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Preparation of dihomoallylic secondary amines through samarium mediated allylation of oximes

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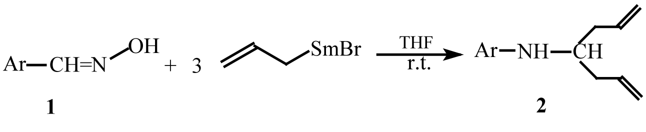
Abstract—The addition of allylsamarium bromide to oximes derived from aromatic aldehydes and methyl aryl ketones was studied and the dihomoallylic secondary amines were obtained in moderate to high yields under mild conditions. © 2002 Elsevier Science Ltd. All rights reserved.

The reactions of allylic organometallics have attracted much attention from organic chemists since it was shown that addition to carbonyl compounds is such an important synthetic method for the construction of carbon–carbon bonds.[1] In addition, compounds containing carbon–nitrogen unsaturated bonds are also good electrophiles capable of reacting with organometallics. In particular, the addition of allylic organometallics to the carbon–nitrogen double bond in imines constitutes an important method for the preparation of homoallylic amines, which are useful precursors for a variety of compounds by subsequent functionalization of the double bond.[2] In contrast to the large body of information on imines, the addition of allylic organometallics to the carbon–nitrogen double bond in oximes has been less investigated.[3]

Over the last decade, there has been growing interest in the use of samarium reagents in organic synthesis. The chemistry of samarium(II) iodide, an exceptional reagent used for promoting reductive reactions has already been well documented in several reviews,[4] and reactions mediated by metallic samarium and other samarium reagents have also been reported.[5] Wu has reported the Barbier-type allylation of ketones[6a] and carboxylic esters[6b] with allyl bromide mediated by metallic samarium, for which a mechanism including an allylsamarium bromide intermediate was suggested. In our initial work in this area, we found that the allylsamarium bromide reagent can be conveniently prepared and successfully used as an effective allylation reagent for imines,[2e] nitriles,[7] lactams and acyclic amides[8] to generate a host of compounds bearing homoallylic group(s). In continuation of our efforts to broaden the scope of the application of allylsamarium bromide in organic transformations, we report herein the diallylation of oximes with allylsamarium bromide, which, to our knowledge, has not been studied so far.

When 1 mmol of benzaldoxime **1a** was treated with 3 mmol of allylsamarium bromide in THF at ambient temperature, the purple color of allylsamarium bromide disappeared rapidly and TLC analysis showed that **1a** was consumed completely within 20 min. Subsequent isolation from the reaction mixture gave a colorless oil

Table 1. Reaction of aldoximes with allylsamarium bromide



Entry	Ar	Reaction time (min)	Yield (%)[a]
a	C_6H_5	20	91
b	4-$CH_3C_6H_4$	20	90
c	4-$CH_3OC_6H_4$	20	82
d	3-BrC_6H_4	40	87
e	4-ClC_6H_4	40	86
f	4-FC_6H_4	30	93

[a] Isolated yields based on aldoximes.

Keywords: allylsamarium bromide; oximes; dihomoallylic secondary amines.

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as the main product, the structure of which was unambiguously confirmed as **2a** by the results of IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analyses. Oximes derived from other aryl aldehydes also reacted readily with allylsamarium bromide and gave the corresponding dihomoallylic secondary amines in high yields (Table 1). Furthermore, it should be noted that when the ratio of allylsamarium bromide to aldoximes **1** was less than 3:1, products **2** were obtained in lower yields together with some recovered starting material **1**.

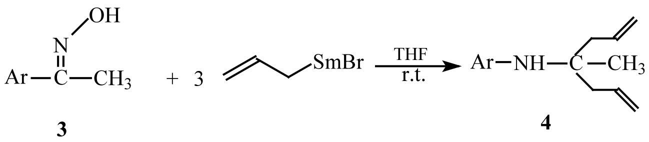
Several allylic organometallics have already been reported to react with benzaldoxime.[3a] Of these, allylmagnesium bromide added to benzaldoxime to afford the Beckmann rearrangement product **2a** in high yield, but the completion of this process needed as long as 16 h. Under similar reaction conditions, allylzinc bromide and allyllithium reacted with benzaldoxime with much lower chemo-selectivity and yields. Compared with these allylmetallic reagents, the allylation of aldoximes with allylsamarium bromide has considerable advantages, such as higher chemo-selectivity and yields, much shorter reaction times and milder reaction conditions.

