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Samarium-induced convenient reductive dimerization of aromatic ketones in aqueous methanol: a mechanistic approach

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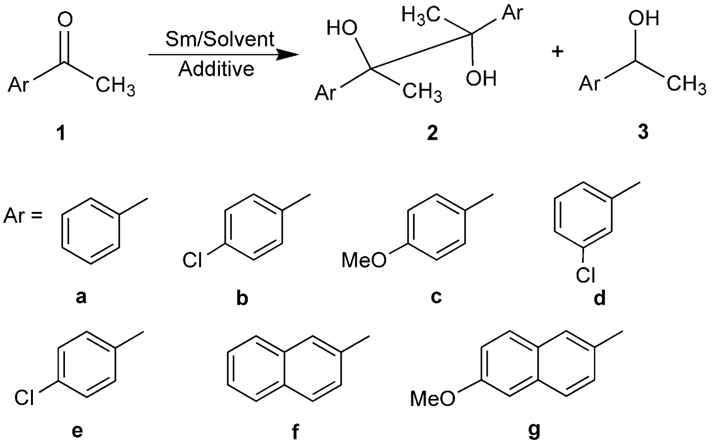
Abstract—Samarium metal has been used for the reductive dimerization of aromatic ketones in the presence of additives; the most probable mechanism has been advanced to explain the diastereoselectivity of this dimerization reaction.

Dissolving metal reduction of carbonyl compounds is a very attractive procedure.[1] Many metals, such as Li, Na, Mg, Ca, In, Zn, and Al, can be used in the presence of different solvent compositions.[2] Samarium metal is well suited to overcoming the drawbacks of dissolving metal reductions because of its stability in air and strong reducing power. The operational simplicity of using samarium metal in various chemical reactions has been demonstrated in recent publications.[3,4]

In this letter, we report a facile, convenient method of reductive dimerization of aromatic ketones by samarium metal in the presence of different additives (Scheme 1). Interestingly, samarium metal/ammonium chloride or bromide in aqueous methanol has been identified as the best reagent for the reductive dimerization of carbonyl compounds. A most probable mechanism is also presented herein to explain the diastereoselectivity of this dimerization reaction.



Scheme 1.

Keywords: Samarium; Reductive dimerization; Aromatic ketones; Electron transfer.

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Reductive coupling of carbonyl compounds to pinacols using samarium/iodine in methanol (a mixture of *dl* and *meso*) and samarium/iodine-titanium isopropoxide (*meso* preferred) was achieved.[4e] A bivalent salt-free samarium bis (trifluoromethanesulfonate) complex was used for intermolecular pinacol coupling reactions of aromatic ketones to diols with a high level of diastereoselectivity (*dl* isomer was predominantly formed).[6] Diastereoselective pinacol coupling of alkyl aryl ketones with samarium in the presence of trimethylsilyl chloride was accomplished.[7] Sm/Et_2AlI was used for the reductive coupling of carbonyl compounds.[8] These reactions were performed under anhydrous and inert atmosphere.

During the course of our study of metal-induced reactions, we discovered that the reductive coupling of aromatic ketones can be accomplished very efficiently using Sm/NH_4Cl in aqueous methanol.[5] Interestingly, ultrasonic exposure of the same reaction mixture resulted in a 20–30% reduction product. The steric crowding of aromatic ketones has posed no problems in dimer formation when the reaction was performed in aqueous methanol using NH_4Cl/NH_4Br. In addition, it improved the ratio of the dimers (*dl* and *meso*). In a detailed study, it was realized that the best yield could be obtained when the proportion of methanol and water was kept at 9:1 or 8:2 (Table 1). An increase in the amount of water resulted in a decrease of the yield of the product. This change was so significant that the reaction did not proceed more than 10% in aqueous media. The reaction did not proceed at all, however, when NaCl or NaBr was used as the metal salt under identical conditions. The NH_4Cl/aqueous methanol and NH_4Br/aqueous methanol-mediated reactions were faster than alkyl halides-mediated reactions. In the present study, *dl* isomer was the predominant product. Inverse addition of the reagents to the substrates was not helpful in further improving the isomeric ratios. For example, addition of the reagent system generated via reaction of the samarium metal/NH_4Cl/water/methanol to acetophenone and 4-chloroacetophenone produced *dl* as the predominant isomer over the *meso* (80:20). In the inverse addition method, the ratio of the isomer distribution and dimerization depended on how well the reagents could be added to the ketones. The mixed reagent generated via reaction of samarium/NH_4Cl or Sm/NH_4Br in aqueous methanol looked like a dark suspension. For better yield, it was necessary to add the whole reagent suspension slowly to the ketones. The yield of the products decreased considerably when solid materials were removed via filtration and the filtered reagent solution was added to the ketones. It has been demonstrated that insoluble samarium has a profound role in some reaction.[3–5]

