The Chemistry of Alkylstrontium Halide Analogues, Part 2: Barbier-Type Dialkylation of Esters with Alkyl Halides[‡]

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The chemistry of an alkylstrontium halide analogue was examined. In the presence of metallic strontium, the Barbier-type alkylation of esters with alkyl iodides proceeded smoothly at room temperature, under argon, to afford the corresponding dialkylated alcohols in good yields.

Introduction

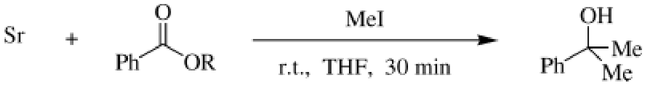
Organometallic compounds are some of the most versatile reagents in organic synthesis and among them are organometallic compounds of alkaline-earth elements.[1–3] Numerous reports have been published on the so-called Grignard reaction using metallic magnesium and alkyl halides, and these include well-established methods for dialkylation of esters using Grignard reagents that proceed smoothly to afford the corresponding adducts in good yields.[4] However, for the Grignard procedure, the metallated alkylating agent, if not commercially available, must be prepared as a first step. In contrast, the Barbier reaction comprises a single step, one-pot protocol that may be considered more convenient than its Grignard-type counterpart, even though historically, the Grignard procedure was derived from Barbier's methodology and has been more widely exploited.

Attention was drawn to the development of Barbier-type reactions since Kagan and Namy et al. reported Barbier-type alkylation of carbonyl compounds using samarium diiodide.[5] The many reports that followed described Barbier-type alkylations of aldehydes and ketones using samarium diiodides or other metallated reagents but mainly focused on allylation reactions.[6,7] In contrast, fewer studies of the Barbier-type alkylation of esters have been reported,[8] which include the samarium diiodide mediated reactions.[9] Hence, convenient and useful Barbier-type dialkylations of esters have yet to be developed.

While there are also various reports on the preparation and reactivity of the organometallic compounds of calcium and barium, as these alkaline-earth elements are similar to magnesium,[2,3] there are comparatively fewer studies on the preparation and reactivity of organostrontium compounds to be found in the literature.[10,11] We have investigated synthetic reactions using strontium compounds and have already reported the alkylation of aldehydes or imines with alkyl iodides using metallic strontium.[12] When we extended our investigation to include esters, we found that the Barbier-type alkylation of esters with alkyl iodides using strontium metal proceeded smoothly to afford the corresponding adducts in good yields. To the best of our knowledge, such reactions are hitherto unknown in the literature, and we wish to describe our results herewith.

First, with the use of methyl benzoate, alkylation of the ester with methyl iodide was examined under various reaction conditions. It was found that when 2.5 molar amounts of methyl iodide were added to a THF suspension of 2.5 molar amounts of metallic strontium[13] and 1.0 molar amounts of methyl benzoate at room temperature, the reaction proceeded to completion within 30 minutes to afford the corresponding dimethylated alcohol in excellent yield (Entry 1 in Table 1). We then investigated the influence of steric crowding by using various increasingly bulky benzoates with methyl iodide; these benzoates are shown in Table 1. By using a bulky ester such as *tert*-butyl benzoate

Table 1. Dialkylation of various benzoates with methyl iodide.



Entry	R	Molar amounts (Sr, MeI)/ester	Yield [%]
1	Me	2.5	96
2	Et	2.5	96
3	*i*Pr	3.0	91
4	*t*Bu	3.0	74

[‡] Part 1: See ref. [12b].

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and slightly increasing the amount of methyl iodide (3.0 molar amounts), the corresponding product was afforded in good yield (Entry 4 in Table 1). In each case, we did not obtain the dihydride product (α-methylstyrene). Although we also tried the reaction under similar conditions using magnesium metal, good and easily reproducible results were hard to obtain. In contrast, our method is simple and easy, and good results can consistently be obtained.

