The Barbier-Type Alkylation of Aldehydes with Alkyl Halides in the Presence of Metallic Strontium

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In the presence of metallic strontium, the Barbier-type alkylation of aldehydes with alkyl iodides proceeded smoothly at -15 °C under an argon atmosphere to afford the corresponding alkylated alcohols in moderate to good yields. The unusual addition reaction of ethyl benzoate with *tert*-butyl iodide took place to give the *p-tert*-butylated alkylated product (the 1,6-adduct of the benzoate) in 55% yield. Using strontium isopropoxide, the Meerwein–Ponndorf–Verley-type reduction of the aldehyde proceeded smoothly under reflux conditions in 2-propanol.

Organometallic compounds comprise some of the most versatile reagents in organic synthesis, and among them are organometallic compounds of alkaline-earth elements.^{1,2} Numerous reports have been published on the Grignard (or Barbier) reaction using metallic magnesium and alkyl halides, which is one of the most useful and convenient methods for performing alkylation of carbonyl compounds.³ Furthermore, there are various reports on the preparation and reactivity of the organometallic compounds of calcium and barium.² In contrast, fewer studies on the preparation and reactivity of organostrontium compounds are found in the literature.^{4,5} Lindsell et al. described the character of alkylstrontium halides in the literature⁴ as follows: "The organostrontium compounds are very reactive solids, and decompose rapidly in moist atmosphere and slowly in vacuo at ambient temperature to give some species. The freshly prepared organostrontium compounds are moderately soluble in the more polar ethereal solvents, recrystallization being possible from these solvents." They also reported that alkylstrontium halides, prepared with specially treated metallic strontium and alkyl halides, reacted with carbonyl compounds to afford the corresponding products in low yields, with the exception of the reaction with benzophenone.⁴ We have re-investigated synthetic reactions using strontium compounds and herein wish to report the alkylation of aldehydes with alkyl iodides using metallic strontium, the unusual addition reaction of ethyl benzoate with tert-butyl iodide, and the first example of the reduction of aldehydes using strontium isopropoxide.

Discussion

First, the alkylation of aldehydes with methyl iodide was examined under various reaction conditions. When methyl iodide was reacted with metallic strontium at -15 °C in THF followed by the addition of 3-phenylpropanal (the Grignard-type procedure), the methylated compound was obtained in low yield (vide infra), although the aldehyde disappeared on TLC. Using benzaldehyde instead of 3-phenylpropanal, the desired product was obtained in 89% yield by estimation with ¹H NMR. However, isolation of the product was problematical and the material balance was inaccurate, possibly because of the volatility of 1phenylethanol. Therefore, in order to find the optimum reaction conditions, we examined the reaction using 2-naphthaldehyde. When methyl iodide was added to a THF suspension of the aldehyde and metallic strontium at -15 °C (the Barbier-type procedure), methylation of the aldehyde proceeded smoothly to afford the desired product, in contrast to the Grignard-type procedure. Further, we investigated the Barbier-type procedure under various reaction conditions at -15 °C, the results of which are shown in Table 1. Using slight excesses of methyl iodide and metallic strontium compared to the amount of aldehyde, the reaction proceeded smoothly to give the corresponding adduct in good yields (Entries 4-8). The reactions conditions which gave the highest yield (Entry 6, Table 1) were assumed to be optimum and were therefore adopted in future experiments.

Next, the scope and versatility of the present reaction were investigated by using various aldehydes and various alkyl iodides. The results are summarized in Table 2. 2-Naphthaldehyde reacted with ethyl iodide or butyl iodide instead of methyl

 Table 1. Investigation of the Molar Ratio of Methylation Reagent to 2-Naphthaldehyde

Sr	-15 °C, THF) CH₃I → ───→		
Entry	Aldehyde/mmol	MeI/mmol	Sr/mmol	Yield/%
1	1	1	0.5	37
2	1	1	1	61
3	1	2	1	51
4	1	3	1	74
5	1	1.2	1.5	75
6	1	1.3	2	82
7	1	2	2	78
8	1	3	3	75

Table 2.	Alkylation	of Various	Aldehydes	by Using	Alkyl	Iodides	in the	Presence	of Met	allic
Stronti	um ^{a)}									