Given the nature of the products, the most probable mechanism would be a reaction very similar to our

Table 1. Reductive coupling of aromatic ketones with samarium and different additives

Entry	Ketone	Additive	Diol (yield %)[a]	*dl*:*meso*[b]	Alcohol (yield %)[a]	Time (h)
1	**1a**	Allyl bromide[c]	**2a** (69)	58:42	**3a** (2)	3
2	**1a**	Allyl iodide[c]	**2a** (65)	55:45	**3a** (2)	3
3	**1a**	4-Bromo-1-butane[c]	**2a** (60)	55:45	**3a** (5)	4
4	**1a**	Ethylene dibromide[c]	**2a** (50)	58:42	**3a** (5)	6
5	**1a**	Ammonium chloride[c]	**2a** (69)	58:42	**3a** (10)	0.5
6	**1a**	Ammonium chloride[d]	**2a** (72)	60:40	**3a** (15)	0.08
7	**1a**	Ammonium chloride[e]	**2a** (80)	80:20	**3a** (5)	0.5
8	**1a**	Ammonium chloride[f]	**2a** (82)	80:20	**3a** (5)	0.5
9	**1a**	Ammonium bromide[f]	**2a** (82)	80:20	**3a** (5)	0.5
10	**1a**	Diethyl aluminum iodide[g]	**2a** (61)	82:18	**3a** (10)	3.5
11	**1a**	sodium chloride[e,f]	**2a** (0)		**3a** (0)	5
12	**1b**	Allyl bromide[c]	**2b** (59)	59:41	**3b** (11)	5
13	**1b**	Allyl iodide[c]	**2b** (58)	60:40	**3b** (10)	5
14	**1b**	Ammonium chloride[c]	**2b** (70)	60:40	**3b** (10)	0.5
15	**1b**	Ammonium chloride[d]	**2b** (70)	60:40	**3b** (15)	0.08
16	**1b**	Ammonium chloride[f]	**2b** (80)	75:25	**3b** (5)	0.5
17	**1b**	Ammonium chloride[f]	**2b** (80)	75:25	**3b** (5)	0.5
18	**1c**	Allyl bromide[c]	**2c** (59)	59:41	**3c** (11)	5
19	**1d**	Allyl bromide[c]	**2d** (57)	59:41	**3d** (9)	5
20	**1e**	Allyl bromide[c]	**2e** (50)	58:42	**3e** (8)	5
21	**1f**	Allyl bromide[c]	**2f** (49)	60:40	**3f** (24)	5
22	**1g**	Allyl bromide[c]	**2g** (15)	100:0	**3g** (20)	20
23	**1b**	Diethyl aluminum iodide[g]	**2b** (60)	57:43	**3b** (0)	4
24	**1c**	Diethyl aluminum iodide[g]	**3c** (71)	82:18	**3c** (0)	4
25	**1f**	Diethyl aluminum iodide[g]	**3f** (43)	55:45	**3f** (0)	4
26	**1a**	Samarium-complex[g]	**2a** (99)	90:10	**3a** (0)	0.5

[a] Isolated yield.

[b] Calculated from 300 MHz NMR.

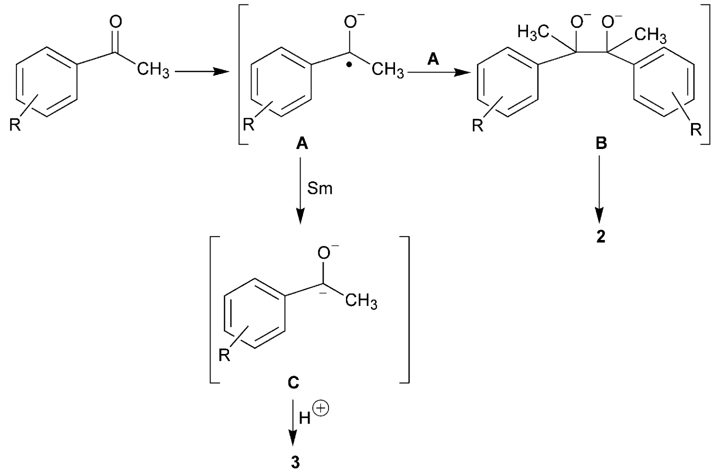
[c] Methanol as the solvent.

