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SHORT COMMUNICATION

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Chemoselective *O*-Benzylation of the Propargylic Hydroxy Group in Polyols

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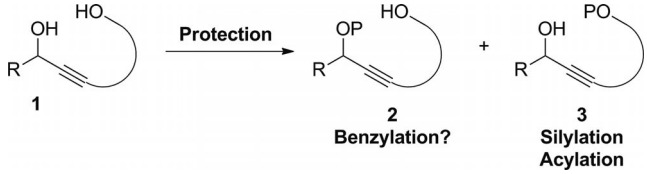
We have discovered the highly chemoselective benzylation of propargylic hydroxy groups in the presence of other hydroxy groups under very usual conditions involving benzyl bromide and sodium hydroxide in DMF at room temperature. This methodology has a high synthetic utility for the selective protection of hydroxy groups at the propargylic position among various other hydroxy groups in complex molecules.

Introduction

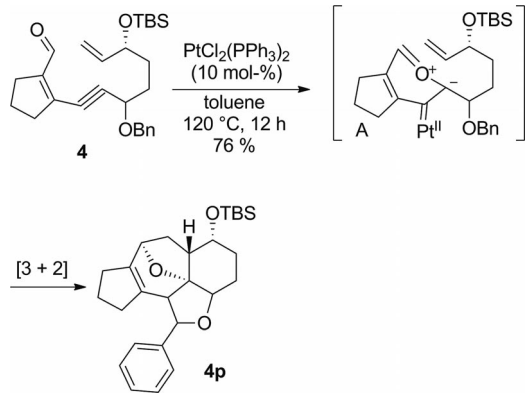
Hydroxy groups are present in a number of biologically and synthetically interesting carbohydrates, steroids, nucleosides, and other natural products,[1] and the chemoselective differentiation of several hydroxy groups within a molecule has long been a major issue for synthetic chemists.[2,3] In the majority of cases reported so far, the selective *O*-protection of polyols generally occurs faster for primary OH groups than for secondary or tertiary OH groups, mainly as a result of steric reasons.[4] For instance, most the commonly used protecting groups, such as the *tert*-butyldimethylsilyl,[5] acetyl,[6] or benzoyl group,[7] tend to form the corresponding silyl ether, acetate ester, or benzoate ester smoothly on the primary hydroxy group despite the presence of other hydroxy groups (Scheme 1). There have also been a few reports on the chemoselective silylation of propargylic alcohols in the presence other hydroxy groups.[8]



Scheme 1. Selective protection of OH groups.

The most important protecting groups for alcohols are ethers, which vary from the very stable methyl ether to the highly elaborate trityl ether. Although there are many reports on the chemoselective *O*-alkylation of primary OH groups over other OH groups, only a few methods for the chemoselective *O*-alkylation of secondary and tertiary OH groups over primary OH groups are known.[9] Benzylation is one of the most widely used methodologies for the protection of OH groups because the benzylated products are quite stable and easy to debenzylate by hydrogenation.[10] Although many benzylation reactions occur under a wide variety of mild conditions, their chemoselectivities have remained unsolved.

Recently, while exploring Au- and Pt-catalyzed reactions of enynal systems like **4** bearing a propargylic ether group, we faced a problem in the selective protection of a propargylic OH group in the presence of other hydroxy groups (Scheme 2).[11]



Scheme 2. Pt-catalyzed cyclization of **4** to **4p**.