Although the detailed mechanism of the above reaction has not been established, a plausible mechanism for the formation of **2** is proposed based on the literature[3a] (shown in Scheme 1). In the first step, allylsamarium bromide abstracts the active hydrogen of oxime **1** to give intermediate **A**. With attack by another equivalent of allylsamarium bromide, intermediate **A** is transformed into intermediate **B**, from which imine **C** is formed through a Beckmann rearrangement process. With the addition of a third equivalent of allylsamarium bromide, **C** is transformed into **D**, which, on treatment with water, is hydrolyzed to afford **2** as the final product.

To broaden the scope further, the reaction between acetophenone oxime **3a** and allylsamarium bromide was also studied. When **3a** was treated with allylsamarium bromide in THF at room temperature, the purple color of allylsamarium bromide disappeared gradually in 4 h and **4a** was obtained in moderate yield, which was rather surprising. While aldoximes have been reported to react with Grignard reagents to give Beckmann rearrangement products,[9] previous studies showed that acetophenone oxime reacts with organometallics, such as EtMgBr, to give 2-ethyl-2-phenylaziridine, or 1-amino-2-phenyl-2-butanol, depending on the method of hydrolysis used.[10] Later work by Deady showed that some methyl aryl ketoximes undergo condensation reactions when treated with EtMgBr to give 3,5-diaryloxazines.[11] Moreover, Felix has reported that allylmagnesium bromide adds to oximes derived from trifluoromethyl ketones to give allylated hydroxylamines.[3d] In our hands, allylsamarium bromide added to methyl aryl ketoxime **3a** to give a diallylated Beckmann rearrangement product **4a** in moderate yield. To the best of our knowledge, this is the first example reported of this type of reaction between a ketoxime and an allylic organometallic. We propose that the formation of **4a** involves a Beckmann rearrangement process, similar to that proposed for the formation of **2** (Scheme 1), in which a disubstituted intermediate is formed firstly and allylated subsequently to give a diallylated secondary amine bearing a quaternary carbon center. Oximes of other methyl aryl ketones were also studied and were found to react smoothly with allylsamarium bromide to give **4** in moderate yields. The results are listed in Table 2.

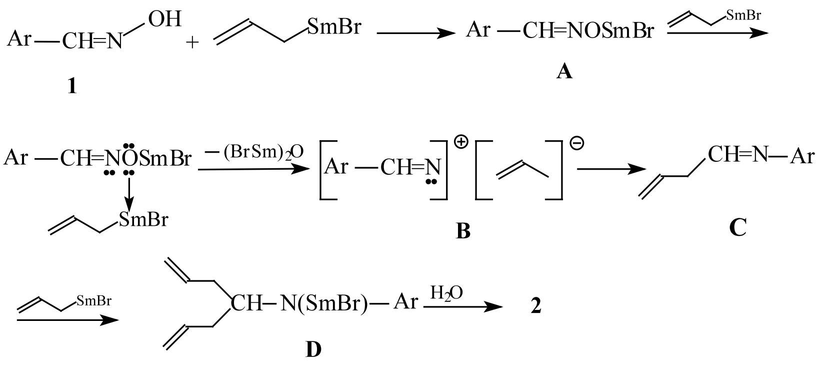
Furthermore, the reactivity of the methyl ethers (**5** and **6** in Scheme 2) of the corresponding oximes (**1b** and **3b**) with allylsamarium bromide were also investigated.

Table 2. Reaction of ketoximes with allylsamarium bromide

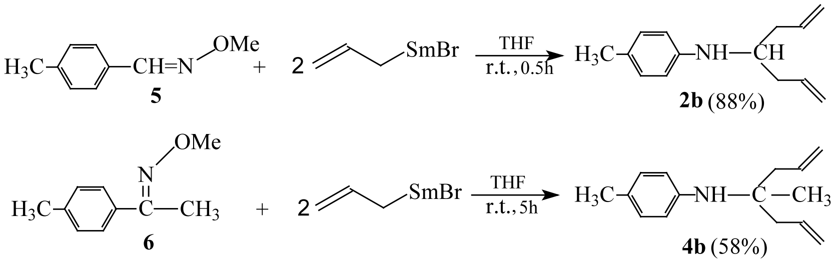


Entry	Ar	Reaction time (h)	Yield (%)[a]
a	C_6H_5	4	65
b	4-$CH_3C_6H_4$	4	68
c	4-$CH_3OC_6H_4$	4	62
d	4-BrC_6H_4	6	62
e	4-ClC_6H_4	6	59

[a] Isolated yields based on oximes.



