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Samarium-induced alkyl halide mediated reductive coupling of ketones

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Abstract

Reductive coupling of aromatic ketones was achieved by samarium metal in the presence of alkyl halides. © 2000 Published by Elsevier Science Ltd. All rights reserved.

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The use of samarium diiodide as single electron transfer reagent in organic synthesis has been explored extensively.¹ In recent years the chemistry of samarium metal has received increasing attention from the synthetic community.² The operational simplicity of using samarium metal over commercially available samarium diiodide has been demonstrated in our recent publications. We have shown a facile reduction of the aromatic nitro compounds³ and imines⁴ by samarium metal in the presence of catalytic amounts of iodine.

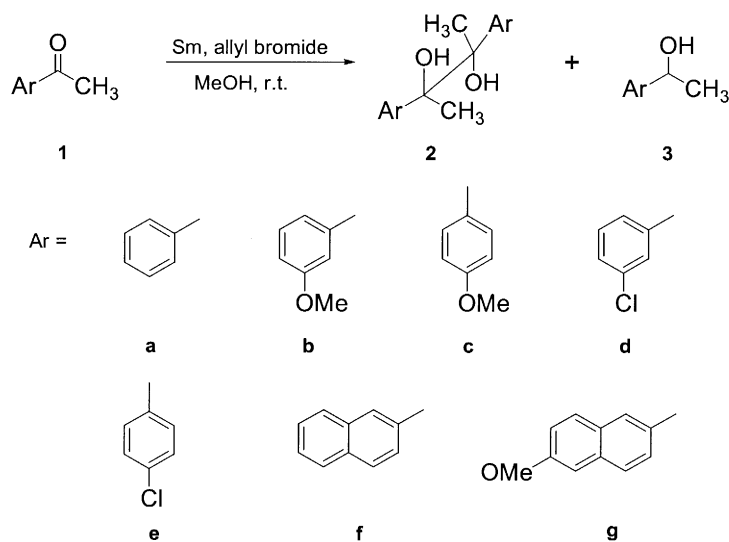
In continuation of our ongoing research into the application of samarium metal in organic synthesis, we decided to investigate Barbier-type addition of allyl group to ketones in presence of samarium metal.

Treatment of acetophenone (**1a**) with allyl bromide in the presence of samarium metal unexpectedly produced the alcohol derivative **2a**. No trace of the allyl group was detected in the crude reaction mixtures. After additional experimentation, we found that with 2.5 equiv. of samarium metal and 0.6 equiv. of allyl bromide, acetophenone was completely converted to the diol **2a** in 3 h in 69% yield (dl: *meso*=58:42).⁵ No trace of the alcohol **3a** was obtained (Scheme 1).

Kagan et al.⁶ reported similar pinacol type of coupling of ketones using 1.1 equiv. of samarium dibromide in tetrahydrofuran. The preparation of air-sensitive samarium dibromide is a two-step synthetic operation and requires samarium trioxide, hydrobromic acid, methyl formate and lithium dispersion. In contrast, we have used allyl bromide (0.6 equiv.) and samarium metal as the reactants.

Therefore, we decided to apply this mild and efficient protocol of reductive coupling (pinacolization) of aromatic ketones to a number of substrates (Table 1). 3-Methoxy acetophenone (**1b**) under identical

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Scheme 1.

reaction conditions produced the diol **2b** as the exclusive product in 59% yield with a *dl:meso* ratio of 59:41. 4-Methoxy acetophenone (**1c**) produced the diol **2c** in 57% yield and similar diastereoselectivity along with the simple reduction product **3c** in 11% yield. Both 3-chloro-acetophenone (**1d**) and 4-chloro-acetophenone (**1e**) underwent reaction producing the diols **2d** and **2e**, respectively, in comparable yields and diastereoselectivity along with small quantities of reduction products. 2'-Acetonaphthone (**1f**) produced the diol **2f** in slightly higher diastereoselectivity in 49% yield along with the alcohol **3f** in 24% yield. In case of 6'-methoxy-2'-acetonaphthone (**1g**), the reaction did not proceed to completion even after 20 h. The major product was the alcohol **3g** (20%). The diol **2g** was obtained in 15% yield as a single diastereomer. About 40% unreacted ketone was recovered. From the above results, it is evident that as the bulk of the aromatic part of the ketone increased, the tendency of forming the simple reduction product increased.

In order to determine the generality of the reaction, several other ketones were reduced under identical conditions. For example, when benzophenone (**4a**) was used as the substrate (Scheme 2), the reductive coupling product **5a** was exclusively formed in 59% yield. Similarly, when the substrate was 4,4'-dichlorobenzophenone (**4b**), the product was exclusively the diol **5b** in 57% yield. On the other hand, tricyclic fluorenone (**6**) gave a mixture of fluorenol (**8**, 37%) along with the dimeric product (**7**, 23%).

