

A Convenient Catalytic Method for the Synthesis of Ethers from Alcohols and Carbonyl Compounds

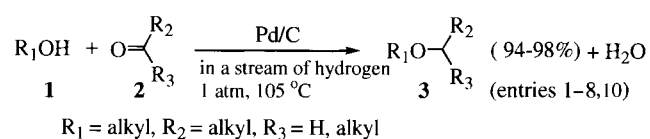
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Unsymmetrical ethers are obtained in excellent yields by the catalytic etherification of alcohols with ketones or aldehydes in the presence of Pd/C under an atmospheric pressure of hydrogen when water produced by the reaction is continuously removed by bubbling hydrogen through the reaction mixture.



The Williamson synthesis¹ has been used for the synthesis of unsymmetrical ethers, in spite of requiring strongly basic conditions and generating a stoichiometric amount of waste salts. In view of the environmentally benign organic chemistry, an alternative catalytic method with minimal waste is desired.²⁻⁴ The catalytic methods for the synthesis of unsymmetrical ethers reported previously⁵⁻⁷ may be unavailable for the alternative because of their various limitations as pointed out by Lemaire et al.⁸ Recently, Lemaire et al.⁸ and we⁹ have independently found that unsymmetrical ethers can be obtained from alcohols and carbonyl compounds in good yields (> 80%) by use of Pd/C as a catalyst under hydrogen atmosphere. The proposed methods, however, require a relatively high pressure of hydrogen (> 40 atm, where use of an autoclave is unavoidable) and a dilute solution of substrates (~ 0.2 mol dm⁻³). Under lower hydrogen pressure, the ratio of side reactions increase and the yields decrease remarkably; 1-butanol reacted with octanal to give only 39% of butyl octyl ether at 10 atm of hydrogen.¹⁰ These limitations are disadvantageous not only in laboratories but especially in industries. In this paper we report a useful catalytic method that can be successfully employed even under an atmospheric pressure of hydrogen for the synthesis of unsymmetrical ethers (Scheme 1).



Scheme 1.

Under an atmospheric pressure of hydrogen, ethers were scarcely formed from primary alcohols and ketones using Pd/C as a catalyst,¹¹ in contrast to moderate to high yields of ethers at relatively high hydrogen pressure (> 40 atm).^{8,9} On the other hand, when a stream of hydrogen was bubbled through the reaction mixture during the reaction,¹² primary alcohols reacted with either ketones or aldehydes to give the corresponding ethers excellent yields even under an atmospheric pressure of hydrogen (Table 1, entries 1-8), except for diisopropyl ketone (entry 9). Paracetaldehyde, which could generate acetaldehyde, can be used as a reactant to synthesize ethyl ether (entry 7). Symmetrical ether was also obtained (entry 4). Secondary alco-

Table 1. Pd/C-catalyzed etherification of alcohols **1** with carbonyl compounds **2** under an atmospheric pressure of hydrogen^a

Entry	Alcohol 1	Carbonyl compound 2	Product 3 ^b	Yield ^c / %
1 ^d	1-octanol	4-methyl-2-pentanone	3a	97
2 ^d	1-hexadecanol	4-methyl-2-pentanone	3b	98
3 ^e	1-tetradecanol	2-methylpropanal	3c	96
4 ^e	1-octanol	octanal	3d	97
5 ^e	1-hexadecanol	octanal	3e	96
6 ^e	C ₄ H ₉ OCH ₂ CH ₂ OH	octanal	3f	95
7 ^e	C ₄ H ₉ OCH ₂ CH ₂ OH		3g	96
8 ^f	1,6-hexanediol	4-methyl-2-pentanone	3h	94
9 ^d	1-octanol		no reaction	
10 ^e	2-octanol	octanal	3i	95
11 ^d	2-octanol	4-methyl-2-pentanone	no reaction	

^aAll reactions were carried out under a stream of hydrogen (180 ml/min).¹² ^bAll products were characterised by IR, NMR and Mass spectra. **3a**: 1,3-dimethylbutyl octyl ether. **3b**: 1,3-dimethylbutyl hexadecyl ether. **3c**: 2-methylpropyl tetradecyl ether. **3d**: dioctyl ether. **3e**: hexadecyl octyl ether. **3f**: 2-butoxyethyl 2-octoxyethyl ether. **3g**: 2-butoxyethyl 2-ethoxyethyl ether. **3h**: 1,6-bis(1,3-dimethylbutoxy) hexane. **3i**: 1-methylheptyl octyl ether. ^cIsolated yields based on the starting alcohols. ^d105 °C, 8 h. ^e160 °C, 10 h. Aldehydes were added dropwise during a period of 8 h. ^f105 °C, 48 h.

hol also reacted with aldehyde in high yields by the hydrogen-bubbling (entry 10), whereas the corresponding ether was not obtained with ketone (entry 11). The reduction of the carbonyl compounds to corresponding alcohols was minimal in our etherification process.

