An Efficient One-Pot Procedure for Methyl Ethers Derived from Tertiary Acetylenic Alcohols; Strong Influence of Lithium Bromide upon the Coupling between Propynyllithium and Cyclopentanone or Cyclohexanone

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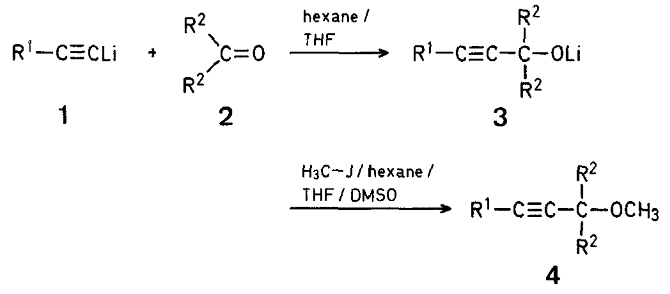
Ethers containing the structural system $>C-C\equiv C-C-O-$ have been shown to be useful starting compounds in syntheses of conjugated enynes[1,2] and cumulenes[3,4]. Some years ago, economic procedures for allenes based on 2-alkynyl ethers were described[5,6]. For our continuing study in the field of allene and cumulene chemistry we needed ethers (**4**) derived from *tertiary* acetylenic alcohols. The *O*-methylation of tertiary acetylenic alcohols with dimethyl sulphate is reported to proceed in low yield[5]. It appeared during our investigations that *O*-alkylation of the alcohols by treating the alkoxides with alkyl iodide in liquid ammonia gave poor results: the main reaction was ammonolysis of the alkyl iodide.

Since most alcohols are produced in excellent yields by coupling of lithiated acetylenes (**1**) with ketones (**2**) in a mixture of hexane and tetrahydrofuran, it seemed attractive to combine this reaction in the same reaction vessel with a subsequent alkylation after addition of a suitable polar co-solvent. If, after the formation of the alkoxide, a sufficient amount of dimethyl sulphoxide was added (ratio hexane : THF : DMSO about 2:2:3), the desired alkylation could be realised generally within 1–2 hours at slightly elevated temperatures and with excellent overall yield.



In a number of cases use of hexamethylphosphoric triamide alone also gave high yields of the ethers **4**, but the required reaction times for the alkylation were considerably longer[8].

Reactions performed with easily enolizable ketones such as cyclopentanone [**2**; $R^2-R^2=-(CH_2)_4-$] and cyclohexanone [**2**; $R^2-R^2=-(CH_2)_5-$] and the slightly soluble propynyllithium (**1**; $R^1=CH_3$) gave low yields of the tertiary methyl ethers (**4**); much of the ketone was recovered after the aqueous work-up. The poor results are most probably due to predominating proton abstraction from the ketones by the lithium alkynide. A considerable improvement, however, was obtained when, prior to the reaction of propynyllithium with the cycloalkanones, a small amount of anhydrous lithium bromide was added. Optimal results were realised when using 50 mol-% of lithium bromide. Addition of lithium bromide had also some influence upon the yield of the methyl ether of the cyclohexanone alcohol of $HC\equiv C-CH_2OCH_3$, but since in the absence of the salt reasonable yields were obtained, the effect was less dramatic. It should be noted that the lithium derivative $LiC\equiv C-CH_2OCH_3$ is much more soluble in the hexane/tetrahydrofuran mixture than is **1** ($R^1=CH_3$). We have not yet carried out a more detailed investigation concerning this effect of lithium bromide, and any explanation is therefore speculative.

Recently, the preparation of a 2-alkynyl ether derived from propyne, benzophenone, and methyl iodide was reported[9]. In the methylation step, no co-solvent was used. The solution of the alkoxide was refluxed during 17 hours with a large excess of methyl iodide. When the same compound is prepared by the procedure given below, methylation is complete within two hours.

