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$CO_2(CO)_8$-Assisted synthesis of propargylic unsymmetrical ethers by reaction of alcohols with propargylic alcohols

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Abstract

Lewis acid treatment of alcohols with $CO_2(CO)_6$-propargylic alcohols yielded propargylic ethers after cobalt demetallation. The procedure is highly effective for the preparation of symmetrical and unsymmetrical ethers derived from primary alcohols and primary and secondary propargylic alcohols. The method permits the use of a wide range of alcohols including those having halogens in their structures. © 2000 Published by Elsevier Science Ltd.

Keywords: propargylic ether; Nicholas reaction; cobalt complexes.

Access to linear ethers containing two different alkyl groups is difficult starting from alcohols and mineral acids, since the mixture of two alcohols in the presence of an acid usually leads to a mixture of the three possible products.[1] The Williamson reaction is the best-known and most widely used method for the preparation of unsymmetrical ethers.[2] The procedure involves treatment of a halide or a sulfonate ester with alkoxide or aryl oxide anions prepared from an alcohol or phenol under S_N2 conditions.[3] However, the reaction is not useful when the ethers are sensitive to the basic conditions, such as for instance halogenated ethers due to collateral elimination reactions.

Propargylic ethers are particularly important regarding the wide range of functional group interconversions that the triple bond permits.[4] In this communication we describe a simple method for the preparation of such ethers by reaction of alcohols with $CO_2(CO)_6$-complexed propargylic alcohols under acidic conditions (Scheme 1).[5] The method is based on the alcoholic quenching of the extraordinarily stable $CO_2(CO)_6$-complexed propargylic cations generated under Nicholas reaction conditions.[6]

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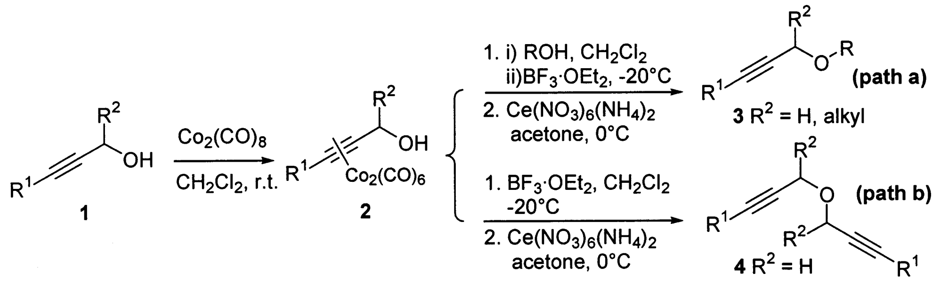


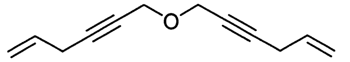
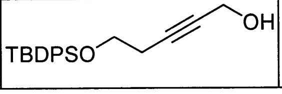
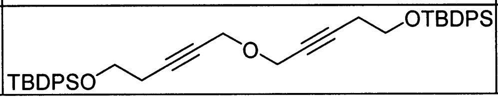
Scheme 1.

A typical experiment for the preparation of these propargylic ethers is illustrated for the preparation of **6**: to a solution of **5** (100 mg, 0.29 mmol) was added dicobalt octadicarbonile (121 mg, 0.35 mmol) in CH_2Cl_2 (3 mL) at rt. The reaction was stirred for 1 h, concentrated and dissolved again in $CHCl_2$ (15 mL) under argon atmosphere at rt. To this mixture was added propargylic alcohol (49 μL, 0.81 mmol) and the flask was cooled to −20°C. Then, $BF_3{\cdot}OEt_2$ (35 μL, 0.27 mmol) was slowly added and the reaction mixture stirred for 1 h at −20°C. The mixture was poured with vigorous stirring into a saturated solution of $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (2×15 mL). The organic layers were dried, concentrated and purified by silica gel column chromatography to obtain the $CO_2(CO)_6$-propargylic ether of **5** as a reddish oil. This complex was dissolved in acetone (2 mL) and the mixture cooled to 0°C. Then, $Ce(NO_3)_6(NH_4)_2$ (480 mg, 0.88 mmol) was added in one portion and the mixture stirred for 5 min. The reaction mixture was concentrated and the resulting residue dissolved in water and extracted with ether (3×10 mL). The combined organic phases were dried with $MgSO_4$, concentrated and purified by silica gel column chromatography to yield **6** (79 mg, 72%) as a colourless oil.