The Lichtenthaler group and the Grice group reported the very selective benzylation of the *axial* OH group of carbohydrate **5a** in the presence of a primary alcohol to afford **5a-B** by using sodium hydride as a base [Equation (1)].[12] This is an example of a reversal of polarity between the primary and secondary hydroxy groups. To our best knowledge, there has been only one report on the chemoselective benzylation of propargylic hydroxy groups over other hydroxy groups [Equation (2)].[13] Wipf and Graham carried out the benzylation of **5b** by controlling the equivalents of NaH (1.0 equiv.) and BnBr (1.0 equiv.) in the

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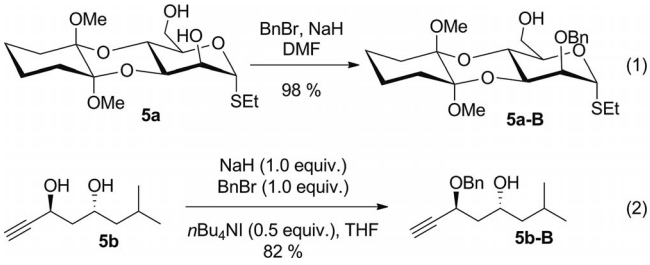
presence of nBu$_4$NI (0.5–2.0 equiv.) as an additive in THF and isolated benzylated product **5b-B** along with unreacted starting material in 82 and 12% yield, respectively.



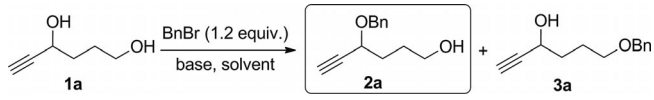
These reports prompted us to find a chemoselective method for the benzylation of specific OH groups. We have postulated that reversal of nucleophilicity of the propargylic OH group might facilitate benzylation and result in a faster reaction than with other hydroxy groups. To test this hypothesis, we examined the pK_a values of various hydroxy groups, where propargyl alcohol, allyl alcohol, and ethyl alcohol have pK_a values of 13.6, 15.5, and 16.0, respectively.[14] This implies that selective deprotonation at the propargylic hydroxy group may be possible by judicious choice of the base and its number of equivalents. Herein, we wish to report our results on the chemoselective *O*-benzylation of propargylic alcohols.

Results and Discussion

We first designed substrate **1a** as a simplified model compound and examined its benzylation under a variety of conditions (Table 1). First, we surveyed bases under the standard conditions: benzyl bromide as the alkylating reagent and DMF as a solvent. The reaction of **1a** with NaH proceeded well at –42 °C (dry ice in acetonitrile) and at room temperature to furnish product **2a** in 92 and 91% yield, respectively, without forming product **3a** (Table 1, entries 1 & 2). Next, lithium hydroxide was explored as a base, but **3a** was formed as a minor product after a prolonged reaction time (Table 1, entry 3). The best base turned out to be sodium hydroxide (Table 1, entries 4 & 5). Both the reactions at –42 °C and at room temperature furnished desired product **2a** almost quantitatively. It is noteworthy that, when the benzylation reaction of **1a** was carried out with an excess amount of benzyl bromide, benzylic ether **2a** was selectively formed without sacrificing the yield (Table 1, entry 6). However, the use of an excess amount of NaOH had a negative effect leading to dibenzylation (Table 1, entry 7).

Next, with the use of NaOH as the base, solvents ranging in polarity from very polar DMSO to THF and 1,4-dioxane to nonpolar toluene were explored (Table 1, entries 8–11). In terms of the yield and the selectivity, these solvents were not better than DMF. This indicates that the solvent polarity is very important for the improvement in the reactivity and selectivity of the *O*-benzylation of polyols. Other weak bases such as K_2CO_3 and organic bases such as iPr$_2$NEt were found to be nearly inactive for this reaction (Table 1, entries 12 & 13). From our systematic studies, we

Table 1. Benzylation of 5-hexyne-1,4-diol (**1a**).



