

Noticeable facilitation of the bismuth-mediated Barbier-type allylation of aromatic carbonyl compounds under solvent-free conditions

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Received 9th April 2003, Accepted 2nd May 2003

First published as an Advance Article on the web 16th May 2003

When milled together with bismuth shot in the presence of allyl halide, aromatic aldehydes readily underwent a Barbier-type allylation to afford the corresponding homoallyl alcohols in good yield. In contrast to the failure in solution reaction, aromatic ketones also underwent allylic carbonyl addition under solvent-free conditions to give the expected tertiary homoallyl alcohols in moderate to good yield.

Introduction

The conversion of carbonyl compounds to homoallylic alcohols is an important process in organic synthesis.¹ This type of functional group transformation has long been carried out using organometallic compounds such as Grignard reagents,² organolithiums,³ organosilanes,⁴ and organostannanes.⁵ In recent years, however, an alternative approach involving a reductive allylation process has become of increasing importance, where a combination of allyl halide and a metal powder or a low valent metal halide is used for the *in situ* generation of allylmetal species. This type of allylic carbonyl addition has been called the Barbier-type allylation,⁶ and the metals employed therein include magnesium,⁷ tin,⁸ indium,⁹ zinc,¹⁰ cadmium,¹¹ amalgamated cerium,¹² manganese,¹³ antimony,¹⁴ and bismuth.¹⁵ The low valent metal halides used include chromium(II) chloride,¹⁶ samarium(II) iodide,¹⁷ and ytterbium(II) iodide.¹⁷ Bimetallic reducing systems consisting of a metal and a metal halide have been successfully employed for the catalytic reductive allylation of carbonyl compounds. They include Fe–SbCl₃,¹⁸ Al–SbCl₃,¹⁸ Mg–BiCl₃,¹⁹ Al–BiCl₃,²⁰ Zn–BiCl₃,²⁰ Zn–InCl₃,²¹ and Al–InCl₃²¹ systems. This methodology has attracted considerable attention, since the reaction can be carried out in aqueous media.²² The reductive allylation based on an electrochemically generated allylmetal species has also been reported.²³

To our knowledge, almost all known Barbier-type allylations have been carried out in the presence of a solvent, stirring a heterogeneous mixture for a specified period of time ranging from several hours to a few days at room temperature or under gentle heating. In the majority of reported cases, the procedure has proved to be ineffective for the allylation of ketones. The dimerization of carbonyl compounds to pinacols, Wurtz-type coupling of allyl halides, isomerization of a branched allylic framework, and Tishchenko reaction leading to esters are the major side reactions which often accompany the reductive allylation of carbonyl compounds in solution.

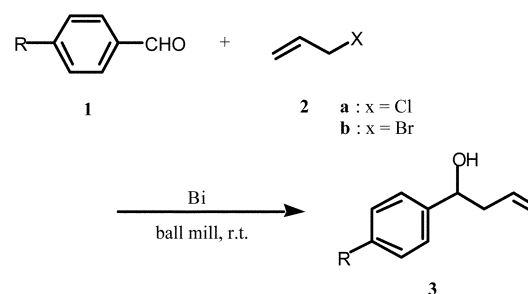
In this paper, we wish to report a remarkable facilitation of the bismuth-mediated Barbier-type allylation observed under ball milling conditions. Under such *completely dry* environments, the reaction time is considerably shortened, and both aldehydes and ketones can be allylated with modest ease to afford the expected homoallylic alcohols in moderate to good yield. It has generally been recognized that the metal-promoted allylation of carbonyl compounds is highly influenced by the nature of the solvent employed. Under the present solvent-free conditions, however, there is no need to be concerned about the choice of solvent. Recently, aromatic Grignard reagents have

been prepared in a dry powdery state from halonaphthalenes and magnesium using the ball milling technique and allowed to react with aromatic ketones.²⁴ Aryl–aryl coupling is the major competitive process observed therein.

The literature to date contains few examples of mechanochemical organic synthesis. The ball milling of aromatic ketones and magnesium metal led to the McMurry and pinacol coupling products along with the expected alcohol and its parent hydrocarbon.²⁴ A redox-type ligand exchange between thallium(I) cyclopentadienide and rare earth metals under ball milling conditions has been employed for the preparation of rare earth cyclopentadienyls such as YbCp₂ and EuCp₃.²⁵ Aromatic hydrocarbons are found to undergo disproportionation by ball-milling in the presence of silica gel and alumina.²⁶ Chlorinated hydrocarbons can be destroyed by milling with magnesium, calcium and calcium oxide.²⁷

Results and discussion

The bismuth-mediated allylation of aldehydes with allyl bromide was first reported by Wada in 1985.¹⁵ As part of our ongoing program on bismuth as a reagent in organic synthesis, we have reinvestigated this pioneering work under ball milling conditions, *i.e.* solvent-free environments. Bismuth is attractive as a reagent for the reductive allylation of aromatic carbonyl compounds, since it is non-toxic and low-priced.²⁸ We found that the Barbier-type allylation of aromatic aldehydes took place smoothly under such completely dry conditions, giving the expected homoallylic alcohols in moderate to good yield (Scheme 1).



