Selective Propargylation of Azo Compounds with Barium Reagents

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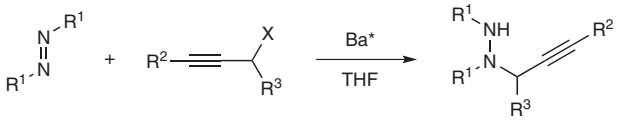
Received 10 March 2010

Abstract: A Barbier-type propargylation of azo compounds with γ-trialkylsilylated propargylic bromides has been achieved using reactive barium as a low-valent metal in THF. Corresponding propargylated hydrazines (α-adducts) were exclusively formed not only from azobenzenes (diaryldiazenes) but also from dialkyl azodicarboxylates. This method is also applicable to γ-alkylated or γ-phenylated propargylic bromides, providing the desired propargylated products only.

Key words: azo compounds, barium, hydrazine, propargylation, propargylic bromides

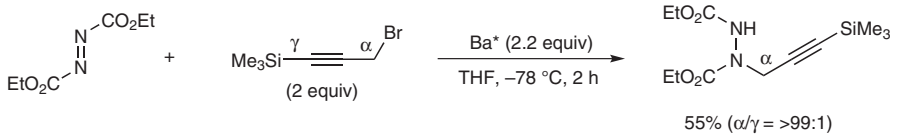
Allylic and propargylic/allenylic barium reagents are known to show regioselectivity and/or stereoselectivity characteristics that markedly differ from those of other group 2 metal reagents.[1] We have previously reported that a trimethylsilylated propargyl bromide reacts with aldehydes and ketones in the presence of reactive Rieke barium[1,2] to afford homopropargylic alcohols almost exclusively.[3] The corresponding regioisomers, allenylic alcohols, can be observed in the Barbier-type reaction promoted by other reactive alkaline-earth metals (Ca and Sr) and reactive magnesium. In particular, in the case of a Grignard reagent, an allenylic alcohol is formed as the major product. Reactive barium has been further found to promote the selective propargylation of imines with trimethylsilylated propargylic bromides, resulting in the predominant formation of homopropargylic amines.[4] We report herein a reactive-barium-promoted Barbier-type reaction of azo compounds with propargylic halides (Scheme 1).



Scheme 1 Barbier-type reaction of propargylic halides with azo compounds promoted by reactive barium

The addition of a propargylic or an allenylic metal reagent to azo compounds is a convenient method for the preparation of propargylic hydrazines.[5,6] First, we examined the utility of diethyl azodicarboxylate (DEAD) as an azo compound in the barium-promoted reaction. When a mixture of DEAD (1 equiv) and (3-bromoprop-1-ynyl)trimethylsilane (2 equiv) was treated with reactive barium (2.2 equiv) in THF at –78 °C for two hours, the anticipated propargylic hydrazine (α-adduct) was furnished in 55% yield. In contrast, the corresponding allenylic hydrazine (γ-adduct) was not detected at all (Scheme 2). Thus, exclusive α-selectivity was also observed for the propargylation of azo compounds with barium reagents.

We then investigated the reaction of various azo compounds with a trimethylsilyl-substituted α-methylated propargylic barium reagent and the results are summarized in Table 1. We initially tested the reactivity of azobenzene. An equimolar mixture of the azo compound and (3-bromobut-1-ynyl)trimethylsilane was treated with reactive barium (1.1 equiv) under standard reaction conditions; however, the reaction proceeded sluggishly and a low yield (16%) of the propargylated product was obtained even after 12 hours (entry 1). The chemical yield was improved when the amount of the propargylic bromide was increased, exceeding 80% when three or more equivalents of the propargylation reagent were used (entries 4 and 5). Employment of the corresponding propargylic chloride resulted in a remarkable decrease in yield (compare entry 3 with entry 4). The effect of azobenzene substituents on the chemical yield was also examined and as a result, electron-donating groups reduced the reactivity of azobenzene (entries 6 and 7), while an electron-withdrawing group enhanced the reaction rate (entry 8). We then attempted the propargylation of diethyl azodicarboxylate. In order to acquire a satisfactory yield of the DEAD adduct, at least two equivalents of the azo compound were necessary (entries 9–11). Sterically bulky azodicarboxylate esters also furnished the desired propargylated products (entries 12 and 13). The propargylation according to



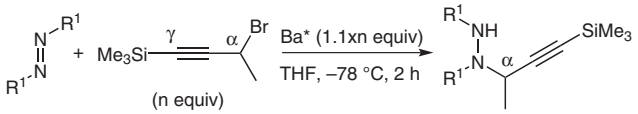
Scheme 2 Regioselective propargylation of diethyl azodicarboxylate with a γ-trimethylsilylated propargylic barium reagent

SYNLETT 2010, No. 10, pp 1515–1518
Advanced online publication: 25.05.2010
DOI: 10.1055/s-0029-1219944; Art ID: U01510ST

the Barbier-type technique was superior to the one using a preformed propargylic/allenylic barium reagent in terms of isolated yield (entries 4 and 10).

