A Convenient Procedure for the Synthesis of Propargyl Ethers Derived from Secondary Alcohols

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A new and efficient two-step synthesis of propargyl ethers derived from secondary alcohols, involving the formation of 1-propynyl ethers followed by isomerization with potassium 3-aminopropylamide, is described. The process is insensitive to the steric hindrance of the starting alcohol.

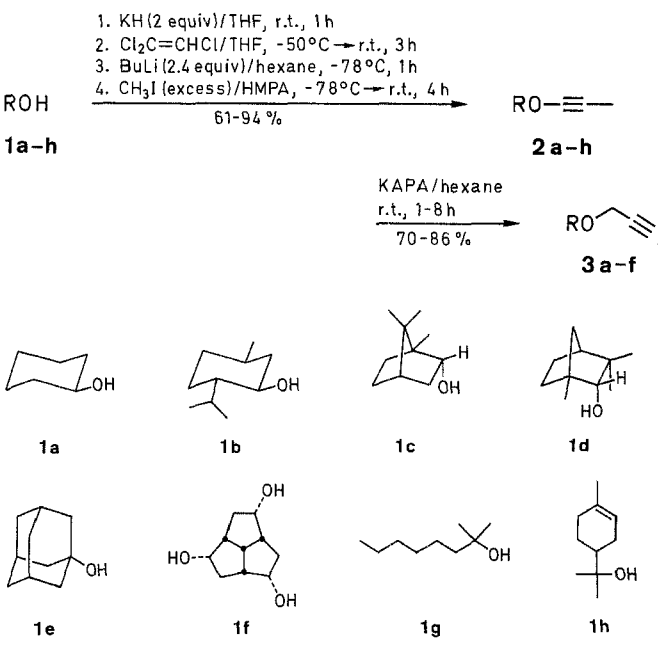
Propargyl ethers are versatile synthetic intermediates, as evidenced by recent applications in acyclic stereocontrol through [2,3] Wittig rearrangements,[1] synthesis of cage compounds by oxidative coupling[2] and intramolecular Diels–Alder reactions.[3,4]

The direct conversion of alcohols into their corresponding propargyl ethers is usually carried out by nucleophilic attack of the alkoxide to propargyl bromide. While this reaction gives good yields when applied to phenols[2] or primary alcohols,[1,3,5] there are few reports in the literature concerning its use with secondary[4] or tertiary[6] alcohols.

In connection with a research program in the chemistry of diacetylenes, we required a series of propargyl ethers derived from secondary alcohols **1a–d**. Much to our surprise, we found that the reaction of a moderately hindered secondary alkoxide such as sodium menthyloxide [generated by treatment of (−)-menthol (**1b**) with sodium hydride in tetrahydrofuran] with an excess of propargyl bromide was extremely slow and after three days under reflux we were able to isolate the corresponding propargyl ether **2b** only in very low yields (8%) together with a 92% of starting alcohol. The reaction could not be made to go to completion either by changing the solvent (dimethyl sulfoxide or dimethylformamide), the cation (potassium or lithium), the propargyl derivative (propargyl methanesulfonate) or by adding anionic activation catalysts (tetrabutylammonium iodide or crown ethers), since even after prolonged reaction times (up to nine days) substantial amounts of the starting alcohol were still present in the reaction mixture. The best conditions found for (−)-menthol were the use of hexamethylphosphoramide as a co-solvent, in which case, and after fifteen days of reaction, the desired propargyl ether was isolated in a modest 55% yield. Similar results were obtained with the other secondary alcohols subject of the present study.

Clearly the need of such a long reaction time is a serious drawback that must be attributed to the lack of nucleophilicity of the alkoxides towards a relatively poor electrophile like propargyl bromide, since the reaction of the same alkoxides with a stronger electrophile like allyl bromide was essentially quantitative after 3–4 hours under reflux in tetrahydrofuran. Consequently, the need for alternative procedures which could avoid the use of the poorly electrophilic propargyl derivatives is clearly warranted.

Accordingly, we decided to investigate an alternative strategy, which involves the preparation of intermediate 1-propynyl ethers and the subsequent isomerization to the desired propargyl derivatives.



The present procedure is based on a recently developed, high-yield one-pot synthesis of acetylenic ethers starting from the corresponding alcohols.[7] This reaction allowed the preparation of the desired 1-propynyl ethers **2a–h** corresponding to the

Table 1. 1- and 2-Propynyl Ethers from Alcohols

Starting Alcohol	1-Propynyl ether	Yield (%)	2-Propynyl ether	Reaction time (h)	Yield (%)	bp (°C/Torr) or (mp, °C)	Molecular Formula[a]
1a	**2a**	87	**3a**	1	73	75–80/30	$C_9H_{14}O$ (138.2)
1b	**2b**	91	**3b**	8	81	50/0.7	$C_{13}H_{22}O$ (194.3)
1c	**2c**	92	**3c**	8	80	50–55/0.2	$C_{13}H_{20}O$ (192.3)
1d	**2d**	94	**3d**	8	79	15–20/0.1	$C_{13}H_{20}O$ (192.3)
1e	**2e**	88	**3e**	4	70	(36–38)[c]	$C_{13}H_{18}O$ (190.3)
1f	**2f**	67[b]	**3f**	5	86[b]	(85–87)[c]	$C_{19}H_{22}O_3$ (298.4)
1g	**2g**	80					
1h	**2h**	61					

[a] Satisfactory microanalyses obtained: C ±0.40, H ±0.30.
[b] Yield per OH group.
[c] Recrystallized from pentane.