Scheme 1

Thus, benzaldehyde (1; R = H), allyl bromide 2b, bismuth shot, and small stainless steel balls were placed in a stainless steel vial with a screw cap. The reaction vessel was shaken using a laboratory ball mill apparatus at a rate of 30 Hz for 0.5–1.5 h.

Table 1 Bi-mediated allylation of aromatic aldehydes **1** under ball mill conditions

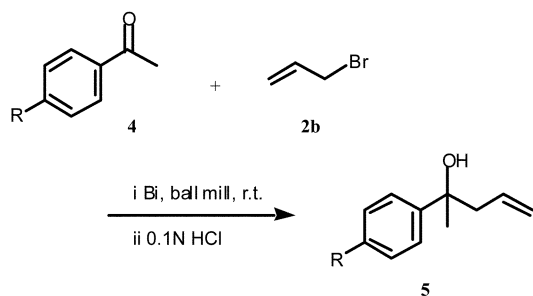
Entry	R	X	Aldehyde 1 /halide 2 /bismuth ratio ^a	Milling time (h)	Yield ^{b,c} (%)
1	H	Br	1/2/8	0.5	81
2	H	Br	1/2/8	1.5	88
3	H	Br	1/1.5/8	1.5	94
4	Me	Br	1/1.5/8	0.5	69
5	CN	Br	1/1.5/8	0.5	80
6	CN	Br	1/1.5/8	1.0	91
7	NO ₂	Br	1/1.5/8	0.5	84
8	NO ₂	Br	1/1.5/8	1.0	95
9	NO ₂	Cl	1/1.5/8	1.5	34

^a Molar ratio. ^b Yield refers to the isolated compound. All products are known. To promote efficiency of milling bismuth shot was used in a large excess. No effort was made to optimize milling conditions against product yield. ^c Extraction of the product was made with 0.1 M HCl and EtOAc.

The resulting brown to dark grey pasty mass was extracted with EtOAc by trituration and the extract was evaporated to leave the expected homoallylic alcohol (**3**; R = H). The results are summarized in Table 1. Less reactive allyl chloride **2a** was also usable, but the reaction required a longer milling time to complete (Table 1, entry 9). The chloride usually fails to react in solution.¹⁵ Prolonged ball milling led to a gradual decline of product yield, probably due to the decomposition of the initial product to a diene and its descendents. Loss of allyl halides by the Wurtz-type coupling was not observed.

The bismuth-mediated reaction of benzaldehyde and allyl bromide can be carried out in protic solvents such as alcohol and water.¹⁵ Thus, anticipating that an extent of asymmetric induction might arise during the allylic carbonyl addition, the bismuth-mediated Barbier-type reaction of 4-trifluoromethylbenzaldehyde (**1**; R = CF₃) and allyl bromide **2b** was performed in the presence of a chiral powdery medium such as cane sugar or a potato starch. However, the enantiomer ratio of the resulting homoallylic alcohol (**3**; R = CF₃), determined by gas chromatography using a chiral column, was close to the unity, and therefore, we could not draw any definite conclusion as to possible asymmetric induction under the present ball milling conditions. The enantiomers appeared as a pair of peaks of different height on the gas chromatogram, but the ratio of integrated peak areas was near to unity.

Generally speaking, aromatic ketones are quite sluggish or fail to undergo the Barbier-type allylation in solution.¹⁵ However, they were able to undergo the reaction with moderate ease under the solvent-free conditions (Scheme 2). In this case, attempted extraction of the resulting pasty solid with EtOAc alone led to a low yield of the expected product. However, when the solid was first triturated with 0.1 M HCl and then extracted with EtOAc, the product yield was dramatically improved. Seemingly, the tertiary homoallyl alcohols **5** formed as the bismuth alkoxide in the pasty solid. Pinacols that often accompany the Barbier-type reaction of ketones in solution were not detected. It is of note that sensitive functional moieties such as nitro and cyano groups remained intact throughout the reaction (Table 2). Both commercial bismuth shot and powder (Ishizu, ~100 mesh) were used as received and provided almost identical results. The physical form of the metallic bismuth does not seem to have much influence on the product yield.