Methyl 2-Alkynyl Ethers 4; General Procedure:

To a solution of *n*-butyllithium (0.20 mol) in hexane (~140 ml) is added with cooling below −30 °C pure, dry tetrahydrofuran (120 ml). Subsequently, the acetylenic compound [0.21 mol of 3-methoxypropyne[7] or 0.23 mol of propyne or 1-butyne as a cold solution in tetrahydrofuran (30 ml)] is introduced, while keeping the temperature below −30 °C. Dry acetone (0.22 mol) is then added at the same temperature. Benzophenone (0.20 mol) is added as a solution in tetrahydrofuran (30 ml). In the reactions of cyclopentanone or cyclohexanone (0.20 mol) with **1** ($R^1=CH_3$ or H_3COCH_2), addition of these ketones is preceded by addition of a solution of anhydrous lithium bromide (0.10 mol) in tetrahydrofuran (25 ml). After the ketone has been introduced, the cooling bath is removed and the temperature is allowed to rise to −5 °C. In case of **1** ($R^1=CH_3$), the white precipitate, initially present, has disappeared completely and an almost clear solution is formed. To the solution is added at −5 °C a mixture of dry dimethyl sulphoxide (200 ml) and methyl iodide (0.30 mol).

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Table. Methyl 2-Alkynyl Ethers **4**

Product No.	R^1	$2\ R^2$ or $R^2\quad R^2$	Yield [%]	n_D^{20}	b.p. [°C]/ torr	Molecular formula[a]	^{1}H-N.M.R. (CCl_4/TMS)[b] δ [ppm]
4a	H_3COCH_2	$2\,CH_3$	85	1.4303	63°/20	$C_8H_{14}O_2$ (142.2)	4.04 (s, 2H); 3.28 (ds, 6H); 1.40 (s, 6H)
4b	CH_3	$-(CH_2)_4-$	82	1.4624	66°/15	$C_9H_{14}O$ (138.2)	3.21 (s, 3H); 1.83 (s, 3H); 1.5–1.9 (br, 8H)
4c	CH_3	$-(CH_2)_5-$	86	1.4701	80°/15	$C_{10}H_{16}O$ (152.2)	3.24 (s, 3H); 1.85 (s, 3H); 1.2–1.9 (br, 10H)
4d	C_2H_5	$-(CH_2)_5-$	92	1.4658	86°/20	$C_{11}H_{18}O$ (166.3)	3.24 (s, 3H); 2.21 (q, 2H); 1.14 (t, 3H); 1.2–1.9 (br, 10H)
4e	H_3COCH_2	$-(CH_2)_5-$	86	1.4690	114°/15	$C_{11}H_{18}O_2$ (182.3)	4.08 (s, 2H); 3.30 (ds, 6H); 1.2–1.9 (br, 10H)
4f	CH_3	$2\,C_6H_5$	89 (83)[9]	m.p. 67 °C (from hexane)		Ref.[9] m.p. 68–69 °C	7.0–7.6 (m, 10H); 3.25 (s, 3H); 1.86 (s, 6H)

[a] Satisfactory microanalyses obtained (C ±0.32, H ±0.11); exception: **4a**, H −0.59%.

[b] Varian EM-390 90 MHz spectrometer.

The cooling bath is removed and the temperature is allowed to rise. Separation of salt starts after some minutes. When the (slightly) exothermic reaction (temperature rise to about 35 °C) has subsided, the flask is heated in a water bath of 50 °C for two hours, while the mixture is stirred vigorously. Two layers are formed. After cooling to room temperature ice/water (300 ml) is added and four extractions with pentane are carried out. The combined organic solutions are washed with saturated ammonium chloride solution, dried with magnesium sulphate, and subsequently concentrated in vacuo. Distillation of the residue through a 30 cm Vigreux column affords the methyl 2-alkynyl ethers **4** (see Table). All compounds showed a purity of >97% by G.L.C. analysis (Varian Aerograph 1520, 3% silicone OV-1 on Gaschrom Q 80–100 mesh, column temperature 120–160 °C).

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