Entry	Base (1.3 equiv.)	Solvent	T [°C]	Time [h]	Product (% yield)[a]
1	NaH	DMF	–42	3	**2a** (92)
2	NaH	DMF	r.t.	1	**2a** (91)
3	LiOH	DMF	r.t.	10	**2a** (87), **3a** (11)
4	NaOH	DMF	–42	4	**2a** (96)
5	NaOH	DMF	r.t.	1	**2a** (94)
6	NaOH[b]	DMF	r.t.	1	**2a** (92)
7	NaOH[c]	DMF	r.t.	8	**2a** (41)[d]
8	NaOH	DMSO	r.t.	6	**2a** (82), **3a** (15)
9	NaOH	THF	r.t.	12	**2a** (75), **3a** (21)
10	NaOH	dioxane	r.t.	24	**2a** (72)
11	NaOH	toluene	r.t.	24	**2a** (trace)
12	K_2CO_3	DMF	r.t.	12	**2a** (trace)
13	iPr$_2$NEt	DMF	r.t.	12	**2a** (trace)

[a] Isolated yield. [b] Three equivalents of benzyl bromide were used. [c] Six equivalents of base was used. [d] Dibenzylated product was isolated as a byproduct in about 20% yield.

were delighted to find an effective, inexpensive, and chemoselective method for the benzylation of propargylic alcohols in the presence of other hydroxy groups.

To explore the scope of the present chemistry, diverse substrates for selective *O*-benzylation were prepared. Successful chemoselective benzylation of these substrates was observed in most cases. We prepared propargylic alcohols **1b–j** bearing primary, secondary, and/or allylic OH groups (Figure 1) and carried out selective benzylations under the optimized conditions. Products **2b–j** were obtained, and these products were benzylated exclusively at the propargylic OH group even though various other primary, secondary, and allylic hydroxy groups were present in the substrates. Substrates **1b** and **1c** gave the expected products in 92 and 86% yield, respectively. Excellent chemoselectivity toward **1d** and **1e** bearing an allylic OH group was also obtained. Notably, when **1d** was protected with *p*-methoxybenzyl chloride (PMBCl) under our conditions, **2d-PMB** was isolated in 88% yield. This implied that our protocol would extend to similar benzylations. More functionalized substrates **1f** and **1g** worked as expected. Substrate **1h** bearing primary, secondary, and propargylic hydroxy groups was benzylated only at the propargylic position in 98% yield. From the ^{1}H NMR spectrum of each of the crude products, the chemoselectivity was able to be determined easily by observing the coupling partner of a leaning doublet due to the benzylic protons. The high chemoselectivity for the benzylation of propargylic alcohols is greatly important. The preference for benzylation at a propargylic hydroxy group could serve as a very useful tool for a selective protecting group that could be applied to the development of efficient organic syntheses. Although this selectivity is not unambiguously explained, it should be pointed out that it is probably due to the acidity of the propargylic OH group over the other hydroxy groups. In contrast to acety-