[d] Methanol as the solvent in the presence of ultrasound.

[e] Methanol/water (8:2) as the solvent.

[f] Methanol/water (9:1) as the solvent.

[g] Acetonitrile as the solvent.

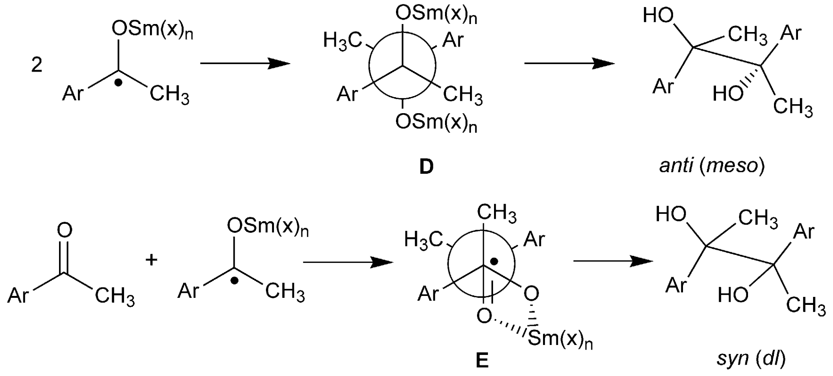


Scheme 2.

samarium/iodine-induced reduction reaction of the imines.[5b] Single electron transfer to an unsaturated carbon–oxygen bond can generate the ion radical **A**, and, because of the stability of the benzylic radical, the self-coupling process **A** to **B** (**D** or **E**) is feasible. As a result, the pinacol-type compound **2** is formed. Further electron transfer to the ion radical **A** can be a competitive path to the dianion **C**, which can be easily protonated by methanol to generate the alcohol **3** (Scheme 2). If the reaction is fast, electron transfer to form the dianion path does not seem to be favorable, as the normal reduction of the ketone has been found to be minimal when NH_4Cl/NH_4Br is the additive. If it proceeds slowly, however, this reaction produces a significant amount of the *meso* product. This has been established by the fact that performing the reaction in the presence of alkyl/allyl halides produces a considerable amount of the *meso* isomer. Summarizing the results on the diastereoselectivity, a hypothetical transition-state model could be proposed.

When the substrate is added to the reagent system and the reaction is relatively slow, two competitive paths may follow: combination of an ion radical to generate a sterically favored transition state **D** or combination of an ion radical with the remaining ketone (**E**). The resulting product is a mixture of *meso* and *dl* (Scheme 3). This happens when alkyl halides are the additives. When the reaction is fast, particularly if it is an NH_4Cl and NH_4Br-induced reaction, the high stereoselectivity of pinacolic coupling can be explained by the chelation model, in which samarium binds with two oxygens of the carbonyl groups. It is assumed that the use of ammonium salts can enhance this type of chelation.

As a result of this chelation, there is no difference in diastereoselectivity when an alternative mode of addition is used. Inverse addition would provide even better *dl* selectivity if there is no chelation. In the inverse addition method, the concentration of the reagent is not very high in the reaction media particularly at the initial stages, when compared with the concentration of the substrates. Therefore, a portion of the ketyl radical should then react with the ketone due to coordination of its carbonyl oxygen with the samarium species of the ion radical, leading to a higher *dl* ratio. In an earlier publication, the stereoselectivity of the products was rationalized by considering the chelation of samarium or aluminum with an oxygen atom.[8] In contrast to the existing method,[8] our approach is simple, moisture insensitive, and works well in the presence of inexpensive reagent. However, the conditions of those experiments were clearly different than our present approach.



Scheme 3.

In conclusion, we have developed an efficient methodology for reductive coupling of aromatic ketones to produce the corresponding diols in aqueous methanol under environmentally friendly conditions using ammonium salts as the promoter in good yield and with excellent selectivity.[9]

Acknowledgments

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9. Representative experimental procedure: A mixture of acetophenone **1a** (0.1 g, 0.83 mmol), samarium metal (0.375 g, 2.49 mmol), ammonium chloride (5 equiv) in methanol/water (10:1, 5 mL) was stirred at room temperature, the reaction was monitored by TLC. After the ketone was consumed (30 min), the reaction mixture was diluted with CH_2Cl_2 and 0.5 mL of a saturated $NaHCO_3$ solution was added and then passed through a pad of Celite. The filtrate was dried (Na_2SO_4) and concentrated, and the residue was subjected to silica gel chromatography. The diol **2a** was obtained in 79% yield as a mixture of diastereomers (*dl*:*meso* = 80:20).