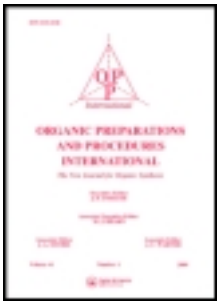

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A RAPID WILLIAMSON SYNTHESIS UNDER MICROWAVE IRRADIATION IN DRY MEDIUM

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A RAPID WILLIAMSON SYNTHESIS UNDER MICROWAVE IRRADIATION IN DRY MEDIUM

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Over the last few years there has been a growing interest in the use of microwave heating in organic synthesis.[1] The use of such unconventional reaction conditions has several advantages such as short reaction times compared to conventional heating, ease of work-up, reduction in the usual thermal degradation, and better selectivity. The simplest method for conducting microwave-assisted reactions involves irradiation of reactants in an open vessel. Such a method, termed *microwave-organic reaction enhancement* (MORE), was developed by Bose *et al.*[2] During the reaction, the reactants are heated by microwave irradiation in a polar, high-boiling solvent so that the temperature of the reaction mixture does not reach the boiling point of the solvent. For reactions at reflux, domestic microwave ovens have been modified by insertion of a shielded opening to prevent leakage, and through which the reaction vessel is connected to a condenser.[3] Pressurized conditions for microwave reactions were first reported by Gedye[4] and Giguere.[5] Gedye *et al.* used a domestic microwave oven, and commercially available screw-on pressure vessels made from either PET or Teflon. Microwave heating has been proven to be of particular benefit for the reactions in "dry" media (i. e., in the absence of a solvent, on solid support with or without catalysts) which has a number of advantages; solvents are often expensive, toxic, and difficult to remove in the case of aprotic solvents with high boiling point. Liquid-liquid extraction can be avoided for the isolation of reaction products. Moreover, the absence of solvent reduces the risk of explosions when reaction takes place in a microwave oven. Reactions under "dry" conditions were originally developed in the late 1980s.[6]

The preparation of ethers is an important reaction for which a wide variety of procedures have been developed during the last hundred years.[7] The most commonly used method is Williamson synthesis for the preparation of symmetrical and unsymmetrical ethers. Although the normal method involves treatment of a halide with an alkoxide, it is also possible to mix the halide and alcohol

directly with solid KOH and DMSO[8] or with HgO and HBF_4 in CH_2Cl_2.[9] Recently, several new procedures for Williamson synthesis have been developed[10] in which the phase-transfer catalysis (PTC) procedures appear to be the most useful in terms of mildness of conditions, yield, and convenience.[11] Optimum PTC conditions for the formation of unsymmetrical ethers are reported to consist of five-fold excess of 50% of aqueous NaOH relative to the alcohol, an excess of alkyl halide (preferably used as solvent), and 3-5% of tetrabutylammonium hydrogen sulfate for several hours with stirring.[12] An alternative procedure for the ether synthesis in the PTC system is to carry out a reaction in a solid/liquid medium in the presence of polyethers as catalysts.[13] We sought to develop a general method of the alkylation of organic compounds. Such a procedure should retain the convenience of PTC methods but should be free from some of the limitations related to PTC systems[11] and much faster.[14] Therefore we decided to explore the use of microwave heating under solvent free PTC conditions for alkylation of alcohols. The first example of ether synthesis (i.e., alkylation of 4-cyanophenolate anion) under pressurized microwave conditions has been shown by Gedye *et al.*[15] In the absence of solvent, Loupy *et al.* repeated the same reaction in presence of Aliquat/potassium hydroxide.[16] Also *O*-alkylation of potassium acetate on silica or alumina has been reported by Loupy *et al.*[17] Recently, Yuan *et al.* reported the synthesis of several ethers directly from alcohols and alkyl halides under microwave irradiation in the presence of a quaternary ammonium salt.[18]

$$\mathrm{R{-}OH} + \mathrm{R'{-}X} \xrightarrow[K_2CO_3,\ KOH,\ TBAB]{\textit{Microwave Irradiation, 45-100s}} \underset{(45\text{-}91\%)}{\mathrm{R{-}O{-}R'}}$$

We now report here a remarkably rapid synthesis of symmetrical and unsymmetrical ethers in 'dry' media under microwave irradiation. The reactions were carried out by simple mixing of the alcohol with 50% excess of an alkyl halide and a catalytic amount of tetrabutylammonium bromide (TBAB). The mixtures were adsorbed either on a mixture of potassium carbonate and potassium hydroxide or on potassium carbonate alone and then irradiated in an open vessel in a domestic microwave oven for 45-100 s. In the absence of the ammonium salt, ethers either were not detected or were obtained in unsatisfactorily low yield. The results are summarized in Table 1.