Table 2. Selected Spectral Data for 1- and 2-Propynyl ethers

Compound	IR, ν(cm^{-1}) C≡C	^{1}H-NMR δ C_2CH_3	Compound	IR, ν(cm^{-1}) C≡CH	^{1}H-NMR δ, J(Hz) $OC\underline{H}_2$, $C_2\underline{H}$	^{13}C-NMR δ, J(Hz) $\underline{C}H_2\underline{C}\equiv\underline{C}H$	GC-MS[a] (C.I., NH_3)
2a	2280	1.75 (s)	**3a**	3310, 2120	4.5 (d, J = 2); 2.7 (t, J = 2)	54.9 (t); 80.6 (s); 76.6 (d)	156
2b	2280	1.76 (s)	**3b**	3320, 2130	4.2, part AB of ABX syst., J = 16, J' = 2; 2.4 (t, J = 2)	55.2 (t); 80.7 (s); 77.9 (d)	212
2c	2280	1.72 (s)	**3c**	3310, 2120,	4.5, part AB of ABX syst., J = 14, J' = 2; 2.7 (t, J = 2)	57.2 (t); 80.9 (s); 84.4 (d)	210
2d	2270	1.70 (s)	**3d**	3310, 2120	4.1, part AB of ABX syst., J = 16, J' = 2; 2.37 (t, J = 2)	58.9 (t); 81.0 (s); 92.2 (d)	210
2e	2270	1.75 (s)	**3e**	3250, 2130	4.1 (d, J = 3); 2.4 (t, J = 3)	48.6 (t); 73.2 (s); 72.9 (d)	208
2f	2290	1.71 (s)	**3f**	3290, 2120	4.1 (d, J = 2); 2.4 (t, J = 2)	56.8 (t); 80.1 (s); 74.1 (d)	316
2g	2300	1.75 (s)					
2h	2280	1.75 (s)					

[a] $(M+18)^+$

alcohols **1a–h**. Yields are given in Table 1, whereas spectroscopic properties are summarized in Table 2. The crude products were filtered through triethylamine-pretreated silica gel and submitted to the second step without further purification.

Although the isomerization of some simple 1-propynyl ethers into propargyl ethers induced by sodium amide in liquid ammonia had been reported several years ago,[8] we found that these conditions were not suitable for the isomerization of the more hindered alkoxypropynes with which we deal in the present study. This transformation was conveniently effected however by using a moderate excess of potassium 3-aminopropylamide (KAPA)[9] in 1,3-propylenediamine as a solvent at room temperature. The yields were in general very good, although the optimum reaction time was not the same for all of the studied compounds. The resulting propargyl ethers **3** could be easily purified by column chromatography on silica gel, and analytical samples were obtained in all cases either by bulb-to-bulb distillation at reduced pressure or by recrystallization from adequate solvents. Yields, isomerization time and physical properties are given in Table 1, whereas Table 2 summarizes relevant spectroscopic data.

The isomerization reaction was successful for 1-alkoxy-1-propynes **2a–e**, derived from secondary alcohols **1a–d** and from 1-adamantanol (**1e**), and more remarkably, even with the tris(propynyl ether) **2f** corresponding to the tricyclic triol **1f**,[10] but failed in the case of the dimethylcarbinol-derived acetylenic ethers **2g** and **2h**. Whereas in the attempted isomerization of **2g** the reaction product was a complex mixture of olefinic hydrocarbons, the corresponding reaction of **2h** afforded *p*-cymene in high yield. These results tend to indicate that the basic conditions required for the isomerization were able to induce some elimination process in 1-*tert*-alkoxypropynes with alkyl groups not subjected to geometrical restrictions. In fact, it is known[11] that limonene, which is the expected primary product in a base-induced elimination from **2h**, can be efficiently dehydrogenated to *p*-cymene by potassium 3-aminopropylamide.

In summary, we have developed an efficient procedure for the preparation of propargyl ethers derived from secondary alcohols. Contrary to what is commonly observed when propargyl ethers are prepared by nucleophilic substitutions, the present method appears to be insensitive to the steric hindrance of the starting alcohols. Overall reaction times are much shorter (the whole sequence can be performed in a day) than in the classical methodology, and the use of a large excess of propargyl bromide is avoided.