**Scheme 2**

For comparison, the present methodology was extended to the indium- and tin-mediated allylation of aromatic aldehydes. Both metals proved to work similarly, though they somewhat appeared to favor the formation of byproducts. The advantageous use of bismuth over indium and tin in the chemoselective Barbier-type allylation was well manifested in the allylation of 4-nitrobenzaldehyde (**1**; R = NO₂) and 4-nitroacetophenone (**4**; R = NO₂). Bismuth afforded the expected alcohols (**3** and **5**; R = NO₂) in good to moderate yields (Table 1, entries 7 and 8 and Table 2, entries 4–6), but indium and tin gave a complex mixture containing the azo and azoxy compounds. This may be attributed to the higher reducing ability of tin (Sn to Sn²⁺, –0.137 V) and indium (In to In⁺, –0.338 V) as compared with bismuth (Bi to Bi³⁺, +0.317 V).²⁹

With an intention to see the effect of steric factors on the solvent-free carbonyl allylation, two types of ketones with different steric requirements around the carbonyl function, **6** and **8**, have been reacted with allyl bromide **2b** under the same conditions. Cyclohexanone **6** reacted with moderate ease, but sterically more crowded benzophenone **8** reacted with less ease (Scheme 3). The reactivity of these ketones in the known Barbier-type allylation considerably differs in solution reaction. The former ketone can undergo reductive allylation under certain circumstances, whereas the latter often fails to react or suffers reductive coupling to give a pinacol. However, the difference in reactivity between them is not so significant under the solvent-free environments. Thus, the steric factor seems to be of less influence in the solvent-free reaction than the solution reaction. The ease with which carbonyl compounds undergo reductive allylation can be ranked in the order, aromatic aldehydes > aryl methyl ketones > cycloalkanones > diaryl ketones. Aromatic carbonyl compounds bearing an electron-withdrawing group afforded a higher yield relative to other ones, while those bearing an electron-donating group led to a lower yield.

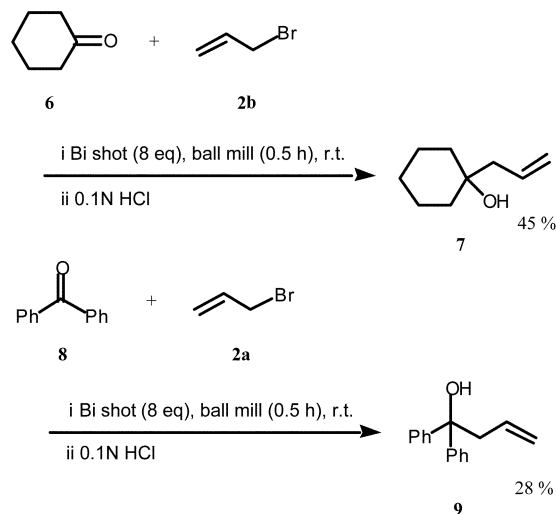
**Scheme 3**

Table 2 Bi-mediated allylation of aromatic ketones **4** under ball mill conditions

Entry	R	Bi form	Ketone 4 /halide 2b /bismuth ratio ^a	Yield ^b (%)
1	H	Shot	1/1.5/4	44
2	H	Shot	1/1.5/8	46
3	H	Powder	1/1.5/8	56
4	NO ₂	Shot	1/1.5/4	36
5	NO ₂	Shot	1/1.5/8	70
6	NO ₂	Powder	1/1.5/8	51
7	CN	Shot	1/1.5/4	40
8	Br	Powder	1/1.5/8	69
9	Cl	Powder	1/1.5/8	53
10	Me	Powder	1/1.5/8	50
11	OMe	Shot	1/1.5/4	20 ^d
12	OMe	Powder	1/1.5/4	31 ^d
13	OMe	Powder	1/1.5/8	36 ^d

^a See footnotes in Table 1. For all reactions, milling time was fixed at 0.5 h. ^b Extraction of the product was made with 0.1 M HCl and EtOAc.

^c Determined by ¹H NMR.

Depending on the carbonyl compounds employed, the reaction mixture sometimes became very sticky during the course of ball milling, where the stainless steel balls and bismuth shot clung together to form a doughy lump in the reaction vessel. Under such a circumstance, the allylation did not proceed to completion. This problem could partly be solved by adding some non-reactive co-milling agent such as calcite grains to the reaction mixture.

The mechanism of the reductive allylation of carbonyl compounds under solvent-free conditions is not clear. However, it is most likely that the reaction proceeds *via* an electron-transfer process involving an allylbismuth species generated on the nascent metal surface, which is continuously supplied during the milling process of the bismuth metal. The alkylation of carbonyl compounds with Grignard and organolithium reagents has been shown to occur *via* an electron-transfer mechanism.³⁰

In summary, the bismuth-mediated Barbier-type allylation of aromatic aldehydes with allyl halides has been carried out smoothly under solvent-free conditions using the ball milling technique. In contrast to the failure in solution reaction, aromatic ketones were also allylated with moderate ease under dry conditions, giving the expected tertiary homoallylic alcohols in modest yield. Although more work is needed before the method becomes practically attractive, our study has shown the potential usefulness of carrying out organic reactions under solvent-free environments.

