The Chemistry of Alkylstrontium Halide Analogues: Barbier-type Alkylation of Imines with Alkyl Halides

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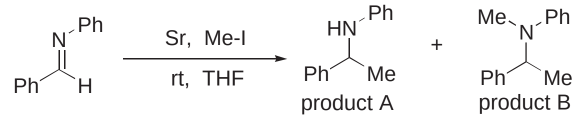
The chemistry of alkylstrontium halide analogues was examined. In the presence of metallic strontium, the Barbier-type alkylation of imines with alkyl iodides proceeded smoothly at room temperature under an argon atmosphere to afford the corresponding alkylated amines in good yields.

Organometallic compounds are some of the most versatile reagents, 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 in organic synthesis.[3] Also 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] We have investigated synthetic reactions using strontium compounds and have already reported the alkylation of aldehydes with alkyl iodides using metallic strontium.[6] When we extended our investigation to include the addition reaction of imines, we found that alkylation of imines with alkyl iodides using strontium metal proceeded smoothly to afford the corresponding adducts in good yields. Although the addition of organometallic reagents to C=N bonds of imine derivatives is an established and well-known reaction,[7] it's development has been limited compared to additions to aldehydes and ketones. One of reasons may be the poor electrophilicity of the azomethine carbon. To increase the electrophilicity of C=N bonds, several strategies were developed such as the introduction of electron-withdrawing groups at N atoms, or the activation of the C=N bonds by coordination to a Lewis acid.[8] Nevertheless, Barbier-type additions of simple imines have been severely limited, except for allylations.[9] Thus, to our knowledge, strontium-mediated Barbier-type alkylations are hitherto unknown in the literature.

Table 1. Investigation of the molar ratio of methyl iodide to *N*-benzylideneaniline[a]



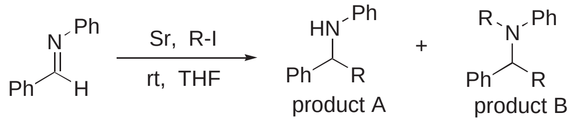
Entry	m.a.(Sr)	m.a.(MeI)	Yield(A)/%[a]	Yield(B)/%[b]
1	1.0	1.3	19	41
2	2.0	1.3	23	27
3	2.0	2.2	14	82
4	1.5	3.3	trace	90
5	2.0	5.2	trace	93

[a]See ref. 16 for a reaction procedure. [b]Isolated yields.

First, using *N*-benzylideneaniline (PhCH=NPh), the alkylation of imine with methyl iodide was examined under various reaction conditions. As shown in Table 1, when 1.3 molar amount of methyl iodide was added to a THF[10] suspension of 2.0 molar amounts of metallic strontium[11] and 1.0 molar amount of *N*-benzylideneaniline at room temperature, reaction proceeded to afford C-monomethylated amine and N,C-dimethylated amine in 23% and 27% yields, respectively (Entry 2). Increasing the amount of methyl iodide led to a corresponding increase in N,C-dimethylated amine, which was obtained as a sole product in 90% yield using 3.3 molar amounts of methyl iodide and 1.5 molar amounts of metallic strontium to the imine (Entry 4).

Next, the scope and versatility of the present reaction were investigated by using various alkyl iodides, and the results are summarized in Table 2. We found that, in contrast to using methyl iodide, *N*-Benzylideneaniline reacted with other alkyl iodides to afford the corresponding C-monoalkylated adducts as main or sole products in good yields. It is assumed that, during reaction, the steric hindrance presented by these more bulky alkyl halides, influenced the products obtained.[12] It was noteworthy, as shown in Entries 4 and 5, that the reactions of *N*-benzylideneaniline with a *sec*-alkyl or *tert*-alkyl iodide, such as isopropyl iodide or *tert*-butyl iodide, proceeded smoothly to give the corresponding adducts in moderate to good yields (55% or 61%, respectively). It is well-known that as the size and branching of alkyl groups at imines increases, addition yields decrease and reduction products such as pinacol-type self-coupling products are often generated.[13] However, in the reaction of organometallic reagents with *N*-benzylideneaniline, the addition of $MgBr_2$ (2 equiv.) to solutions of organometallic reagents (such as ethylmagnesium bromide, diethylcadmium, or diethylzinc) results in dramatic yield improvements.[14] In the absence of other metal salts, increasing yield requires a 1:2 ratio of *N*-benzylideneaniline to Grignard reagent.[15] However, with our method it is not necessary to use any additives, and it is sufficient to use 1.5

