A New Synthetic Method for Methyl Ketones from Carboxylic Acids Using Metallic Strontium and Methyl Iodide

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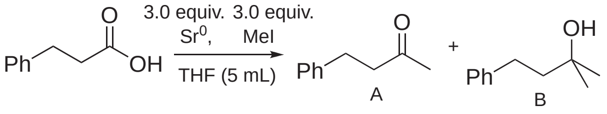
Carboxylic acids reacted with metallic strontium and methyl iodide to give methyl ketones preferentially in moderate to good yields.

Few studies on the preparation and reactivity of organostrontium compounds were found in the literature[1–3] until the current decade. We have been investigating synthetic reactions using strontium compounds, and we reported the alkylation of aldehydes or imines with alkyl iodides using metallic strontium.[4] When we recently extended our investigation to include addition reactions of esters, we found that dialkylation of esters with alkyl iodides using strontium metal proceeded smoothly to afford the corresponding adducts in good yields.[5] When we attempted the reaction with carboxylic acids instead of esters, the monoalkylated ketone, rather than the dialkylated alcohol, was obtained preferentially (eq 1).



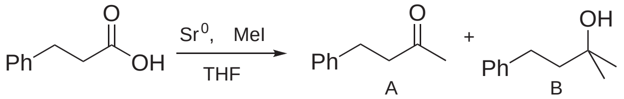
(1)

Total yield 63% (A:B = 76:24)

In the alkylation of esters using strontium, only the dialkylated adducts were produced in good yields; monoalkylated ketones were not obtained. It is not usually easy to control the over-addition of alkylating agents to carboxylic derivatives.

The preparation of monoalkylated ketones from carboxylic acids is one of the important transformations in organic synthesis. It is well known that the lithium carboxylates react with alkyl- and aryl-lithium reagents to afford the ketones in good yields.[6] Although the early literature[7] records a number of examples of ketones synthesis by reactions of the Grignard reagents to carboxylic acids or metal carboxylates, this method has generally been found less satisfactory than the corresponding reaction of organolithium compounds.[8] To our knowledge, there are no reports of practical syntheses using "carboxylic acids" besides the above and modified versions thereof, although there are a large number of works using "carboxylic derivatives" such as acid chlorides with organocuprates[9] or organocadmiun reagents,[10] and Weinreb's amides[11] with organolithium reagents, etc.[12] This prompted us to inverstigate monoalkylation of carboxylic acids using strontium metal.

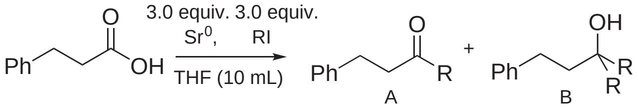
Table 1. Investigation of reaction conditions



Entry	Sr, MeI/equiv.	THF/mL	Total yield/%[a]	A:B
1	2.0	5	39	46:54
2	2.5	5	44	59:41
3	3.0	5	63	76:24
4	3.5	5	62	74:26
5	3.0	2.5	46	67:33
6	3.0	10	84	75:25

[a] Isolated yields.

Table 2. Investigation of several alkyl iodides



Entry	R-	Total yield/%[a]	A:B
1	Me	84	75:25
2	Et	48	73:27
3	*n*-Bu	41	73:27
4	*i*-Bu	22	77:23

[a] Isolated yields.

We examined the reaction using 3-phenylpropanoic acid and methyl iodide under various conditions. Investigation of the molar ratio of the methylating agents showed that 3 molar equivalents of agents were required (Table 1, Entry 3). Moreover, we investigated the effects of varying the amount of solvent, and it was found that dilute conditions (THF 10 mL) resulted in an improvement in the yields (84%) with moderate selectivity towards the monomethylated ketone rather than the dimethylated alcohol (75:25) (Entry 6).

Next we investigated the reactions of various alkyl iodides using 3-phenylpropanoic acid. Alkyl iodides other than methyl iodide were found to cause a reduction in the yield with similar selectivities (Table 2).

The reaction was applied to various carboxylic acids, and the results are summarized in the "Direct method" column in Table 3. When aromatic or aliphatic carboxylic acids were used, the reactions proceeded smoothly to afford the corresponding products in good yields with moderate selectivities (Entries 1–7). It is noted that carboxylic acids containing several functional groups such as chloro, bromo, or olefin reacted to give the corresponding adducts in good yields (Entries 3, 6, and 7).