	Sr <u>R'CHO</u> -15 °C, TH	$\overrightarrow{F} \xrightarrow{R^2 I} \xrightarrow{OH} H^2$	
Entry	R ¹ CHO	R ² I	Yield/% ^{b)}
1	СНО	CH ₃ I	82
2		CH ₃ CH ₂ I	52
3		CH ₃ CH ₂ CH ₂ CH ₂ I	45
4		(CH ₃) ₂ CHI	6
5	_	(CH ₃) ₃ CI	2
6	Сно	CH ₃ I	88
7			27 ^{c)}
8	СН ₃ О-СНО	CH ₃ I	43
9	Ph	CH ₃ I	56
10	CH ₃ (CH ₂) ₇ CHO	CH ₃ I	43
11	Ph	CH ₃ I	49

a) The reaction was carried out using an aldehyde:an alkyl iodide:metallic strontium = 1:1.3:2. b) Isolated yield. c) The reaction was carried out at -20 °C. 4-Allylbenzaldehyde and 1,2-diphenyl-1,2-ethanediol were obtained in 11% and 7% yields, respectively.

iodide to afford the corresponding adducts in moderate to good yields (Entries 2 or 3). However, as shown in Entries 4 and 5, the reactions of 2-naphthaldehyde with a sec-alkyl or tert-alkyl iodide, such as isopropyl iodide or tert-butyl iodide, were sluggish and gave the corresponding adducts in low yields (6% or 2%, respectively). Benzaldehyde reacted smoothly with methyl iodide to afford the methylated product in good yield, but in the reaction with p-anisaldehyde, the yield decreased (Entries 6 and 8). Using the aliphatic aldehydes, the reactions also proceeded smoothly to give the desired adducts in moderate to good yields (Entries 9 and 10), although it is noteworthy that the products were obtained in low yields when a Grignard-type procedure was used. α , β -Unsaturated aldehydes such as cinnamaldehyde predominantly gave the 1,2-addition product (Entry 11). Lindsell et al. reported that the alkylstrontium halides, prepared with specially treated metallic strontium and alkyl halides, reacted with carbonyl compounds.⁴ However, they reported that the reaction proceeded smoothly only with benzophenone to afford the corresponding methylated product in 69% yield, and that using benzaldehyde the desired product was obtained in only 21% yield.⁴ In our method, the reaction of several alkyl iodides with various aldehydes proceeded smoothly with commercially available metallic strontium to afford the corresponding alkylated products in moderate to good yields.

Benzaldehyde also reacted with methyl iodide to obtain 1phenylethanol in very good yield (88%) (Entry 6), although the reaction of benzaldehyde with allyl iodide gave the corresponding allylated alcohol, 1-phenyl-3-buten-1-ol, in 27% yield (Entry 7). In this case, we investigated the by-products in detail. As shown in Eq. 1, in addition to 1-phenyl-3-buten-1-ol, the pinacol coupling product, hydrobenzoin, and 4-allyl-benzaldehyde were obtained in 11% and 7% yields, respectively. In this reaction, allylation of the carbonyl group of benzaldehyde and at the *p*-position of the aromatic ring of benzaldehyde occurred competitively.



We were interested in the *p*-allylated product because this allylation reaction is unusual in these conditions. We tried the reaction of allyl iodide with various carbonyl compounds or aryl compounds such as benzaldehyde, phenyl alkyl ketones, benzoic acid, benzoate, benzonitrile, nitrobenzene or chlorobenzene. Among them, only the reaction of allyl iodide with ethyl benzoate, similar to the reaction of allyl iodide with benzaldehyde, proceeded to afford the corresponding *p*-allylated product in low yield. When we examined a similar reaction using *tert*-bu-



Scheme 1.

tyl iodide, which produces the stable radical species as well as allyl iodide, a mixture of p-alkylated compound and the 1,6-adduct were obtained in moderate to good yield, although it was difficult to separate the reaction mixtures. As a result of the investigation of the reaction conditions, the reaction took place at -20 °C, and, in order to purify the crude products, the mixture was successively oxidized using 2,3-dichloro-5,6-dicyano-1,4benzoquinone (DDQ) to afford ethyl 4-tert-butylbenzoate as the sole product in 55% yield (Eq. 2). There are only a few reports of the *p*-alkylation of aromatic carbonyl compounds. Yamamoto et al. reported that the *p*-alkylation of benzaldehyde with butyllithium took place using a special sterically bulky aluminium catalyst.⁶ Hattori and Miyano reported that the *p*-alkylation of benzoate with butyllithium proceeded using a particularly sterically bulky ester.⁷ However, our reaction system is simpler than the above reactions. Further investigation is now in progress.



