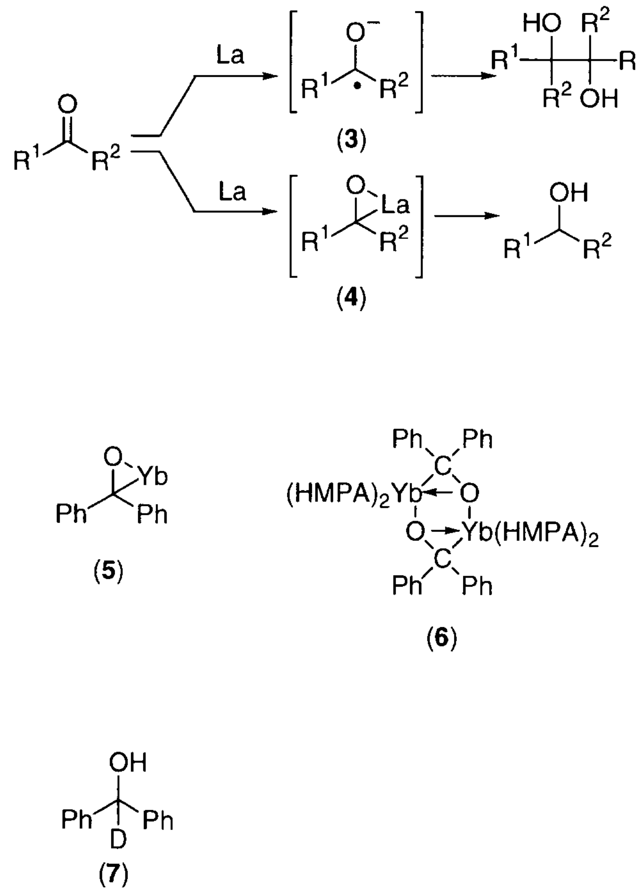
[b] Isolated yield based on substrate used.

[c] Determined by ^1H NMR.

[d] 2-Octanol (15%) was formed.

[e] Cyclohexanol (20%) was formed.

[f] Yield at 1,2-Diphenyl-1,2-cyclopropanediol.



SCHEME 1 A plausible reaction pathway

ceeded in isolation of Yb(II)benzophenone dianion (**6**) by the reaction of benzophenone with Yb metal in the presence of HMPA. Then, we also assumed that the formation of alcohol might occur through the intermediate (**4**). In fact, quenching with DCl/D_2O instead of HCl/H_2O gave the corresponding C-deuterated alcohol (**7**).

We have found that lanthanum metal can be used as a reducing agent for carbonyl compounds in the presence of a catalytic amount of iodine. The results shown here provide a new way of using lanthanum metal in organic synthesis.

Further utilization of lanthanum metal in organic synthesis is now in progress.

EXPERIMENTAL

Instruments

^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-GSX-400 (400 and 99.5 MHz) spectrometer using $CDCl_3$ as a solvent, with tetramethylsilane as the internal standard. FT-IR spectra were obtained on a Perkin Elmer Model PARAGON 1000 spectrophotometer. Mass spectra were measured on a Shimadzu Model QP-5050A instrument. Gas chromatography (GC) was carried out on a Shimadzu GC-14A instrument equipped with a flame ionizing detector using a capillary column (Hicap-CBP-1-S25-025, 0.25 mm × 25 m).

Reagents

Carbonyl compounds, iodine, and lanthanum metal were commercially available high grade products and were used without purification. The other reagents and solvents were purified by the usual methods before use.

General Procedure for the Reaction of Carbonyl Compounds Using Lanthanum Metal in the Presence of a Catalytic Amount of Iodine

Lanthanum powder (139 ~ 417 mg, 1 ~ 3 mmol) was placed in a three-necked flask. Iodine (51 ~ 153 mg, 0.2 ~ 0.6 mmol), THF (5 mL), and the carbonyl compound (1 mmol) were added to the flask, and the mixture was stirred at 25 or 67°C for 8 hours under a nitrogen atmosphere. The color of the solution gradually darkened. After the reaction was complete, aqueous HCl (3 M, 5 mL) was added to the reaction mixture that was then extracted with diisopropyl ether (20 mL × 5). The organic layer was washed with brine (100 mL) and dried over $MgSO_4$. The organic solvents were removed under reduced pressure. Purification by column chromatography (benzene:AcOEt = 8:1) on silica gel afforded the corresponding pinacol. The structure of the product was assigned by their ^{1}H NMR, ^{13}C NMR, IR, and GC mass spectra. The detailed reaction conditions are shown in Tables 1 and 2.

7,8-Dimethyl-7,8-tetradecanediol (*Mixture of meso and dl Isomers*)

^{1}H NMR δ 0.89 (t, J = 6.8 Hz, 6H, $C\underline{H}_3$), 1.14 (s, 2.74H, $C(OH)C\underline{H}_3$), 1.15 (s, 3.26H, $C(OH)C\underline{H}_3$), 1.30–1.57 (m, 20H), 1.95 (s, 2H, $O\underline{H}$); ^{13}C NMR: δ 14.3, 22.9, 25.9, 26.3, 29.5, 29.9, 31.4, 32.0, 33.9, 74.7, 74.9; IR: 3448, 2928, 2858, 1463, 1376, 1139 cm^{-1}.

8,9-Hexadecanediol (Mixture of meso and dl Isomers)

^{1}H NMR δ 0.88 (t, J = 6.8 Hz 6H, $C\underline{H}_3$), 1.27–1.52 (m, 24H), 2.12 (s, 0.80H, $O\underline{H}$), 2.25 (s, 1.20H, $O\underline{H}$), 3.40 (s, 1.20H, $C(OH)\underline{H}$), 3.60 (s, 0.80H, $C(OH)\underline{H}$); ^{13}C NMR: δ 14.3, 22.9, 25.9, 26.3, 29.5, 29.9, 31.4, 32.0, 33.9, 74.7, 74.9; IR: 3304, 2918, 2852, 1468, 1216, 1072, 757 cm^{-1}.

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[5] We can purchase lanthanoid metals (50 mesh) (La: ¥25,900/25 g, Ce: ¥13,000/10 g, Sm: ¥2,600/1 g, Yb: ¥13,600/5g) from Aldrich Chemical Co.

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[9] Fukuzawa has reported that lanthanum metal assisted the reaction of α-halo esters with carbonyl compounds to give the corresponding lactones in moderate to good yields along with a small amount of pinacol as a by-product. See Ref. [2b].

[10] It is already known that carbonyl compounds are converted into the corresponding pinacols by lanthanide compounds such as Ce-I_2 [11], Cel_3/n-BuLi [12], Sml_2 [13], $SmBr_2$ [14], Sm/Me_3SiCl/Nal [15], Sm/Et_2All [16], Sm/l_2 [17], Sml_2/Mg [18], Sm/Me_3SiCl/i-PrOH [7],Sm/Me_3SiCl/H_2O[19], Yb [20], $Yb(OTf)_3$/n-BuLi [21], $Yb(OTf)_3$/n-RMgX [22], and Yb/Me_3SiBr [23].

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