Subsequently, we studied the propargylation of DEAD with various propargylic halides under the optimized reaction conditions (Table 2). Propargylic bromides showed superior reactivity to propargylic chlorides (compare entries 1 and 10 with entries 2 and 11, respectively). The introduction of a long alkyl substituent to the α-position of the trimethylsilyl-substituted propargylic bromide did not affect the regioselectivity and in fact, the targeted propargylated product was gained exclusively in 77% yield (entry 3). Remarkable reactivity was also seen for bulky trialkylsilyl-substituted propargylic bromides except a triisopropylsilylated substrate (entries 4–6). In addition to γ-trialkylsilyl-substituted propargylic bromides, γ-alkyl- or γ-phenyl-substituted propargylic bromides could be employed as propargylation reagents (entries 7–10). Noteworthy was the fact that even 3-bromo-1-phenylbut-1-yne, which afforded a mixture of α- and γ-adduct in its reaction with an imine,[4] exhibited exclusive α-selectivity (entry 10).

Table 1 Reactive-Barium-Promoted Selective Propargylation of Various Azo Compounds with (3-Bromobut-1-ynyl)trimethylsilane[a]



Entry	R^1	n	Yield (%)[b]
1[c]	Ph	1	16[d]
2	Ph	2	50[d]
3[e]	Ph	3	59[d]
4	Ph	3	82[d] (76)[d]
5	Ph	4	87[d]
6	4-MeC_6H_4	3	73[d]
7	4-$MeOC_6H_4$	3	52[d]
8	4-FC_6H_4	3	92[d]
9[f]	EtO_2C	1	62
10	EtO_2C	2	80 (79)[d]
11	EtO_2C	3	81
12[f]	*i*-PrO_2C	2	82
13	*t*-BuO_2C	2	62

[a] Unless otherwise specified, the reaction was carried out using (3-bromobut-1-ynyl)trimethylsilane (n equiv), azo compound (1 equiv), and reactive barium (1.1 × n equiv) in anhyd THF at –78 °C for 2 h.
[b] Isolated yield. Values in parentheses are isolated yields of products from a preformed propargylic/allenylic barium reagent.
[c] The reaction was performed for 12 h.
[d] The yield was determined by ^1H NMR.
[e] The reaction was performed using (3-chlorobut-1-ynyl)trimethylsilane.
[f] The reaction was performed for 3 h.

In contrast, γ-trialkylsilyl-substituted propargylic bromides except a triisopropylsilylated substrate (entries 4–6). In addition to γ-trialkylsilyl-substituted propargylic bromides, γ-alkyl- or γ-phenyl-substituted propargylic bromides could be employed as propargylation reagents (entries 7–10). Noteworthy was the fact that even 3-bromo-1-phenylbut-1-yne, which afforded a mixture of α- and γ-adduct in its reaction with an imine,[4] exhibited exclusive α-selectivity (entry 10).

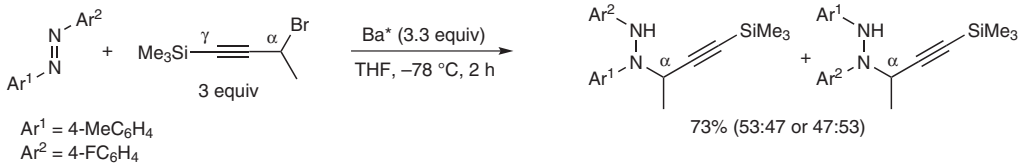
To investigate the electronic effect on the site selectivity of the two nitrogen atoms, we carried out the propargylation of an asymmetric azobenzene derivative possessing an electron-donating group on one benzene ring and an electron-withdrawing group on another benzene ring and as a consequence, an almost 1:1 mixture of the two regioisomers was obtained as the product (Scheme 3). Thus, the difference in electron density between the two nitrogen atoms was found to be small in this case.

A plausible reaction mechanism is indicated in Scheme 4. Two pathways are suggested for propargylic hydrazines (α-adducts). A barium reagent generated from a trimethylsilyl-substituted propargylic bromide is considered to exist in equilibrium between allenic isomer **A** and acetylenic isomer **B**.[7] Thus, propargylic hydrazines can be formed from both isomers **A** and **B** by their reaction with an azo compound via transition state structure **C** or **D**. However, transition state **D** is more probable because of its minimal steric repulsion. In contrast, allenylic hydrazines (γ-adducts) are obtainable from **B** via its S_E2'-type reaction with the azo compound through six-membered cyclic transition state **E**, which is, however, destabilized by the trimethylsilyl group.

In summary, we have achieved a Barbier-type propargylation of azo compounds with propargylic halides, which is promoted by reactive barium. This method is synthetically useful with regard to regioselectivity and gives diverse propargylic hydrazines in moderate to high yields. It is worthy of note that the ester moieties of dialkyl azodicarboxylates are unaffected by barium reagents. Further studies of related reactions promoted by barium reagents are in progress.