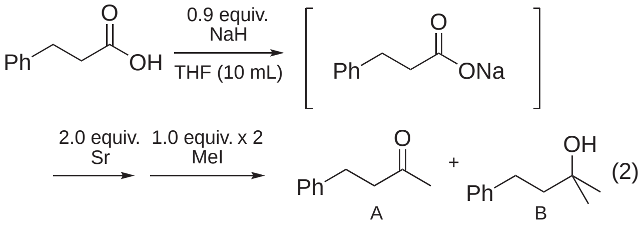
Further investigation was carried out in order to obtain increased selectivities. On the basis of the results obtained,[13] a reaction was developed in which the carboxylic acid was converted into its sodium salt using sodium hydride, followed by 2 molar equiv. of strontium metal and 2 molar equiv. of methyl iodide (in two separate portions) were added to the reaction mixture. This resulted in a slightly decrease in the yield (69%), but helped to prevent the over-addition of the methylating agent and giving a dramatically improvement in high selectivities of 93:7

Table 3. Investigation of methyl ketones synthesis from various carboxylic acids[a] or sodium salts[b]

Entry	RCOOH	The direct method[a]		Sodium salt's method[b]	
		Total yield/%[c]	A:B	Total yield/%[c]	A:B
1	PhCOOH	76	76:24	59	93:7
2	4-$CH_3C_6H_4COOH$	83	81:19	76	88:12
3	4-ClC_6H_4COOH	84	80:20	75	92:8
4	$Ph(CH_2)_2COOH$	84	75:25	69	93:7
5	$CH_3(CH_2)_8COOH$	84	77:23	64	84:16
6	$CH_2{=}CH(CH_2)_8COOH$	83	73:27	53	92:8
7	$Br(CH_2)_5COOH$	77	80:20	50	94:6

[a]See Ref. 14 for the reaction conditions. [b]See Ref. 15 for the reaction conditions. [c]Isolated yields.

(eq 2).[16] The reaction was applied to various carboxylic acids under these conditions, and the results are summarized in Table 3 (sodium salt's method). The reaction proceeded smoothly to afford the monoalkylated adducts in moderate to good yields with high selectivities.



Total yield 69% (A:B = 93:7)

In summary, a new method of synthesizing methyl ketones from carboxylic acids was demonstrated. The reaction of sodium carboxylates with 2.0 molar equivalents of methyl iodide and metallic strontium took place smoothly to give the corresponding methyl ketones with high selectivities. Further applications of the practical method are now in progress.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

References and Notes

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13 We also attempted to convert the carboxylic acid to lithium salt using butyllithium for a similar reaction, but we obtained no good result.

14 A typical reaction procedure using carboxylic acid (the direct method): Under an argon atmosphere, 3-phenylpropanoic acid (153 mg, 1.02 mmol), THF (10 mL), and methyl iodide (445 mg, 3.13 mmol) were added successively to metallic strontium (267 mg, 3.04 mmol) at room temperature. After stirring for 30 min, the reaction mixture was quenched with an aqueous solution of 0.2 M hydrochloric acid (20 mL) ($1\,M = 1\,mol\,dm^{-3}$). The organic materials were extracted with diethyl ether (30 mL × 3), and the combined organic layers were washed successively with 5% $NaHSO_3$ (aq), 2 M NaOH (aq) and brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by thin layer chromatography on silica gel (hexane:ethyl acetate = 8:1) to give the corresponding monomethylated product, 4-phenyl-2-butanone (95 mg, 63% yield) as yellow oil and the corresponding dimethylated product, 4-phenyl-2-methyl-2-butanol (35 mg, 21% yield) as yellow oil.

15 A typical reaction procedure using sodium carboxylate (sodium salt's method): Under an argon atmosphere, 3-phenylpropanoic acid (151 mg, 1.00 mmol) was added to a THF (10 mL) suspension of 60% sodium hydride (36 mg, 0.89 mmol) washed with anhydrous hexane at room temperature. After stirring for 30 min, metallic strontium (184 mg, 2.10 mmol), methyl iodide (162 mg, 1.14 mmol) and another portion of methyl iodide (161 mg, 1.13 mmol) were added successively to the reaction mixture at interval of 15 min at room temperature. After stirring for 45 min, the reaction mixture was quenched with an aqueous solution of 0.2 M hydrochloric acid (20 mL) ($1\,M = 1\,mol\,dm^{-3}$), followed by a work-up similar to that carried out in the previously described reaction (direct method) to give the corresponding monomethylated product (94 mg, 64% yield) as yellow oil and the corresponding dimethylated product (8 mg, 5% yield) as yellow oil.

16 These selectivities seem to be influenced by the formation of metal alkoxy acetals intermediates, but the details are not yet clear.

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