We obtained an unexpected product when we investigated the methylation of aldehydes. We tried a Grignard-type procedure in which methyl iodide (2.0 molar amounts to the aldehyde) was added to a THF suspension of metallic strontium (2.0 molar amounts to the aldehyde) at room temperature under an argon atmosphere and, after a 30 min interval, 3-phenylpropanal was added to the reaction mixture. The unexpected dimethylated product, 2-methyl-4-phenyl-2-butanol, was obtained in low yield instead of the desired monomethylated product, 4-phenyl-2-butanol (Eq. 3). We were interested in the unexpected dimethylated product although a number of unidentified by-products were also obtained. Therefore, we tried some experiments to find out the mechanism of dimethylation using benzaldehyde. When methylstrontium iodide, prepared in situ from 2 molar amounts of methyl iodide and 2 molar amounts of metallic strontium, was reacted with an equimolar amount of benzaldehyde, three products, 1-phenylethanol, benzyl alcohol, and 2-phenylpropene were obtained in 52%, 20%, and 16% yields, respectively (Eq. 4).8 However, the dimethylated alcohol, 2-phenyl-2-propanol, was not obtained. Based on the above result, we propose the reaction mechanism shown in Scheme 1: 1) Methylstrontium iodide reacts with benzaldehyde to afford the mono-methylated product, 1-phenylethanol. 2) The Meerwein-Ponndorf-Verley (MPV) type reduction between strontium 1-phenylethoxide and benzaldehyde occurs to give acetophenone and benzyl alcohol. 3) Acetophenone reacts immediately with the remaining methylstrontium iodide to produce 2-phenyl-2-propanol. 4) The dimethylated alcohol changes to 2-phenylpropene because 2-phenyl-2-propanol is easily dehydrated.



$$\begin{array}{c} O \\ Ph H \\ Sr + CH_{3}I \\ 2.0 \text{ mol amt} \\ 2.0 \text{ mol amt} \\ 2.0 \text{ mol amt} \\ \end{array} \begin{array}{c} O \\ H \\ 1.0 \text{ mol amt} \\ THF, r.t., 19 \text{ h} \end{array}$$

$$(4)$$

$$\begin{array}{ccccccc} OH & CH_3 \\ Ph + CH_3 + Ph OH + Ph \\ 52\% & 20\% & 16\% \end{array}$$

In the case of 3-phenylpropanal, the results suggested that an MPV-type reduction proceeded between the aldehyde and the strontium alkoxide of the monomethylated adduct, and that the dimethylated adduct was produced by the methylation of methyl ketone, 4-phenyl-2-butanone, generated by the above Oppenauer oxidation. To our knowledge, this is the first report of a reduction by strontium alkoxide. Although the reaction mechanism is not clear; it is also presumed that strontium hydride, generated by the strontium alkoxide, reduced the aldehyde.⁹

These results prompted us to examine the MPV-type reduction of 2-naphthaldehyde with strontium alkoxide. 2-Naphthaldehyde reacted with strontium isopropoxide in THF under reflux condition to give the reduced product in only 6% yield (Eq. 5). However, when the solvent was changed to 2-propanol, the reaction of 2-naphthaldehyde with strontium isopropoxide proceeded smoothly under reflux conditions to afford the corresponding product in good yield (Table 3). Thus, we were able to decrease the amount of strontium isopropoxide to 0.5 the molar amount compared to an equimolar amount of aldehyde and still obtain the desired product in 67% yield (Entry 1 in Table 3).



In summary, in the presence of metallic strontium, the Barbier-type alkylation of aldehydes with alkyl iodides proceeds smoothly at -15 °C under an argon atmosphere to afford the corresponding alkylated alcohols, and the unusual addition re-

Table 3. The Reduction of 2-Naphthaldehyde Using Strontium Diisopropoxide

CHO	Sr(O ⁱ Pr) ₂	ОН		
	ⁱ PrOH, reflux, 4 h			
Entry	$Sr(O^iPr)_2/mol amt$	Yield/%		
1	0.5	67		
2	1.0	75		
3	2.0	66		

action of ethyl benzoate with *tert*-butyl iodide proceeds to give ethyl *p-tert*-butylbenzoate in moderate to good yield. Under reflux conditions in 2-propanol, the Meerwein–Ponndorf–Verleytype reduction proceeded between aldehydes and strontium isopropoxide. To our knowledge, this reduction by strontium alkoxide is the first to be reported.

Experimental

General Methods. ¹H NMR spectra were recorded with a JEOL EX-90A spectrometer and chemical shifts (δ) were reported in ppm using tetramethylsilane as an internal standard. IR spectra were obtained using a HORIBA FT-IR 210 spectrometer. Commercially available metallic strontium ingot in liquid paraffin was cut into small pieces with a cutter in preparation for the start of each reaction. Tetrahydrofuran was freshly distilled from sodium diphenylketyl. Preparative thin layer chromatography (TLC) was performed on silica gel (Wakogel B-5F). All reagents were commercially available and used without further purification.