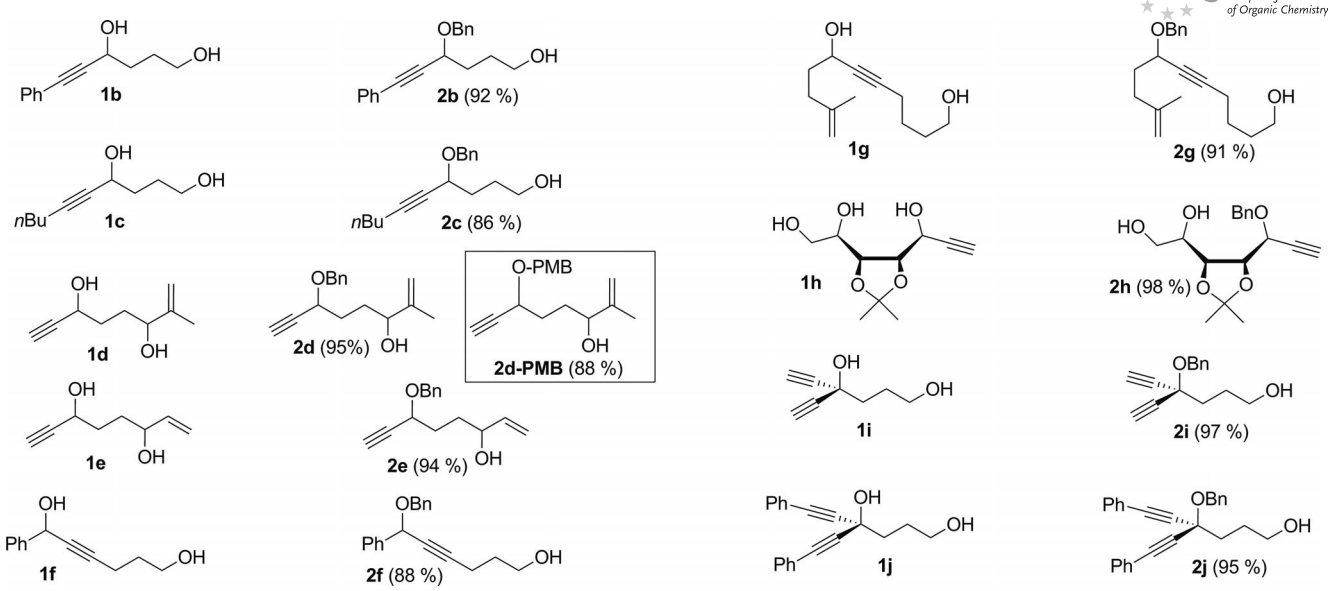
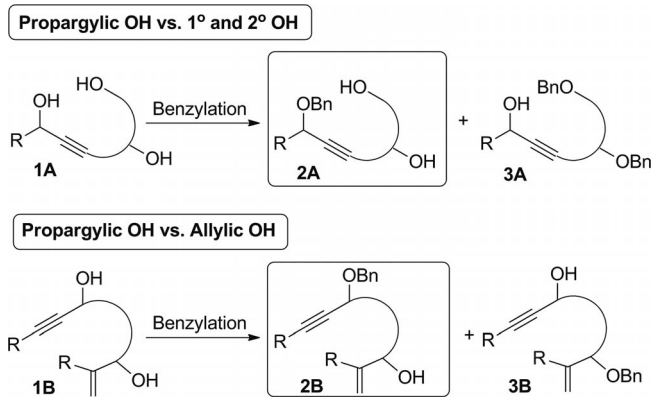


Figure 1. Chemoselective benzylation of various alcohol substrates.

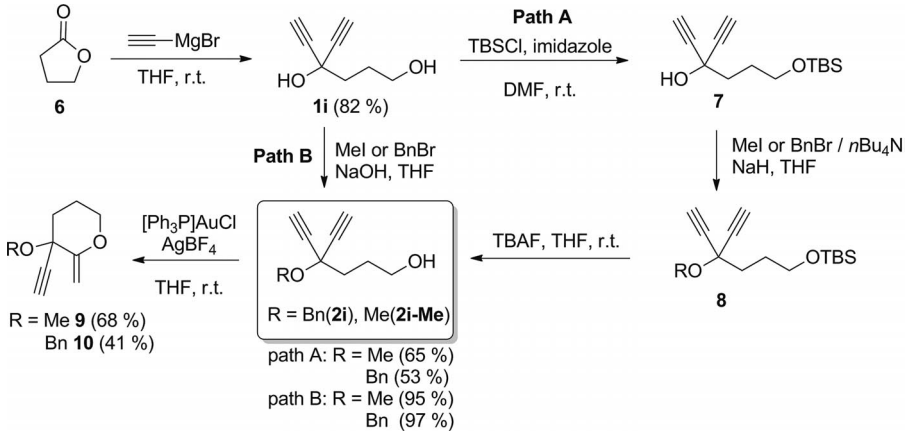
lation, benzoylation, or silylation using amine-type bases, selective benzylation using inorganic bases is more sensitive to the acidity of the hydroxy group. It is worth noting that the formation of the oxyanion prior to *O*-benzylation would occur. Thus, the acidity of the various hydroxy groups in the polyols might affect the population of each oxyanion in solution and their reactivity. As a result, the oxyanion from the propargylic hydroxy group would be more reactive towards benzyl bromide than the other hydroxy groups, making chemoselective *O*-benzylation possible (Scheme 3).

