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SYNTHESIS OF AROMATIC ETHERS UNDER MICROWAVE IRRADIATION IN DRY MEDIA.

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Abstract: Under microwave irradiation a number of phenols react remarkably fast with a number of primary alkyl halides to give aromatic ethers. The procedure is alternative to those which rely on the use of dipolar aprotic solvents, sodium, sodium hydride, sodium amide and several procedure that rely on "standard" PTC methods

Introduction

Results and Discussion

Experimental

References

Introduction
[*first page*]

In the last few years there has been a growing interest in the use of microwave heating in organic synthesis [1-4]. The use of such unconventional reaction conditions reveals several features like: a short reaction time compared to conventional heating, ease of work-up after a reaction, and 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 at al.[5]. During the reaction, reactants are heated by microwave irradiation in a polar, high-boiling solvents so that the temperature of reaction mixture does not reach the boiling point of a solvent. Despite of convenience, a disadvantage of the MORE technique its limitation to high-boiling polar solvents such as DMSO, DMF, N-methylmorpholine, diglyme etc. However, the approach has been adopted to lower-boiling points solvent (e.g. toluene) [6], it generates a potentially serious fire hazard.

For reactions at reflux domestic microwave ovens have been modified by making a shielded opening to prevent leakage, and through which the reaction vessel has been connected to a condenser [7].

The pressurised conditions for microwave reactions first reported by the groups of Gedye [8] and Giguere [9] also have been developed. Gedye at al. used a domestic microwave oven, and commercially available

screw-up pressure vessels made from either PET or Teflon. The 'bomb' strategy has been successfully applied to a number of synthesis, but it always generates a risk of hazardous explosions. Recently, Majetich and Hicks [10] reported 45 different reactions with a commercial microwave oven and and PET vessels designed for acid digestion.

Microwave heating has been proven to be of benefit particularly for the reactions under "dry" media (i.e., in the absence of a solvent, on solid support with or without catalysts) and offers a number of advantages: solvents are often expensive, toxic, 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 reduce the risk of explosions when reaction takes place in a microwave oven.

Reactions under "dry" conditions (i.e., in the absence of a solvent, on a solid support with or without catalysts) were originally developed in the late eighties [11]. Synthesis without solvents under microwave irradiation offers several advantages [12]. The absence of solvent reduces the risk of explosions when the reaction takes place in a closed vessel in an oven. Moreover, aprotic dipolar solvents with high boiling points are expensive and difficult to remove from the reaction mixtures. During microwave induction of reactions under dry conditions, the reactants adsorbed on the surface of alumina, silica gel, clay, and others absorb the microwaves whereas the support does not, nor does it restrict the transmission of microwaves. Consequently, such supported reagents efficiently induce reactions under safe and simple conditions with domestic microwave ovens instead of specialised expensive commercial microwave systems.

Results and Discussion
[*first page*]

Preparation of aromatic ethers is an important synthetic reaction for which a wide variety of procedure has been developed during the last hundred years[13]. Most of the commonly used method involve alkylation of parent phenol or derived phenoxide ion, with the latter type being by far the more important. The phenoxide ion is generated by treatment of the phenol with a base such as sodium, sodium hydride or sodium amide in a solvent such as benzene, toluene, or dioxane; alkylation with the appropriate alkylu halide is then normally carried out in the same solvent. This method is usually highly efficient, although some care must be exercised in choice of solvent in order to avoid formation of both C- and O-alkylated products [14], [15].

There are few useful procedures available for the conversion of phenols into aromatic ethers which do not neccesite initial formation of the corresponding phenoxide ion. Direct alkylation with diazomethane can be wide applied[16], but is seldom the method of choice because of the obnoxious nature of the reagent. Alkylation can be also accomplished with alkyl orthocarbonate esters [17], dialkyl oxolate esters [18], and by treatment of phenols with alcohols in the presence of dicyclohexylcarboimide [19]. None of these methods is, however, general with respect to the variety of alkyl groups which can be introduced into aromatic alkyl ethers.