General Procedure for the Methylation of 2-Naphthaldehyde Using Metallic Strontium and Methyl Iodide. Under an argon atmosphere, 2-naphthaldehyde (161 mg, 1.03 mmol), and methyl iodide (183 mg, 1.29 mmol) were added successively to a THF (5 mL) suspension of metallic strontium (180 mg, 2.06 mmol) at -15 °C. After stirring for 7 h, the reaction mixture was quenched with an aqueous solution of 1 M hydrochloric acid (10 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 water and brine, and dried over anhydrous Na₂SO₄. After evaporation of the solvent, the residue was purified by thin layer chromatography on silica gel (hexane:ether = 4:1) to give the corresponding methylated product, 1-(2-naphthyl)ethanol (145 mg, 82% yield).

¹H NMR (90 MHz, CDCl₃) δ 1.5 (3H, d, J = 6.4 Hz), 2.2 (1H, brs), 5.0 (1H, q, J = 6.4 Hz), 7.4–7.8 (7H, m). IR (neat) 3318, 2969, 2923, 2605, 1363, 1124, 1074 cm⁻¹. This product was identified by comparison with an authentic sample prepared from a known procedure.¹⁰

The spectral data of the products were as follows.

1-(2-Naphthyl)-1-propanol. ¹H NMR (90 MHz, CDCl₃) δ 0.9 (3H, t, J = 7.3 Hz), 1.8 (2H, quint, J = 7.2 Hz), 2.1 (1H, brs), 4.7 (1H, t, J = 6.3 Hz), 7.2–7.9 (7H, m). IR (neat) 3375, 3055, 2964, 2931, 2875, 1455, 1271, 1126, 1018, 856, 820, 748 cm⁻¹. This product was identified by comparison with an authentic sample prepared from a known procedure.¹⁰

1-(2-Naphthyl)-1-pentanol. ¹H NMR (90 MHz, CDCl₃) δ 0.9 (3H, brm), 1.3 (2H, brm), 1.7–1.8 (4H, m), 2.1 (1H, brs), 4.8 (1H, t, J = 6.5 Hz), 7.4–7.8 (7H, m). IR (neat) 3375, 3054, 2931, 1602, 1465, 1270, 1126, 1043, 819, 746 cm⁻¹. This product was identified by comparison with an authentic sample prepared from a known procedure.¹⁰

1-Phenylethanol. This product was identified by comparison with an authentic sample.¹¹

1-(4-Methoxyphenyl)ethanol. This product was identified by comparison with the literature.¹²

4-Phenyl-2-butanol. This product was identified by comparison with an authentic sample.¹¹

2-Dodecanol. This product was identified by comparison with the literature.¹²

4-Phenyl-3-buten-2-ol. This product was identified by comparison with the literature.¹²

General Procedure for the *p*-Alkylation of Ethyl Benzoate

Using tert-Butyl Iodide and for the Oxidation of the Resulting Mixture of the p-Butylated Product and 1,6-Adduct. Under an argon atmosphere, ethyl benzoate (362 mg, 2.41 mmol) was added to a THF (10 mL) suspension of metallic strontium (355 mg, 4.05 mmol) at -20 °C, followed by tert-butyl iodide (579 mg, 3.15 mmol). After stirring for 36 h, the reaction mixture was quenched with 1 M hydrochloric acid (10 mL). The organic materials were extracted with diethyl ether (30 mL \times 3), and the combined organic layers were washed successively with water and brine, and dried over anhydrous Na2SO4. After evaporation of the solvent, the residue was reacted with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (453 mg, 1.99 mmol) in toluene (15 mL) under reflux conditions. After stirring for 2 h, the reaction mixture was quenched with water (10 mL). The organic materials were extracted with diethyl ether (30 mL \times 3), and the combined organic layers were washed successively with water and brine, and dried over anhydrous Na₂SO₄. After evaporation of the solvent, the residue was purified by thin layer chromatography on silica gel (hexane:ether = 60:1) to give the corresponding *tert*-butylated product, ethyl 4-tert-butylbenzoate (274 mg, 55% yield). This product was identified by comparison with an authentic sample.¹¹

General Procedure for the Meerwein–Ponndorf–Verley-Type Reduction of 2-Naphthaldehyde Using Strontium Isopropoxide. Under an argon atmosphere, to a solution of strontium isopropoxide (124 mg, 0.604 mmol) in 2-propanol (5 mL) at room temperature was added 2-naphthaldehyde (91 mg, 0.585 mmol). After stirring for 4 h under reflux conditions, the reaction mixture was quenched with an aqueous solution of 1 M hydrochloric acid (10 mL). The organic materials were extracted with diethyl ether (30 mL × 3), and the combined organic layers were washed successively with water and brine, and dried over MgSO₄. After evaporation of solvent, the residue was purified by thin layer chromatography on silica gel (hexane:ether = 4:1) to give the corresponding methylated product, 2-naphthylmethanol (72 mg, 75% yield). This product was identified by comparison with an authentic sample.¹¹

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