# Regioselective Propargylation of Carbonyl Compounds with (3-Bromoprop-1-ynyl)trimethylsilane Promoted by Reactive Barium

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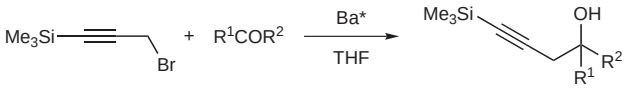
*Received 18 April 2005*

**Abstract:** A Barbier-type propargylation of aldehydes with (3-bromoprop-1-ynyl)trimethylsilane has been achieved using reactive barium as a low-valent metal in THF. This process is effective also for obtaining the desired homopropargylic alcohols in high yields from the corresponding ketones including enolizable ketones such as cyclopent-2-enone.

**Key words:** barium, propargylation, aldehydes, regioselectivity, ketones

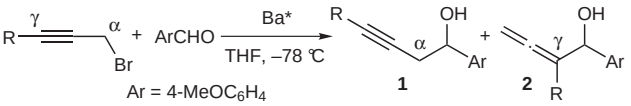
Propargylation of carbonyl compounds is a convenient method for introducing a carbon–carbon triple bond into organic molecules.[1] One drawback of this reaction using a propargylic or allenylic metal reagent is the control of regiochemistry. In general, organomagnesium and zinc reagents generated from γ-alkylated propargyl bromides react with aldehydes preferentially at the γ-position to afford allenylic alcohols.[2] Although the regiocontrolled synthesis of homopropargylic alcohols has been extensively studied, there are still not many satisfactory methods for the selective propargylation.[1c,3] We describe herein a new approach to α-selective reaction of a $Me_3Si$-substituted propargyl bromide with aldehydes and ketones using reactive barium as a promoter (Scheme 1).




**Scheme 1** Barbier-type reaction of a propargylic bromide with carbonyl compounds promoted by reactive barium

We have previously shown that allylic barium reagents are readily generated from the corresponding allylic chlorides and in situ prepared reactive Rieke barium[4,5] and react with carbonyl compounds at the least substituted allylic terminus.[4] We envisioned that if a propargylic barium reagent is selectively formed from a propargylic halide and the reactive barium, the targeted homopropargylic alcohols could be prepared in high yield by treatment of the barium reagent with aldehydes. First, according to the Barbier-type technique, a mixture of *p*-anisaldehyde and 1-bromobut-2-yne was exposed to the reactive barium, which was generated from barium iodide and lithium biphenylide,[6] and a 45:55 mixture of homopropargylic alcohol **1a** and allenylic alcohol **2a** was obtained in 88% combined yield (Table 1, entry 1). Use of a phenyl group-substituted propargyl bromide resulted in a similar result with γ-selectivity (entry 2); however, the homopropargylic alcohol **1c** was formed almost exclusively in the reaction of (3-bromoprop-1-ynyl)trimethylsilane (entry 3).

**Table 1** Reactive Barium-Promoted Barbier-Type Reaction of Various Propargylic Bromides with *p*-Anisaldehyde[a]




| Entry | R | Time (h) | Yield (%)[b] | Products | α:γ[c] |
|---|---|---|---|---|---|
| 1 | Me | 1 | 88 | **1a** + **2a** | 45:55 |
| 2 | Ph | 3.5 | 89 | **1b** + **2b** | 40:60 |
| 3 | $Me_3Si$ | 2.5 | 89 | **1c** + **2c** | > 99:1 |

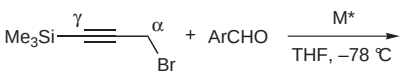
[a] The reaction was carried out using propargylic bromide (1 equiv), *p*-anisaldehyde (0.3 equiv), and reactive barium (1.1 equiv) in dry THF at –78 °C.
[b] Isolated yield.
[c] Determined by $^1$H NMR analysis.

The high α-selectivity is a specific characteristic of the barium reagent, and other alkaline earth metal reagents derived from the $Me_3Si$-substituted propargyl bromide provided a mixture of homopropargylic alcohol **1c** and allenylic alcohol **2c** as shown in Table 2. Among them, the magnesium reagent indicated the lowest **1c**:**2c** selectivity (entry 1).[7]

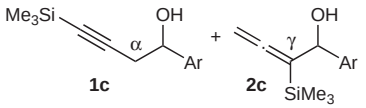
Then, we examined the barium-promoted regioselective propargylation of various aldehydes and the results are summarized in Table 3. As a consequence, not only aromatic aldehydes but α,β-unsaturated and aliphatic aldehydes were also allowed to react with the barium reagent to give the corresponding homopropargylic alcohols in moderate to high yields. In every case no allenylic alcohol was observed at all. In the reaction with cinnamaldehyde, only a 1,2-adduct was obtained (entry 6).