Next, the scope and versatility of the present reaction were investigated by using various alkyl iodides, and the results are summarized in Table 2. Methyl benzoate reacted with primary alkyl iodides to afford the corresponding adducts in good yields. However, the reactions of the ester with a *sec*-alkyl or *tert*-alkyl iodide, such as isopropyl iodide or *tert*-butyl iodide, were sluggish and gave the corresponding adducts in very low yields.

Table 2. Dialkylation of methyl benzoate with various alkyl iodides.

Entry	R	Molar amounts (Sr, RI)/ester	Yield [%]
1	Me	2.5	96
2	Et	2.5	80
3	*n*Bu	3.0	84
4	*i*Bu	3.0	96
5	*i*Pr	3.0	–[a]
6	*t*Bu	3.0	–[a]

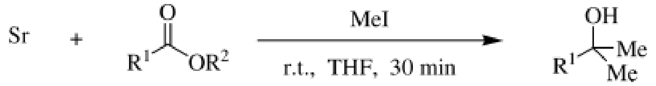
[a] The reactions were sluggish and the desired products were obtained only in negligible amounts. In these cases, we obtained small amounts of the *p*-alkylated product (the 1,6-adduct of the benzoate). See ref.[12a].

The generality of the present reaction was investigated by using various esters and methyl iodide, and the results are summarized in Table 3. It should be noted that functional groups such as olefin or bromide remain intact under the reaction conditions. Interestingly, the reactions proceeded smoothly to give the products in good yields with esters that have an α proton (Entries 3–7 in Table 3). In previous studies,[12] the results for the alkylation of aldehydes that have an α proton or of imines that are derived from enolizable aldehydes were poor. One of the reasons may be that alkylstrontium halide analogues have a strong nucleophilicity, as well as a strong basicity, which obstructs the alkylation of these kinds of aldehydes or imines. However, in this case, when using enolizable esters, dialkylated alcohols were obtained in good yields. Thus, the reason may be that the acidities of α protons in esters are lower than those of aldehydes or imines.

In summary, alkyl halides react with metallic strontium to produce alkylstrontium halide analogues that feature strong nucleophilicity as well as strong basicity, which presents some difficulty in controlling their reactions. Nevertheless, the Barbier-type alkylation of esters with alkyl iodides proceeded smoothly at room temperature under argon to afford the corresponding dialkylated alcohols in good yields. Investigation of the reaction mechanism and further applications are now in progress.

Supporting Information: Representative experimental procedures, and NMR and IR spectra of all products (see footnote on the first page of this article).

Table 3. Dimethylation of various esters with methyl iodide.



Entry	R^1	R^2	Molar amounts (Sr, MeI)/ester	Yield [%]
1	*p*-ClC_6H_4	Me	3.0	90
2	*p*-$CH_3OC_6H_4$	Me	2.5	52[a]
3	$PhCH_2$	Me	2.5	81
4	$PhCH_2CH_2$	Et	3.0	90
5	$CH_3(CH_2)_{14}$	Me	3.0	84
6	$CH_2=CH(CH_2)_8$	Me	3.0	87
7	$Br(CH_2)_5$	Et	3.0	84

[a] Dehydrated olefin was obtain in 19% yield.

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[9] As the rate of intermolecular alkylation of esters mediated by samarium diiodide was very slow, several strategies were developed such as an intramolecular reaction, the addition of metal salts. See, for example: a) G. A. Molander, C. R. Harris, *J. Am. Chem. Soc.* **1995**, *117*, 3705; b) F. Machrouhi, B. Hamann, J.-L. Namy, K. B. Kagan, *Synlett* **1996**, 633, and references cited therein; c) A. D. Scala, S. Garbacia, F. Helion, M.-I. Lannou, J.-L. Namy, *Eur. J. Org. Chem.* **2002**, 2989.

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[13] The chemical purity of strontium metal is >95%. Strontium metal was cut in liquid paraffin because it reacts vigorously with water.

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