Typical Experimental Procedure for the Barbier-Type Propargylation (Entry 10 in Table 1 and Entry 1 in Table 2)

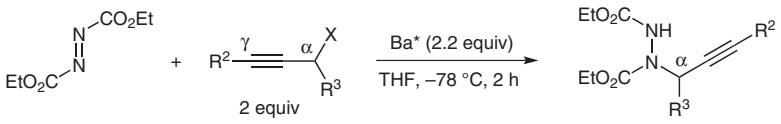
An oven-dried, 20 mL Schlenk flask equipped with a Teflon®-coated magnetic stirring bar was flushed with argon. Freshly cut lithium (16 mg, 2.2 mmol) and biphenyl (340 mg, 2.2 mmol) were put into the apparatus and covered with anhyd THF (5 mL), and the mixture was stirred for 1.5 h at r.t. (lithium was completely consumed). An-



Ar^1 = 4-MeC_6H_4
Ar^2 = 4-FC_6H_4

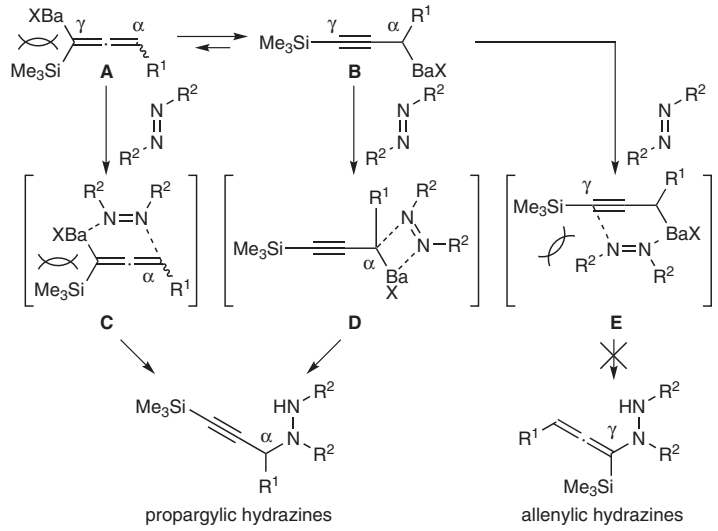
Scheme 3 Reactive-barium-promoted selective propargylation of an asymmetric azo compound with (3-bromobut-1-ynyl)trimethylsilane

Table 2 Reactive-Barium-Promoted Selective Propargylation of Diethyl Azodicarboxylate with Various Propargylic Halides[a]



Entry	R^2	R^3	X	Yield (%)[b]
1	Me_3Si	Me	Br	80
2	Me_3Si	Me	Cl	74
3	Me_3Si	Pr	Br	77
4	$(i\text{-Pr})_3Si$	Me	Br	59
5	Ph_3Si	Me	Br	85
6	$(t\text{-Bu})Me_2Si$	Me	Br	84
7	Me	Me	Br	69
8	*c*-Hex	Me	Br	75
9	*t*-Bu	Me	Br	77
10	Ph	Me	Br	75
11	Ph	Me	Cl	45

[a] The reaction was carried out using propargylic halide (2 equiv), diethyl azodicarboxylate (1 equiv), and reactive barium (2.2 equiv) in anhyd THF at –78 °C for 2 h.
[b] Isolated yield.



Scheme 4 Plausible reaction pathways to propargylic hydrazines and allenylic hydrazines

hyd BaI_2 (430 mg, 1.1 mmol) was placed in a separate oven-dried, 50 mL two-necked flask that was also equipped with a Teflon®-coated magnetic stirring bar under argon atmosphere, and this was covered with anhyd 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 lithium biphenylide in THF under an argon stream. The reaction mixture was stirred for 30 min at r.t. A solution of (3-bromobut-1-ynyl)trimethylsilane (191 μL, 1.0 mmol) and diethyl azodicarboxylate (2.2 M toluene solution, 227 μL, 0.50 mmol) in anhyd THF (4 mL) was added dropwise to the resulting dark brown suspension of reactive barium (1.1 mmol) in THF (10 mL) at –78 °C. After being stirred for 2 h at this temperature, the mixture was treated with sat. NH_4Cl aq solution (10 mL) at –78 °C, and the aqueous layer was extracted three times with Et_2O (10 mL each). The combined organic extracts were washed with 1 N $Na_2S_2O_3$ solution (20 mL), dried over anhyd $MgSO_4$, and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to give the propargylic hydrazine (120.7 mg, 80% yield).

TLC: R_f = 0.26 (EtOAc–hexane = 1:4). IR (neat): 3301, 2985, 2902, 2175, 1760, 1715, 1519, 1472, 1415, 1384, 1314, 1251, 1228, 1112, 1063, 846 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.16 (s, 9 H, 3 CH_3), 1.26–1.31 (m, 6 H, 2 CH_3), 1.41 (d, 3 H, J = 6.8 Hz, CH_3), 4.15–4.28 (m, 4 H, 2 CH_2), 5.11 (m, 1 H, CH), 6.19 (br s, 0.25 H, NH), 6.40 (br s, 0.75 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –0.2 (3 C), 14.3 (2 C), 19.3, 47.0, 61.9, 62.7, 88.1, 103.4, 155.1,

156.2. The above-mentioned spectral data showed good agreement with the reported data.[5b]

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