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# The Convenient and Useful Esterification of Bulky Tertiary Alcohols Using Strontium Compounds

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Various esters reacted with metallic strontium and alkyl iodides to give dialkylated products, followed by adding acid chlorides or acid anhydrides to afford the corresponding bulky *tert*-alcohol esters in good yields.

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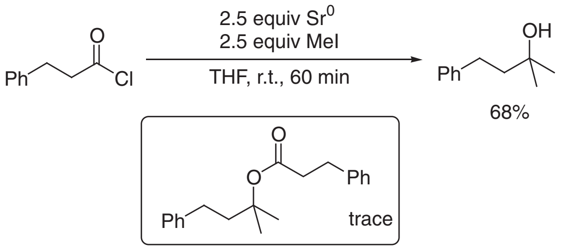
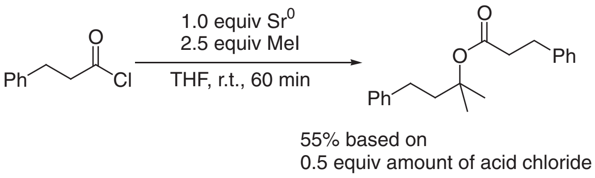
Few studies on the preparation and reactivity of organostrontium compounds have been found in the literature[1–3] outside our study. We have been investigating synthetic reactions using strontium compounds and have reported that the alkylation of aldehydes or imines with alkyl iodides[4] and dialkylation of esters with alkyl iodides[5] proceeded smoothly using metallic strontium to afford the corresponding adducts in good yields. When we recently extended our investigation to include the addition reaction of carboxylic acids, we found that carboxylic acids reacted with metallic strontium and alkyl iodides to give monoalkylated ketones preferentially, in moderate-to-good yields.[6] In addition, the new alkylation method at the *p*-position of the aromatic ring of benzoic acid was demonstrated.[7] In the reaction of 3-phenylpropionyl chloride instead of carboxylic acid with methyl iodide, the dimethylated product was obtained in 68% yields, and the unexpected ester, 3-methyl-1-phenylbutan-3-yl 3-phenylpropionate, was detected in a trace amount (eq 1).



(1)

We thus further investigated this unexpected ester. Esterification of alcohols is one of the most fundamental and important reactions in organic synthesis. However, the preparation of bulky secondary or tertiary alcohol esters is known to be difficult compared with that of primary alcohol esters. Although there are various reports for the synthesis of bulky alcohol esters,[8,9] it is still difficult to prepare these bulky alcohol esters in good yield. This difficulty is due to the reaction which requires long reaction time with a large excess amount of either carboxylic acids or alcohols.[9] This prompted us to try esterification of bulky *tert*-alcohols with carboxylic acid derivatives using strontium metal.

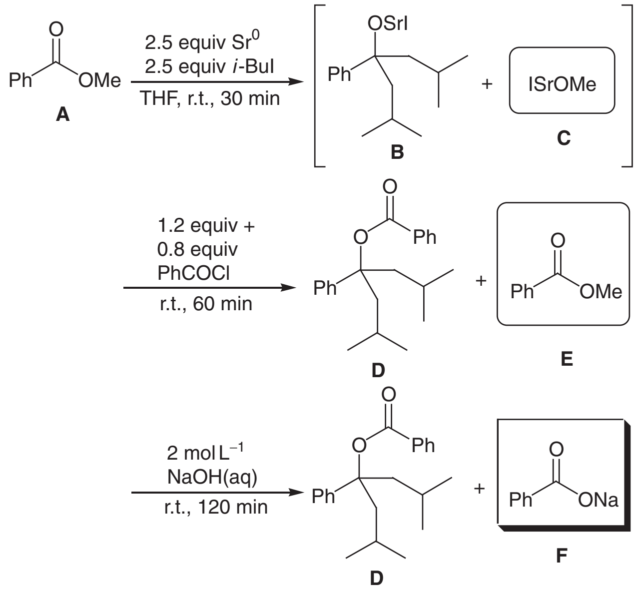
We first examined the reaction using 3-phenylpropionyl chloride and methyl iodide under various conditions. As shown at eq 2, *tert*-alcohol ester was obtained in a 55% yield.