***SYNLETT*** 2005, No. 11, pp 1679–1682
Advanced online publication: 09.06.2005
DOI: 10.1055/s-2005-869874; Art ID: U11505ST

**Table 2** Effect of Metals on the Regioselectivity of the Barbier-Type Reaction of (3-Bromoprop-1-ynyl)trimethylsilane with *p*-Anisaldehyde[a]



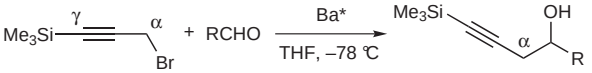

Ar = 4-$MeOC_6H_4$




| Entry | M* | Yield (%)[b] | **1c**:**2c**[c] |
|---|---|---|---|
| 1 | Mg* | 34 | 53:47 |
| 2 | Ca* | 68 | 74:26 |
| 3 | Sr* | 87 | 88:12 |
| 4 | Ba* | 89 | > 99:1 |

[a] The reaction was carried out using (3-bromoprop-1-ynyl)trimethylsilane (1 equiv), *p*-anisaldehyde (0.3 equiv), and reactive metal (1.1 equiv) in dry THF at –78 °C.
[b] Isolated yield.
[c] Determined by $^1$H NMR analysis.

**Table 3** Reactive Barium-Promoted Selective Propargylation of Various Aldehydes with (3-Bromoprop-1-ynyl)trimethylsilane[a]

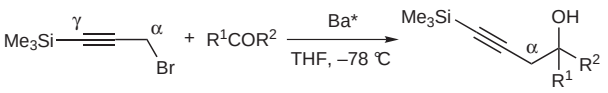


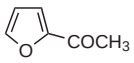
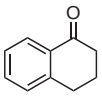

| Entry | RCHO | Yield (%)[b,c] |
|---|---|---|
| 1 | PhCHO | 67 |
| 2 | 4-$MeC_6H_4CHO$ | 96 |
| 3 | 4-$MeOC_6H_4CHO$ | 89 |
| 4 | 1-$C_{10}H_7CHO$ | 78 |
| 5 | 2-$C_{10}H_7CHO$ | 79 |
| 6 | (*E*)-PhCH=CHCHO | 74 |
| 7 | $Ph(CH_2)_2CHO$ | 60 |

[a] The reaction was carried out using (3-bromoprop-1-ynyl)trimethylsilane (1 equiv), aldehyde (0.3 equiv), and reactive barium (1.1 equiv) in dry THF at –78 °C for 1–3 h.
[b] Isolated yield.
[c] The α:γ ratio of the product in each entry was determined to be > 99:1 by $^1$H NMR analysis.

We further studied the addition of the barium reagent to ketones with the anticipation that the selective propargylation also would occur with the bulkier and less reactive carbonyl compounds. In fact, condensation of the barium reagent with various ketones afforded the desired homopropargylic alcohols nearly exclusively in satisfactory yields (Table 4).[8] Cyclic α,β-unsaturated ketones, which

**Table 4** Reactive Barium-Promoted Selective Propargylation of Various Ketones with (3-Bromoprop-1-ynyl)trimethylsilane[a]

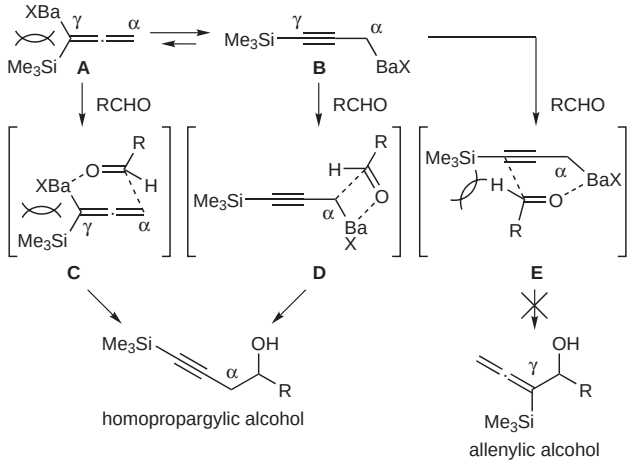



| Entry | $R^1COR^2$ | Yield (%)[b,c] |
|---|---|---|
| 1 | $PhCOCH_3$ | 77 |
| 2 | 4-$MeOC_6H_4COCH_3$ | 85 |
| 3 |  | 52 |
| 4 |  | 89 |
| 5 | (*E*)-$PhCH{=}CHCOCH_3$ | 80[d] |
| 6 |  | 71[d] |
| 7 |  | 94[d] |

[a] The reaction was carried out using (3-bromoprop-1-ynyl)trimethylsilane (1 equiv), ketone (0.3 equiv), and reactive barium (1.1 equiv) in dry THF at –78 °C for 1–3 h.
[b] Isolated yield.
[c] The α:γ ratio of the product in each entry was determined to be > 99:1 by $^1$H NMR analysis.
[d] The 1,2:1,4 ratio of the α-product was determined to be > 99:1 by $^1$H NMR analysis.

are good Michael acceptors, still show an exclusive 1,2-selectivity (entries 6 and 7). Noteworthy is the fact that readily enolizable ketones gave the desired adducts in high yield which means that the nucleophilicity of the barium reagent predominates over its basicity (entries 4 and 7).