All reagents were of commercial quality from freshly opened containers. Reagent quality solvents were used without further purification, except for hexamethylphosphoramide (distilled from calcium hydride and kept over molecular sieves) and tetrahydrofuran, which was distilled from sodium benzophenone ketyl inmediately prior to use. All reactions were conducted in previously dried glassware under an atmosphere of prepurified dry nitrogen. Reagents and solvents were generally introduced via syringe. Mass spectra were obtained on a Hewlett-Packard 5988A spectrometer. IR spectra were recorded on a Perkin-Elmer spectrophotometer model 681, and ^{1}H-NMR (60 MHz) spectra on a Hitachi Perkin-Elmer R-24B spectrometer. ^{13}C-NMR (50.3 MHz) and high-field ^{1}H-NMR spectra were obtained on a Varian XL-200 spectrometer. Elemental analyses were performed at the Microanalytical Service of the "Centro de Investigación y Desarrollo – C.S.I.C.", Barcelona.

***endo*-2-Bornyl 1-Propynyl Ether 2c; Typical Procedure:**

To a suspension of KH (13 mmol) in THF (12 mL) is added slowly a solution of (–)-borneol (1.0 g, 6.5 mmol) (**1c**) in THF (12 mL). The mixture is stirred at room temperature for 1 hour. After cooling at –50 °C, a solution of trichloroethylene (0.854 g, 6.5 mmol) in THF (5 mL) is added in one portion. The mixture is stirred at room temperature for 3 hours and cooled again at –78 °C. *n*-Butyl lithium (1.6 M in hexane, 10 mL, 16 mmol) is then slowly added, and stirring is maintained at the same temperature for 1 hour. A solution of methyl iodide (4.6 g, 32.5 mmol) in hexamethylphosphoramide (HMPA, 8 mL) is rapidly added, and the mixture is allowed to warm up to room temperature and stirred for 4 hours. A few drops of methanol are added in order to destroy the excess KH, and the reaction mixture is poured into sat. aq. NH_4Cl solution (100 mL). The resulting mixture is extracted with hexane (100 mL). After drying ($MgSO_4$), elimination of the solvents and column chromatography on triethylamine-pretreated silica gel using hexane as eluent, the desired 1-propynyl ether **2c** is obtained; yield: 1.17 g (94%).

MS (C.I., NH_3): m/z = 154 $(M-C_3H_2)^+$; 137 $(M-C_3H_2O)^+$.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.98 (s, 3 H, CH_3); 1.08 (s, 3 H, CH_3); 1.20 (s, 3 H, CH_3); 1.3–1.9 (m, 7 H, ring protons); 1.70 (s, 3 H, C_2CH_3); 3.50 (m, 1 H, CHOR).

Isomerization of 2c to *endo*-Bornyl Propargyl Ether (3c); Typical Procedure:

Propane-1,3-diamine (4.1 mL) is added to KH (5.2 mmol), and the resulting mixture is stirred at room temperature for 1 h. After cooling at 0 °C, a solution of **2c** (0.25 g, 1.3 mmol) in hexane (0.5 mL) is added dropwise. Stirring is continued at room temperature for 8 h. After cooling again at 0 °C, water (5 mL) is added slowly, and the mixture is poured into hexane (50 mL). The organic phase is separated, washed with 2 M aq. HCl (15 mL) and water (15 mL), and dried ($MgSO_4$). The solvent is evaporated, and the crude product is chromatographed on a silica gel column using hexane as eluent to give **3c** as a colorless oil; yield: 0.20 g (80%). An analytical sample is obtained after bulb-to-bulb distillation at reduced pressure (50–55 °C/0.2 Torr).

$C_{13}H_{20}O$	calc.	C 81.25	H 10.42
(192.3)	found	81.45	10.41

MS (C.I., NH_3): m/z = 210 $(M+18)^+$.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.2 (s, 3 H, CH_3); 1.2 (s, 3 H, CH_3); 1.2 (s, 3 H, CH_3); 1.1–1.6 (m, 3 H, ring protons); 2.0 (m, 2 H, ring protons); 2.3 (m, 1 H, ring proton); 2.5 (m, 1 H, ring proton); 2.7 (t, J = 2 Hz, 1 H, C_2H); 4.1 (m, 1 H); 4.4 (part A of ABX system, J_{AB} = 14 Hz, J_{AX} = 2 Hz, 1 H, OCH_2); 4.5 (part B of ABX system, J_{AB} = 14 Hz, J_{BX} = 2 Hz, 1 H, OCH_2).

^{13}C-NMR ($CDCl_3$/TMS): δ = 13.8 (q); 18.7 (q); 19.8 (q); 26.6 (t); 28.2 (t); 35.9 (t); 45.0 (d); 47.9 (s); 49.2 (s); 57.2 (t); 73.4 (d); 80.9 (s); 84.4 (d).

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