Encouraged by these results above and to investigate whether this type of pinacol coupling is feasible with other alkyl halides, we selected allyl iodide, 4-bromo-1-butene and ethyl bromoacetate to study the reaction in detail. Surprisingly, the reaction of acetophenone (**1a**) with these halides in the presence of samarium metal under identical conditions afforded **2a** in 50–60% yield, although the progress of the reaction was found to be slower compared to the allyl bromide reaction.

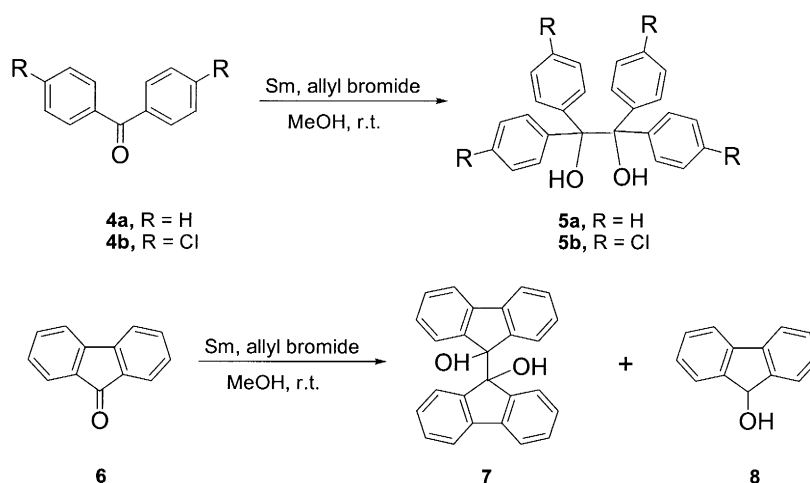
In order to investigate the mechanism of the reaction, acetophenone was treated with samarium metal and 0.6 equivalent of 1,2-dibromoethane and the diol was obtained in 67% yield as the only isolated product after 2 h. Kagan et al.⁶ reported that samarium dibromide cannot be obtained from the reaction of samarium metal and 1,2-dibromoethane.

Reduction of benzophenone by following Kagan's method afforded benzhydrol. However, in contrast to Kagan's observation we isolated the diols **5a** and **5b** as the exclusive products from the reductive coupling of benzophenones **4a** and **4b**. Reaction of acetophenone (**1a**) by samarium metal in the presence

Table 1
Reductive coupling of ketones with samarium metal and allyl bromide

Entry	Ketone	Diol (yield %) ^a	dl : meso ^b	Alcohol (yield %) ^a	Time (h)
1	1a	2a (69)	58 : 42	-	3
2	1b	2b (59)	59 : 41	-	5
3	1c	2c (57)	59 : 41	3c (11)	12
4	1d	2d (50)	58 : 42	3d (9)	5
5	1e	2e (57)	60 : 40	3e (8)	5
6	1f	2f (49)	61 : 39	3f (24)	5
7	1g	2g (15) ^c	Single isomer	3g (20)	20
8	4a	5a (59)	-	-	6
9	4b	5b (57)	-	-	6
10	6	7 (23)	-	8 (37)	8

^aIsolated yield; ^bcalculated from 300 MHz NMR, ^cabout 40% unreacted ketone recovered



Scheme 2.

of catalytic amounts of bromine failed to produce any alcohol derivatives indicating that the free halogen has no role in the present reaction.

The present methodology for the reductive coupling of ketones offers distinct advantages over the existing methods by Kagan⁶ and Flowers.⁷ These include a single step reaction of a wider number of substrates with relatively stable reagents. Though the mechanism of the reaction is not clear at present, we are reasonably confident that it does not take place through samarium dibromide.

In conclusion, we have developed a mild, efficient and mechanistically interesting reductive coupling method⁸ of ketones to produce the corresponding diols in good yield and moderate selectivity.

Acknowledgements

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8. Representative experimental procedure: a mixture of acetophenone (**1a**) (0.1 g, 0.83 mmol) and allyl bromide (0.06 g, 0.49 mmol) in MeOH (5 ml) was added to samarium metal (0.31 g, 2.07 mmol) at room temperature under argon. After a few minutes, an exothermic reaction occurred and the color of the mixture turned to blackish-green and gradually to yellowish-green. After the ketone was consumed (3 h), the reaction mixture was diluted with CH₂Cl₂, 0.5 ml saturated NaHCO₃ solution added and passed through a pad of Celite. The filtrate was dried (Na₂SO₄), concentrated and residue subjected to silica gel chromatography. The diol **2a** was obtained in 69% yield (0.069 g) as a mixture of diastereomers (dl:*meso*=58:42).