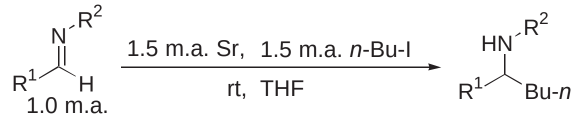
Table 2. Investigation of alkylation using several alkyl iodides[a]



Entry	R-	m.a.(Sr)	m.a.(R-I)	Yield(A)/%[b]	Yield(B)/%[b]
1	Et	1.5	1.5	87	trace
2	*n*-Bu	1.5	1.5	95	trace
3	*i*-Bu	2.0	2.2	82	trace
4	*i*-Pr	2.0	2.2	55	trace
5	*t*-Bu	3.0	3.0	61	trace

[a]See ref. 16 for a reaction procedure. [b]Isolated yields.

Table 3. Investigation of alkylation using several imines[a]



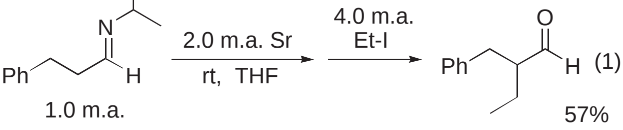
Entry	R^1-	R^2-	Yield/%[b]
1	4-$CH_3OC_6H_4$	C_6H_5	82
2	4-$CH_3C_6H_4$	//	84
3	4-ClC_6H_4	//	65
4	$C_6H_5CH{=}CH$	//	66
5	C_6H_5	//	95
6	//	4-$CH_3OC_6H_4$	83
7	//	4-ClC_6H_4	74
8	//	CH_3	49
9	//	Bn	40
10	//	*t*-Bu	29

[a]See ref. 16 for a reaction procedure. [b]Isolated yields.

molar amounts of alkylstrontium halide analogues to the imine.

Furthermore, the applications of the present reaction were investigated by using various imines. The results are summarized in Table 3. The reaction with the imines derived from aromatic aldehydes and aniline, 4-chloroaniline or 4-methoxyaniline gave the corresponding adducts in good yields (Entries 1–7). However using N-aliphatic imines, the reaction became complicated and yields decreased (Entries 8–10).

When the reaction was applied to imines derived from enolizable aldehydes, poor results were obtained. Under similar conditions, the reaction of ethyl iodide with the imine formed from 3-phenylpropanal and isopropyl amine gave α-ethylated aldehyde, 2-ethyl-3-phenylpropanal, in 30% yield. This result indicated to us that alkylstrontium halide analogues had strong nucleophilicity besides strong basicity. Using 4.0 molar amounts of ethyl iodide and 2.0 molar amounts of metallic strontium to 1.0 molar amount of the imine, the α-ethylated reaction proceeded to afford 2-ethyl-3-phenylpropanal in 57% yields (Eq 1).



In summary, alkyl halides reacted with metallic strontium to produce alkylstrontium halide analogues, which strong nucleophilicity besides strong basicity presented some difficulty in controlling their reactions. Nevertheless, the Barbier-type alkylation of imines with alkyl iodides proceeded smoothly at room temperature under an argon atmosphere to afford the corresponding alkylated amines in good yields. Investigation of the reaction mechanism and further applications are now progress.

References and Notes

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11 Commercially available metallic strontium ingot in liquid paraffin was cut into small pieces using a sharp knife in preparation for the start of each reaction.

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16 A typical reaction procedure: Under an argon atmosphere, *N*-benzylideneaniline (188 mg, 1.04 mmol) and butyl iodide (281 mg, 1.53 mmol) were added successively to a THF (5 mL) suspension of metallic strontium (138 mg, 1.57 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with an aqueous solution of 0.2 M hydrochloric acid (5 mL) (1 M = 1 mol dm^{-3}), and successively with 5% Na_2SO_4 aqueous solution (30 mL), filtered through a cake of celite. The organic materials were extracted with diethyl ether (30 mL × 3), and the combined organic layers were washed successively with 5% $NaHSO_3$ aqueous solution and brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on aluminum oxide (hexane:ethyl acetate = 20:1–4:1) to give the corresponding alkylated product, *N*-(1-phenylpentyl)aniline (218 mg, 95% yield) as a colorless oil.

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