(2)

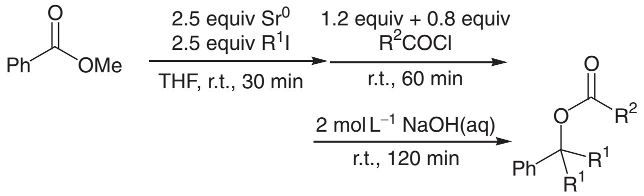
Next, in order to increase the yields, we attempted a reaction of strontium bulky *tert*-alkoxide produced by strontium-mediated dialkylation into ester with carboxylic acid chloride. Investigating the molar ratio and adding methods of each agent using methyl benzoate and isobutyl iodide, it was found that 2.5 molar equivalents of isobutyl iodide was added to the THF suspension of methyl benzoate and 2.5 molar equivalents of metallic strontium. This was followed by adding benzoyl chloride as follows; 1.2 molar equivalents of benzoyl chloride was added, successively 0.8 molar equivalents of benzoyl chloride was added after 15 min. The crude products were purified by chromatography on silica gel to give the corresponding ester **D** in 86% yield (Scheme 1).

Although a good yield was obtained from the ester **D**, a new problem has arisen. In the reaction of ester **A**, not only the desired alkoxide **B** but also the undesired alkoxide **C** were produced. Furthermore these reacted with acid chloride to derive ester **D** and **E** in equal amounts which was difficult to separate. In order to purify the crude products, the mixture was treated with 2 mol L$^{-1}$ NaOH(aq) to hydrolyze with only ester **E** and to



**Scheme 1.** Formation of ester and removement of coproducts.

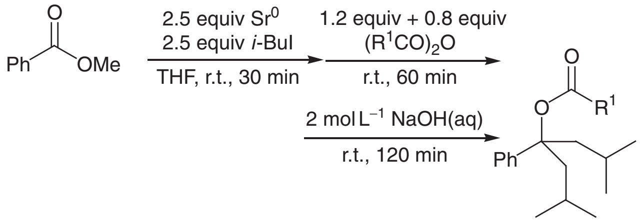
**Table 1.** Investigation of the reaction of methyl benzoate with various alkyl iodides using various acid chlorides



| Entry | R$^1$ | R$^2$ | Yield/%[a] |
|---|---|---|---|
| 1 | *i*-Bu | Ph | 90 |
| 2 | *i*-Bu | *t*-Bu | 88 |
| 3 | *i*-Bu | $PhCH_2CH_2$ | 17 |
| 4 | *n*-Bu[b] | Ph | 87 |
| 5 | Et | Ph | 95 |
| 6 | Me | Ph | 92 |

[a]Isolated yields. [b]Using 3.0 equiv of Sr and *n*-BuI.

**Table 2.** Investigation of the reaction using acid anhydrides



| Entry | R$^1$ | Yield/%[a] |
|---|---|---|
| 1 | Ph | 81 |
| 2 | Me | 76[c] |
| 3 | $PhCH_2CH_2$[b] | 60 |

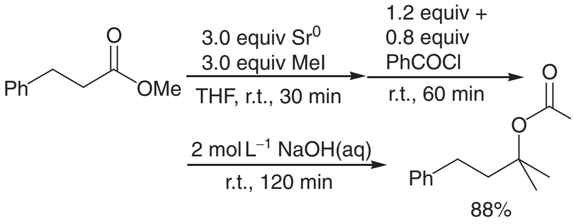
[a]Isolated yields. [b]Using 3.0 equiv of Sr and *i*-BuI. [c]Hydrolysis was not performed.

afford only ester **D** in 90% yield. Because the bulky *tert*-alcohol esters are more stable under basic conditions rather than methyl benzoate.

The reaction was applied to methyl benzoate with various alkyl iodides using various acid chlorides, and proceeded smoothly to afford the bulky *tert*-alcohol esters in good yields, which were summarized in Table 1.[10] Among them, using 3-phenylpropionyl chloride, the yield was decreased (Entry 3).

Next, we tried to change the acylating agent from acid chlorides to acid anhydrides as shown in Table 2. The strontium alkoxide **B** was reacted with 3-phenylpropionic anhydride instead of 3-phenylpropionyl chloride to give the corresponding ester in moderate to good yield (Entry 3).

Furthermore, the reaction of methyl 3-phenylpropionate having an $\alpha$-proton as a starting ester with methyl iodide and benzoyl chloride as an acylating agent also proceeded smoothly obtaining the corresponding adduct in good yield (eq 3).



(3)

When the strontium-mediated reaction was compared with the reaction using alkyllithium or Grignard reagent under similar reaction conditions at Entry 4 in Table 1, reactions proceeded slowly to obtain the corresponding esters in only 22% or 12% yields, and dialkylated alcohols preferentially, respectively.[10]

In summary, various esters reacted with metallic strontium and alkyl iodides to give dialkylated products, followed by adding acid chlorides or acid anhydrides during a short reaction time to afford the corresponding bulky *tert*-alcohol esters in good yields. For more practical methods, more increasing yields and further applications are now in progress.

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