In order to minimize the formation of the dimer **4**, resulting from the nucleophilic attack of the propargylic alcohol itself to the generated cation, high dilution conditions (ca. 0.05 M) must be used and the Lewis acid should be added slowly to the reaction flask, followed by an excess (ca. 3 equiv.) of the nucleophilic alcohol (ROH in Scheme 1). When the Lewis acid was added to a solution of complex **2**, the corresponding dimer **4** was obtained in good yield (Table 1).

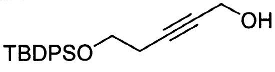
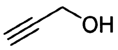
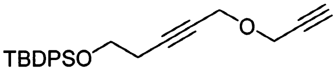
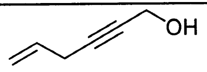
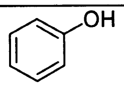
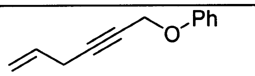
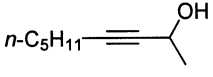
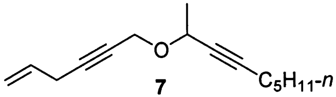
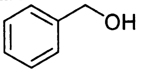
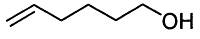
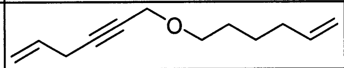
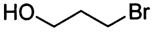
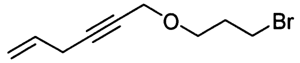
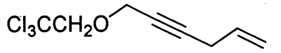
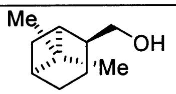
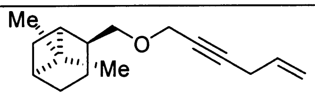
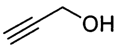
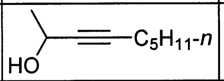
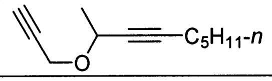
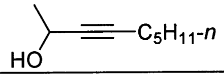
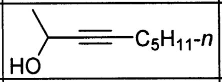
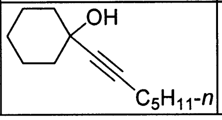
In preceding studies carried out in our group, we have shown the compatibility of many functional groups with the reaction conditions.[7] In order to determine the scope and synthetic limitations of the presented procedure, different nucleophilic and propargylic alcohols were used for experiments (Table 2).

Table 1
Representative examples of symmetrical propargylic ethers (path b)

Entry	1	4	(Yield %)[a]
1			74
2			66

[a] Yields are referred to **1** and not optimized

Table 2
Representative examples of the formation of propargylic ethers (path a)

Entry	1	ROH	3	(Yield %)[a]
1	 **5**		 **6**	74
2				60
3	"		 **7**	58
4	"			68
5	"			71
6	"			63
7	"	CCl_3CH_2OH		66
8	"			60
9				70
10			**7**	88
11	"		- -	- -
12	"		- -	- -

[a]Yields are referred to **1** and not optimized

The method is general to obtain mixed ethers when primary alcohols are used. However, when the propargylic alcohol is secondary, only primary alcohols can be used as nucleophiles (entry 10). The use of secondary or tertiary nucleophilic alcohols provides a very low or null yield of ethers (entries 11 and 12), probably due to competitive elimination reactions. When two differently substituted propargylic alcohols are combined the better yields are achieved for secondary $CO_2(CO)_6$-complexed propargylic alcohols with a primary nucleophilic alcohol (entries 3 and 10 for the preparation of **6**). One interesting feature of our method is the compatibility with halogenated substrates (entries 6 and 7), providing a very convenient method to obtain halide–ethers in good yields that are difficult to obtain by other methodologies.[8]

In summary, we describe a new procedure to obtain highly functionalized linear propargylic ethers. These molecules are currently being used as substrates in cyclization reactions and the results will be published in due course.

Acknowledgements

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8. Satisfactory spectroscopic data and combustion analyses were obtained for all new compounds.