Experimental

General

All reagents and metals were reagent-grade commercial products and used as received. ¹H-NMR spectra were determined in CDCl₃ on a JEOL ECA-300 or a Varian Unity Plus 300 spectrometer using tetramethylsilane as an internal standard. IR spectra were measured on a JEOL FTIR-5300 spectrophotometer against liquid film on NaCl plate and only characteristic peaks were recorded. The optical purity of homoallyl alcohol **3** (R = CF₃) was estimated on a gas chromatograph HP 6890 GC using a chiral column CP-chiral-Dex CB. Milling was performed using a ball mill apparatus (Retsch mixer mill, MM200; Retsch GmbH, Haan, Germany) at a rate of 30 Hz. Since the mechanical performance of our apparatus was fixed, no effort was made to optimize the milling conditions nor product yield. All products are known and identified by direct comparison of their spectral data with those of authentic specimens obtained by other routes.

Bismuth-mediated allylation of aromatic carbonyl compounds with allyl halides

Allylation of aromatic aldehydes. Typical procedure. 4-Nitrobenzaldehyde (38.4 mg, 0.25 mmol), allyl bromide (45.3 mg,

0.37 mmol), bismuth shot (44.9 mg, Wako 99.999%), and two stainless steel ball bearings of 7 mm diameter were placed in a stainless steel vial (1.2 × 4 cm; 5 ml vol.) with a screw cap. The reaction vessel was shaken using a ball mill apparatus at a rate of 30 Hz at room temperature. The vessel warmed somewhat by mechanical friction. After 1 h, milling was stopped and the resulting gray pasty mass was extracted with EtOAc by trituration. The organic phase was filtered on a thin Celite bed and evaporated to leave a pale yellow oil, which was chromatographed on silica gel using hexane–EtOAc as the solvent to give 1-(4-nitrophenyl)but-3-en-1-ol³¹ (46.2 mg, 95%) as an oil. IR (liquid film): 3410 (OH), 1520 (NO₂), 1346 (NO₂) cm⁻¹. ¹H NMR: δ 8.20 (d, 2H, *J* = 8.6 Hz, ArH), 7.53 (d, 2H, *J* = 8.6 Hz, ArH), 5.72–5.86 (m, 1H, CH), 5.20 (d, 1H, *J* = 10.5 Hz, *cis*-vinylic CH), 5.18 (d, 1H, *J* = 17.5 Hz, *trans*-vinylic CH), 4.87 (dd, 1H, *J* = 5.2, 7.2 Hz, CH), 2.52–2.61 (m, 1H, CH₂), 2.41–2.50 (m, 1H, CH₂), 2.32 (s, 1H, OH).

Allylation of aromatic ketones. Typical procedure. 4-Nitroacetophenone (43.1 mg, 0.26 mmol), allyl bromide (45.3 mg, 0.37 mmol), bismuth shot (203 mg), and two stainless steel balls were placed in a stainless steel vial with a screw cap. The reaction vessel was shaken using a ball mill apparatus at a rate of 30 Hz. After 0.5 h, milling was stopped and the resulting pasty solid was first trituated with 0.1 M HCl and then extracted with EtOAc. Attempted extraction with EtOAc alone led to a diminished yield of the product. The organic phase was separated, filtered on a thin Celite bed, and evaporated to leave a pale yellow oil, which was chromatographed on silica gel using hexane–EtOAc as the eluent to give 2-(4-nitrophenyl)pent-4-en-2-ol³² (37.7 mg, 70%) as an oil. IR (liquid film): 3540 (OH), 1518 (NO₂), 1348 (NO₂) cm⁻¹. ¹H NMR: δ 8.20 (d, 2H, *J* = 8.9 Hz, ArH), 7.61 (d, 2H, *J* = 8.9 Hz, ArH), 5.17 (d, 1H, *J* = 10.6 Hz, *cis*-vinylic CH), 5.16 (d, 1H, *J* = 16.1 Hz, *trans*-vinylic CH), 2.69 (dd, 1H, *J* = 6.5, 13.7 Hz, CH₂), 2.54 (dd, 1H, *J* = 8.3, 13.7 Hz, CH₂), 2.17 (s, 1H, OH), 1.58 (s, 3H, CH₃).

Acknowledgements

The authors thank Professor Toyoshi Shimada of Kyoto University for helpful discussions. We also thank Dr. Asato Kina of the same university for estimating the optical purity of a chiral homoallyl alcohol by gas chromatography.

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