Scheme 1.



Scheme 2.

When **5** or **6** was treated with 2.2 equiv. of allylsamarium bromide, the substrate used was consumed within 30 min for **5**, or 5 h for **6** and the Beckmann rearrangement products (**2b** and **4b**) were obtained in moderate to good yields under mild conditions. The fact that 2 equiv. of allylsamarium bromide are enough for the diallylation of **5** and **6** is in agreement with the mechanism proposed for the diallylation of oximes (see Scheme 1). The one equivalent of allylsamarium bromide consumed by the active hydrogen in oximes **1** and **3** can be saved in the case of **5** or **6**, in which the active hydrogen has been substituted by a methyl group.

In conclusion, with high yields, mild conditions as well as easily accessible starting materials, the present work will provide a useful method for the preparation of dihomoallylic secondary amines,[12] which could be used for the preparation of various derivatives by functionalization of the two double bonds and/or the NH function. Further studies to develop other new uses for allylsamarium bromide are now in progress in our laboratory.

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12. General procedure: Allyl bromide (0. 5 g, 4 mmol) and samarium (0.5 g, 3.3 mmol) with a catalytic amount of iodine (0.01 mmol) were mixed in dry THF (20 ml) under a nitrogen atmosphere at room temperature. The mixture was stirred for about 15 min, and a purple color was formed. Then, oxime (1 mmol) was added and the reaction mixture was stirred for 20–40 min for aldoximes **1**, or 4–6 h for ketoximes **3**, then quenched with 0.1 M hydrochloric acid. The resulting mixture was extracted with ether (3×10 mL). The organic phase was successively washed with a saturated solution of $Na_2S_2O_3$ (10 mL), saturated brine (10 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the crude product, which was purified by preparative TLC using ethyl acetate and cyclohexane (1:6) as eluant to yield product **2** or **4**, respectively.

Typical physical data for compounds **2b** and **4b**. Compound **2b** ***N*-(1-allyl-3-butenyl)-*N*-(4-methylphenyl)amine**: oil. IR (KBr) *v* 3408 (NH), 3076, 2923, 1638 (RCH=CH$_2$), 1584, 990, 914, 806, 787 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.22 (s, 3H, CH$_3$), 2.27–2.35 (m, 4H, 2×CH$_2$), 3.42–3.48 (m, 2H, NH, CH), 5.07–5.11 (m, 4H, 2×CH$_2$), 5.76–5.85 (m, 2H, 2×CH), 6.51 (d, 2H, J=8.4 Hz, ArH), 6.97 (d, 2H, J=8.4 Hz, ArH); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.5, 38.2, 52.4, 113.7, 117.7, 126.5, 129.9, 135.0, 145.2; MS m/z (%): 201 (M^+, 19.8), 160 (100), 118 (30.9), 91 (18.0), 77 (5.9). Anal. calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.57; H, 9.56; N, 6.92%. Compound **4b** ***N*-(1-allyl-1-methyl-3-butenyl)-*N*-(4-methylphenyl)amine**: oil. IR (KBr) *v* 3407 (NH), 3074, 1638 (RCH=CH$_2$), 1514, 997, 913, 806 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.23 (s, 3H, CH$_3$), 2.23 (s, 3H, CH$_3$), 2.27–2.42 (m, 4H, 2×CH$_2$), 3.18 (br, s, 1H, NH), 5.06–5.11 (m, 4H, 2×CH$_2$), 5.80–5.90 (m, 2H, 2× CH), 6.67 (d, 2H, J=8.4 Hz, ArH), 6.95 (d, 2H, J=8.4 Hz, ArH); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.5, 25.8, 44.4, 55.9, 118.3, 118.4, 128.2, 129.5, 134.4, 143.9; MS m/z (%): 215 (M^+, 5.5), 174 (100), 132 (49.8), 106 (7.4), 91 (24.4), 77 (7.1). Anal. calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.65; H, 9.85; N, 6.52%.