The reason for the regiochemical outcome has not yet been fully elucidated; however, two pathways leading to a propargylated product (α-adduct) are plausible (Scheme 2). A barium reagent generated from (3-bromoprop-1-ynyl)trimethylsilane and reactive barium is considered to exist at equilibrium between the allenic form **A** and the acetylenic form **B**. The homopropargylic alcohol is obtainable from both isomers in their reaction with an aldehyde via the transition state structure **C** or **D**. The transition state **D** is, however, more favorable in view of its less steric repulsion.[9] The four-membered cyclic transition state model is also supported by the mechanism of the reaction of allylic barium reagents with carbonyl compounds.[4b,c] In contrast, the corresponding allenylic alcohol (γ-adduct) is conceivable to form by a $S_E2'$-type reaction of **B** with the aldehyde via the six-membered cyclic transition state **E**, which is, however, destabilized by a steric hindrance of the $Me_3Si$ group of **B**.




**Scheme 2** Plausible reaction pathways to homopropargylic alcohols and allenylic alcohols

In summary, we have achieved a novel Barbier-type reaction of trimethylsilylpropargyl bromide with aldehydes and ketones using reactive barium as a promoter. This method is superior to those employing other group 2 metal reagents from the viewpoint of regioselectivity and provides a variety of (trimethylsilyl)homopropargylic alcohols in satisfactory yields. The $Me_3Si$ group can be further transformed into other useful functional groups.[10] Studies on related reactions using the organobarium reagent are now in progress.

**A Typical Experimental Procedure for the Barbier-Type Propargylation (Table 3, Entry 2).**

An oven-dried, 30 mL two-necked round-bottomed flask equipped with a Teflon®-coated magnetic stirring bar was flushed with argon. Freshly cut lithium (15.0 mg, 2.16 mmol) and biphenyl (350 mg, 2.27 mmol) were put into the apparatus and covered with dry THF (3 mL), and the mixture was stirred for 2 h at 20–25 °C (lithium was completely consumed). Anhyd $BaI_2$ (450 mg, 1.15 mmol) was placed in a separate oven-dried, 30 mL flask also equipped with a Teflon®-coated magnetic stirring bar under argon atmosphere; this was covered with dry THF (5 mL), and stirred for 20 min at r.t. To the solution of $BaI_2$ in THF was added at r.t. a solution of the lithium biphenylide in THF under an argon stream. The reaction mixture was stirred for 30 min at r.t. A solution of (3-bromoprop-1-ynyl)trimethylsilane (191 mg, 1.00 mmol) and *p*-tolualdehyde (36.0 μL, 0.305 mmol) in dry THF (4 mL) was added dropwise to the resulting dark brown suspension of reactive barium (1.08 mmol) in THF (8 mL) at –78 °C. After being stirred for 2.5 h at this temperature, the mixture was treated with a sat. $NH_4Cl$ aqueous solution (10 mL) at –78 °C and the aqueous layer was extracted with $Et_2O$ (10 mL). The combined organic extracts were washed with 1 N $Na_2S_2O_3$ solution (20 mL), dried over anhyd $Na_2SO_4$, and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to give the homopropargylic alcohol (68.3 mg, 96% yield). The α:γ ratio was determined to be >99:1 by $^1$H NMR analysis. Spectral data of the product: TLC $R_f$ = 0.57 (1:3 EtOAc–hexane). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.15 (s, 9 H, 3 $CH_3$), 2.34 (s, 3 H, $CH_3$), 2.53 (d, 1 H, *J* = 2.7 Hz, OH), 2.62 (d, 2 H, *J* = 6.5 Hz, $CH_2$), 4.79 (dt, 1 H, *J* = 6.5, 2.7 Hz, CH), 7.15 (d, 2 H, *J* = 8.0 Hz, aromatic), 7.25 (d, 2 H, *J* = 8.0 Hz, aromatic). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 0.0 (3 C), 21.1, 31.1, 72.1, 87.7, 103.1, 125.6 (2 C), 129.0 (2 C), 137.4, 139.6. The above-mentioned spectral data indicated good agreement with reported data.[11]

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