In the "hydrogen-bubbling method" described here, the effusion of water with a stream of hydrogen was observed during the reaction, and a corresponding amount of water to that of ethers formed was obtained.¹³ This result suggests that the

dehydration with hydrogen-bubbling accelerates Pd/C-catalyzed etherification to give good yields even under an atmospheric pressure of hydrogen. The removal of water may shift the equilibrium toward the enol ether (followed by the hydrogenation into the corresponding ether) from hemiketal or hemiacetal,¹⁰ which could not be hydrogenolyzed into the ethers directly under these conditions. The use of MgSO₄ as a dehydrating agent instead of the hydrogen-bubbling did not give satisfactory results under an atmospheric pressure.¹⁴ It seems that MgSO₄ did not have enough dehydrating ability to promote the reaction under our condition (1 atm, 105 °C for ketones or 160 °C for aldehydes). Lower levels of reactivity of diisopropyl ketone (entry 9) may be attributed to the steric hindrance.

From the viewpoint of the industrial applications, several advantages in the proposed method are noted as follows; employing ether synthesis (i) under an atmospheric pressure of hydrogen, (ii) without using an autoclave, (iii) without generating any waste salts, (iv) by using 2-fold of carbonyl compounds without using any co-solvents (in contrast to the "autoclave method"^{8,10} requiring very dilute conditions). Further, the amount of hydrogen used could be reduced to less than that in the autoclave method by circulating hydrogen to reuse it during the reaction. On the other hand, it should be pointed out as a limitation that water-soluble and/or low boiling point substrates, e.g., acetone, methanol etc., may not be applied without an alternative procedure for separating water, instead of the "Dean-Stark trap technique" used here.

In conclusion, the Pd/C-catalyzed etherification assisted by the hydrogen-bubbling dehydration (which can be successfully employed even under an atmospheric pressure) may be useful for the synthesis of ethers from alcohols and carbonyl compounds, especially for the environmentally benign industrial production as an alternative method to the Williamson synthesis.

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References and Notes

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- 11 The conversion of alcohol was 12% after 8 h when 1-octanol and 4-methyl-2-pentanone were used as substrates.
- 12 A typical procedure follows: A mixture of 1-octanol (39 g, 0.3 mol), 4-methyl-2-pentanone (60 g, 0.6 mol) and Pd/C (5% palladium-on-carbon 3.1 g, 0.16 g as Pd) was placed in a flask equipped with a tube for introducing hydrogen and a Dean-Stark trap, and was stirred vigorously under a stream of hydrogen (180 mL/min, at atmospheric pressure) at 105 °C. During the reaction, water produced was eliminated from the effluent and substrates effused were returned continuously to the reaction mixture by the "Dean-Stark trap technique". The reaction was monitored by GLC and after completion of reaction (8 h), the reaction mixture was filtered. The product was purified by flash chromatography on silica gel (hexane / ethyl acetate 20 : 1) to afford 1,3-dimethylbutyl octyl ether (**3a**) (62 g, 97%). The structure was characterized by IR, NMR and Mass spectra. **3a**: IR (Neat, cm⁻¹): 1095 (C–O–C), 1371, 1468, 2856, 2927. ¹H-NMR (CDCl₃): 0.89 (t, 3H), 0.92 (d, 6H), 1.11 (d, 3H), 1.2–1.4 (m, 10H), 1.4–1.7 (m, 4H), 1.7–1.9 (m, 1H), 3.2–3.6 (m, 3H). ¹³C-NMR (CDCl₃): 14.11, 20.02, 22.60, 22.72, 23.11, 24.71, 26.36, 29.37, 29.54, 30.32, 31.93, 46.48, 68.51, 73.52. HRMS (CI): Found *m/z* 215.2366 (M+H)⁺. Calcd for C₁₄H₃₀O: M+H, 215.2297.
- 13 In the case of entry 1, 5.0 g of water (93% of theoretical amount) was obtained.
- 14 The conversion of alcohol was 17% after 8 h when 1-octanol and 4-methyl-2-pentanone were used as substrates.