A recent report by Czekelius described a Au-catalyzed cyclization to obtain enol ether **9** and **10** through the multistep synthesis outlined in path A (Scheme 4).[15] These results inspired us to develop a mild and efficient method for the chemoselective *O*-benzylation of polyols. Our protocol was successfully applied to the selective benzylation of the OH group at the propargylic position without attacking the primary OH group in 4-ethynylhex-5-yne-1,4-diol (**1i**) as a dihydroxy compound, which was readily prepared from



Scheme 3. Chemoselective benzylation of propargylic alcohols.

γ-butyrolactone (**6**) with ethynylmagnesium bromide. When **1i** was treated with benzyl bromide and sodium hydroxide in DMF at room temperature, the reaction afforded expected product **2i** as the major product. This idea was



Scheme 4. Efficient reaction pathways involving chemoselective *O*-alkylation.

adapted to a methylation reaction by replacing benzyl bromide with iodomethane. Indeed, methylation of **1i** at room temperature resulted in corresponding product **2i-Me** in 95% yield (Scheme 4). In comparison to the Czekelius synthesis, path B furnished benzylation product **2i** and **2i-Me** directly to provide a more efficient reaction pathway for their syntheses. Furthermore, diol **1j**, prepared from phenylacetylide and **6**, was also benzylated to afford **2j** in 95% yield.

Conclusions

We have discovered the highly chemoselective benzylation of propargylic hydroxy groups in the presence of other hydroxy groups under very usual conditions involving benzyl bromide and sodium hydroxide in DMF at room temperature. This methodology has a high synthetic utility for the selective protection of hydroxy groups at the propargylic position among various other hydroxy groups in complex molecules.

Experimental Section

Representative Procedure: In a dried argon-flushed round bottomed-flask, hex-5-yne-1,4-diol (**1a**; 124 mg, 1.1 mmol, 1.0 equiv.) was dissolved in dry *N*,*N*-dimethylformamide (2.0 mL). Sodium hydroxide (57 mg, 1.3 equiv.) was added to this solution at 0 °C. The mixture was stirred at room temperature for 30 min. The mixture was then treated with benzyl bromide (1.2 equiv.) at 0 °C and stirred for 1 h allowing to warm to room temperature. After complete conversion as indicated by TLC analysis, water was added to the reaction mixture, and the product was extracted with diethyl ether (3×). The combined organic phase was dried with $MgSO_4$. After evaporation of the solvent, the crude product was purified by column chromatography (SiO_2, *n*-hexane/EtOAc = 4:1) to afford pure product **2a** (209 mg, 94%).

Supporting Information (see footnote on the first page of this article): Characterization data, FTIR spectra, HRMS, and copies of the ^1H NMR and ^{13}C NMR spectra for the products.

Acknowledgments

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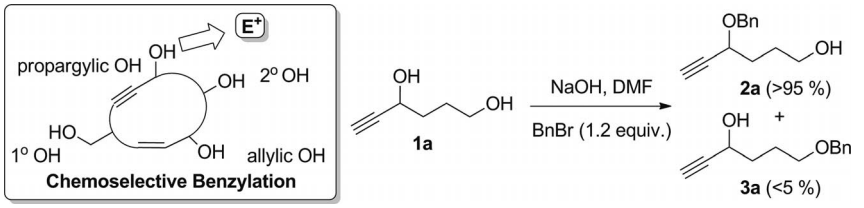

The chemoselective benzylation of propargylic hydroxy groups in the presence of other hydroxy groups under mild conditions by using benzyl bromide and sodium hydroxide in DMF at room temperature is reported. This methodology has high synthetic utility for the selective protection of hydroxy groups at the propargylic position among various other hydroxy groups in complex molecules.

Keywords: Chemoselectivity / Protecting groups / Alkynes / Alcohols / Benzyl ether