Since the shape and size of the reaction vessel are important factors for the heating of dielectric materials in a microwave oven, the preferred reaction vessel is a tall beaker of much larger capacity than the volume of the reaction mixture, and bearing a loose cover.

A large Erlenmeyer flask with a funnel as a loose top cap can be used in place of the beaker. Superheating of liquids is common under microwave irradiation. In this case, the alcohol, and potassium and ammonium salts are likely to get very hot. Thus the strategy is to keep the reaction temperature substantially below the boiling point of each compound used. Since it is difficult to measure temperature in a domestic microwave oven, one solution is to repeat an experiment several times with a slow increase of the power so that vapors do not escape the flask, with the tall vessel allowing condensation of the vapors.

Table 1. Reactions of Alcohols with Alkyl Halides under Microwave Irradiation in Dry Medium

R-OH R_1-X	Product R-O-R_1		Time (s)	bp. (°C/Torr) [lit. bp.]	Temp. (°C)	Yield (%)
$CH_3(CH_2)_9OH$						
Benzyl chloride	$CH_3(CH_2)_9OCH_2Ph$	**(1a)**	50	180-184/3 [177-178/2-3][19]	127	91
1-Bromopentane	$CH_3(CH_2)_9O(CH_2)_4CH_3$	**(1b)**	55	140-145/10[c]	152	83
1-Chlorodecane	$CH_3(CH_2)_9O(CH_2)_9CH_3$	**(1c)**	80	16-18[b] [16][20]	175	45
1-Bromooctane	$CH_3(CH_2)_9O(CH_2)_7CH_3$	**(1d)**	75	316-317 [315.5][21]	160	88
Allyl chloride	$CH_3(CH_2)_9OCH_2CH{=}CH_2$	**(1e)**	45	106-109/8 [107-8.5/8][22]	120	80
$CH_3(CH_2)_7OH$						
Benzyl chloride	$CH_3(CH_2)_7OCH_2Ph$	**(2a)**	55	146-149/9 [90-91/0.05][23]	135	89
1-Bromopentane	$CH_3(CH_2)_7O(CH_2)_4CH_3$	**(2b)**	100	240-242 [240][21]	149	91
1-Chlorodecane	$CH_3(CH_2)_7O(CH_2)_9CH_3$	**(1d)**	95	315-316 [315.5][21]	172	50
1-Bromooctane	$CH_3(CH_2)_7O(CH_2)_7CH_3$	**(2c)**	55	284-286 [286][21]	158	90
Allyl chloride	$CH_3(CH_2)_7OCH_2CH{=}CH_2$	**(2d)**	85	89-91/12 [87-88/12][21]	115	76
$CH_3(CH_2)_3OH$						
Benzyl chloride	$CH_3(CH_2)_3OCH_2Ph$	**(3a)**	55	222-223 [223][24]	122	86
1-Bromohexane	$CH_3(CH_2)_3O(CH_2)_5CH_3$	**(3b)**	50	87-90/95 [89-90/45][25]	136	82
1-Bromooctane	$CH_3(CH_2)_3O(CH_2)_7CH_3$	**(3c)**	55	221-222 [221][21]	139	81
Allyl chloride	$CH_3(CH_2)_3OCH_2CH{=}CH_2$	**(3d)**	50	117-120 [118][26]	98	78

a) Microwave oven power: 300W. b) mp. c) *Anal.* Calcd for $C_{15}H_{32}O$: H 14.12, C 78.87, Found: H 14.29, C 79.18. d) Final temperature of the reaction mixture

After the reaction, the work-up procedure involves simple treatment with an appropriate solvent (e.g., THF or CH_2Cl_2), purification by distillation in a Kugelrohr apparatus or recrystallization. If necessary, before recrystallization compounds may be separated from starting materials by means of flash chromatography. All the products gave satisfactory IR and MS data as well as elemental analyses. Melting and boiling points of all the compounds are in good agreement with data in the liter-

ature. The reaction procedures were not optimized.