During the last years, several new procedures for Williamson synthesis have been developed [20] in which the PTC procedures appear to be the most useful in terms of mildness of conditions, yield, and convenience[21], [22].

We have sought to develop a general method of the O-alkylation of phenols and alcohols. Such a procedure should retain the convenience of PTC methods but should be free from some limitations related to PTC systems [21] and much faster. Therefore we decided to explore the use of microwave heating under solvent free PTC conditions for O-alkylation of phenols.

We now report here the remarkable fast method of synthesis of aromatic ethers in 'dry' media under microwave irradiation Fig. 1.
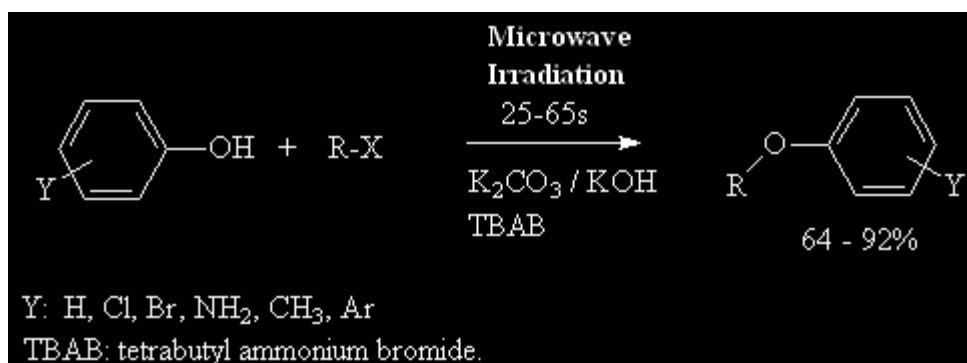
Figure 1. The reaction of phenols with alkyl halides under microwave irradiation.

The reactions were carried out by simply mixing of phenol with 50% excess of an alkyl halide and a catalytic amount of tetrabutylammonium bromide (TBAB). The mixtures were adsorbed either on the mixture of potassium carbonate and potassium hydroxide or potassium carbonate and then irradiated in an open vessel in a domestic microwave oven for 25-65 s. The results are summarized in Table 1.

Table 1. The reactions of phenols with alkyl halides under irradiation in a microwave oven.*

R-Cl	Ar-OH	Product No	Yield [%]	MW Power [W]	Time [s]
benzyl chloride	phenol	1	78	300	50
dimethyl sulphate	phenol	2	87	300	25
benzyl chloride	bisphenol-A	3	66	300	50
benzyl chloride	p-chlorophenol	4	72	300	50
benzyl chloride	p-aminophenol	5	89	300	40
benzyl chloride	m-cresol	6	92	300	50
1-bromobutane	p-bromophenol	7	71	300	40
dimethyl sulphate	o-chlorophenol	8	89	300	25
1-bromohexane	m-cresol	9	72	300	55
1-bromohexane	p-aminophenol	10	79	300	45
1-bromooctane	o-chlorophenol	11	64	300	60
1-bromooctane	p-bromophenol	12	69	300	65

*Reagents ratio: phenol (5 mmol), alkylating agent (6 mmol), tetrabutylammonium bromide(0.5mmol), K_2CO_3 (20 mmol), KOH (20 mmol).

Since the shape and size of the reaction vessel are important factors for the heating of dielectrics 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, thus the strategy of the reactions is to keep the reaction temperature substantially below the boiling point of each compound used for the reaction. Since it is difficult to measure temperature in a household microwave oven, one of the best solutions is to repeat an experiment several times increasing the power slowly so that vapours do not escape outside of the flask.

After the reaction, the work-up procedure is reduced to a 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 can be separated from starting materials by means of flash chromatography.

All the products gave satisfactory IR, ^1 H - NMR, and MS data. Melting and boiling points of all the compounds are in good agreement with literature data. The reaction procedures are not optimised yet.

In conclusion, we have developed a simple method for the synthesis of aromatic ethers that occurs remarkable fast under mild conditions using inexpensive reagents and a household microwave oven as the irradiation source. Moreover, the procedure is alternative to those which rely on the use of dipolar aprotic solvents, sodium, sodium hydride, sodium amide and several procedure that rely on "standard" PTC methods.

Experimental
[*first page*]

A mixture of a phenol (5.0 mmol), alkylating agent (6.0 mmol), tetrabutyl-ammonium bromide - TBAB (0.17 g, 0.50 mmol), and the 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 an appropriate time (see Table ??). After being cooled down, the reaction mixture was extracted with methylene chloride or THF (2 x 25 ml). Then the extract was dried withMgSO_4, filtered, and the solvent was evaporated to dryness. Liquid compounds were purified on Kugelrohr distillation apparatus, while solid compounds were purified by means of flash chromatography to afford desired an aromatic ether, yield: 64-92%.

References
[*first page*]

1. R. A. Abramovitch. 1991. *Org. Prep. Proc. Int*, 23, 685.

2. D. M. P. Mingos , D. R. Baghurst. 1991. *Chem. Soc. Rev.*, 20, 1.

3. R. Laurent, A. Laporterie, J. Dubac, J. Berlan , S. Lefeuvre, M. Audhuy. 1992. *J. Org. Chem.*, 57, 7099.

4. S. Caddick. 1995,*Tetrahedron*, 51, 10403.

5. A. K. Bose, M. S. Manhas, M. Ghosh, M. Shah, V. S. Raju, S. S. Bari, S. N. Newaz, B. K. Banik, A. G. Chaudhary, K. J. Barakat. 1991.*J. Org. Chem.*, 56, 6968.

6. A. Morcuende, S. Valverde, B. Harradon. 1994. *Synlett*, 89.

7. D. R. Baghurst, D. M. P. Mingos. 1990. *J. Oragamet. Chem.*, C57, 384.

8. R. N. Gedye , F. E. Smith, K. C. Westaway. 1988 *Can. J. Chem.*, 66, 17.

9. R. N. Giguere, T. L. Bray, S. M. Duncan, G. Majetich. 1986. *Tetrahedron Lett.*, 27, 4945.

10. G. Majetich, R. Hicks. 1995. *Radiat. Phys. Chem.*, 45, 567.

11. 1992. *Solid Supports and Catalysts in Organic Chemsitry.* Ellis Harwood, London.

12. G. Bram, A. Loupy, D.Villemin. 1992. *in: Solid Supports and Catalysts in Organic Chemsitry.* Ellis Harwood, London.

13. J. March. 1992. *Advanced Organic Chemistry.* John Wiley Sons, New York.

14. E. Wenkert, R. D. Youssefyeh, R. G. Lewis. 1960. . *J. Am. Chem. Soc.*, 82, 4675.

15. N. Kornblum, R. Seltzer, P. Haberfield. 1963. *J. Am. Chem. Soc.*, 85, 1148.

16. C. A. Buehler, D. E. Pearson. 1960. *Survey of Organic Synthesis*, 82, 4675.

17. A. Smith. 1956. *Acta Chimica Scand.*, 19, 1006.

18. E. E. Smissman, M. D. Corbett ,S. Al-Antably, K. C. Kroboth. 1972. *J. Org. Chem.*, 37, 3944.

19. E. Vowinkel. 1966. *Chem. Ber.*, 99, 1479.

20. T. W. Green, P. G. M. Wuts. 1991. *Protective Groups in Organic Synthesis.* John Wiley Sons, Inc..

21. E. V. Dehmlow , S.S. Dehmlow. 1993. *Phase Transfer Catalysis.* VCH.

22. A. McKillop, J. C. Fiaud, R. P. Hug. 1974. *Tetrahedron*, 30, 1379.

[*first page*]

Comments

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