In conclusion, we have improved the Williamson method of synthesis of symmetrical and unsymmetrical ethers; it occurs remarkably fast under mild conditions, using inexpensive reagents and a domestic microwave oven as the irradiation source. Moreover, the procedure is an alternative to those which rely on the use of dipolar aprotic solvents, mercury oxide/tetrafluoroboric acid, and several procedures that rely on "standard" PTC methods.

Table 2. Spectral Data of Ethers

Product	MS [m/e]	IR [cm^{-1}]
1a	M^+, 248 (2), 91 (100).	IR: 3087(w), 3064(w), 3031(m), 2926(s), 2855(s), 1506(w), 1455(s), 1361(m), 1103(s).
1b	M^+, 228 (1), 141 (11), 71 (100).	IR: 2926(s), 2855(s), 1466(m), 1457(m), 1375(m), 1307(w), 1114(s).
1c	M^+, 298, 141 (27), 57 (100).	IR: 2926(s), 2856(s), 1466(m), 1456(m), 1375(m), 1115(s).
1d	M^+, 270 (1), 141 (10), 71 (87), 57 (100).	IR: 2926(s), 2857(s), 1465(m), 1456(m), 1376(m), 1114(s).
1e	M^+, 198 (2), 141 (12), 57 (100), 41 (82).	IR: 3080(w), 2927(s), 2856(s), 1466(m), 1456(m), 1375(m), 1105(s), 998(m), 922(m).
2a	M^+, 220 (3), 91 (100).	IR: 3086(w), 3064(w), 3030(m), 2926(s), 2855(s), 1506(w), 1455(s), 1360(m), 1103(s), 1028(w).
2b	M^+, 200 (1), 113 (8), 71 (100).	IR: 2926(s), 2856(s), 1466(m), 1457(m), 1375(m) 1114(s).
2c	M^+, 242 (1), 113 (25), 71 (100).	IR: 2926(s), 2856(s), 1466(m), 1457(m), 1376(m), 1114(s).
2d	M^+, 170 (1), 71 (93), 57 (100), 41 (83).	IR: 3081(w), 2926(s), 2855(s), 1466(m), 1456(m), 1104(s), 998(m), 921(m).
3a	M^+, 164 (2), 91 (100).	IR: 3088(w), 3064(m), 3031(m), 2958(s), 2932(s), 2866(s), 2796(m), 1506(w), 1495(m), 1455(s), 1363(s), 1102(s).
3b	M^+, 158 (1), 85 (34), 57 (100).	IR: 2958(s), 2932(s), 2860(s), 2796(s), 1466(m), 1457(m), 1375(m), 1121(s).
3c	M^+, 186 (1), 71 (31), 57 (100).	IR: 2959(s), 2932(s), 2862(s), 2797(s), 1466(m), 1457(m), 1375(m), 1120(s).
3d	M^+, 114 (1), 58 (97), 41 (100).	IR: 3080(w), 2981(s), 2932(s), 2869(s), 1466(m), 1457(m), 1072(s), 917(s).

EXPERIMENTAL SECTION

Elemental analyses were performed on a Perkin-Elmer 240 microanalyzer. Melting points were measured on a Boetius-PHMK 05 microscope plates and are uncorrected. ^1H NMR spectra were recorded with a Tesla 487 C spectrometer, TMS being used as a internal standard; the chemical shifts are expressed in δ values downfield from TMS. MS spectra were obtained on a Hewllet-Packard 5985

spectrometer. IR spectra were determined as films on a Bio-Rad FTS –165 spectrophotometer and the wave numbers are given with a precision of 2 cm^{-1}.

General Procedure for the Synthesis of Aliphatic Ethers.- A mixture of the alcohol (5.0 mmol), the alkylating agent (6.0 mmol), tetrabutylammonium bromide (0.17 g, 0.50 mmol), and a mixture of potassium carbonate (2.8 g, 20 mmol) and potassium hydroxide (1.1 g, 20 mmol) was heated in a domestic microwave oven in an open Erlenmeyer flask for the appropriate time (see Table 1). After cooling, the reaction mixture was extracted with methylene chloride or THF (2 x 25 mL). The extract was then dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to dryness. Liquid compounds were purified by Kugelrohr distillation, while compound **1c** was purified by flash chromatography to afford the desired ether.

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