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Ecofriendly Solvent Free Microwave Induced Organic Rearrangements Of Alkyl Phenyl Ethers In Dry Media Conditions


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ABSTRACT

A rapid, cleaner, cost effective and ecofriendly synthesis of exclusive para alkyl anilines in solvent free conditions using solid supports under microwave irradiation is achieved. © 2006 Trade Science Inc. - INDIA

KEYWORDS

Microwave;
 Rearrangement;
 Alkyl phenylethers;
 Solvent free conditions.

INTRODUCTION

In the last few years there has been a growing interest in the use of microwave heating in organic synthesis^[1]. Microwave induced organic reaction enhancement (MORE) chemistry^[2,3] offers a simple, non conventional technique for the synthesis of a wide variety of compounds having medicinal, pharmaceutical and commercial importance. Spectacular accelerations, high yields under milder reaction conditions and higher product purities have all been reported^[4,5]. Highly accelerated reaction rate is the main advantage which enables chemists to carryout synthesis in much lesser time and with reasonable good yields. Currently available classical

methods require elaborate apparatus setup, longer heating time and larger volume of organic solvents and virtually no control over energy input.

In MORE chemistry, reactants in an open vessel are heated by microwave irradiation in a polar, high boiling solvent, so that the temperature of reaction mixture does not reach the boiling point of the solvent used^[6]. Despite of convenience, a disadvantage of the MORE technique is its limitation to high boiling polar solvents such as DMSO, DMF, N-methyl morphine, etc. However, the approach adapted to low boiling solvents such as toluene generates a potentially serious fire hazard^[7]. To carry out reactions at reflux conditions, domestic microwave ovens have been modified by making a shielded opening to pre-

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vent leakage and through which the reaction vessel has been connected to a condenser^[8]. This 'bomb' strategy has been successfully applied to a number of syntheses, but it always generates a risk of hazardous explosions.

Microwave heating has been proven to be of benefit particularly for the reactions under 'dry' media. Solvents are often expensive, toxic and difficult to remove in the case of aprotic solvents with high boiling point. In dry media reactions 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' condition were originally developed in the late eighties. During microwave induction of reactions under dry conditions, the reactants are adsorbed on the surface of the solid supports like alumina, silica gel, clay, charcoal, etc. These solid supports neither absorb nor restrict the transmission of microwaves whereas the reactants absorb the microwaves. Consequently, such supported reagents efficiently induce reactions under safe and simple conditions with domestic microwave ovens instead of specialized expensive commercial microwave systems. Furthermore, it is not always necessary for the reaction components to have high dielectric losses^[9]. Due to all the above advantages, there is an increasing interest in the field of ecofriendly solvent free microwave induced organic reaction enhancement chemistry (Green Chemistry), which is under much investigation by chemists.

Alkyl phenols such as 4-ethylphenol, (p-cuminol), thymol, carvacol, chavicol, etc., are components of natural essential oils, some of which have been used for the production of perfumes. These alkyl phenols are obtained in great number by thermal cracking of natural products such as bituminous coal, brown coal, peat, wood, lignin and crude oil fractions^[10]. Since the boiling points of the alkyl phenols lie very close together, the production of certain alkyl phenols in pure form is not possible by distillation^[11].

Alkyl phenols are produced industrially mainly by alkylation of phenols with olefins in the presence of Friedel-Crafts catalysts^[12]. However these reactions always leads to both ortho- and para- isomers according to rules of electrophilic substitutions. In

addition, etherification of the OH group occurs. Since the monoalkylation products are generally more reactive than the starting material, they are further alkylated. Friedel-Crafts alkylation of phenols also involve side reactions such as dealkylation, di and oligomerisation, cleavage in the alkyl group, dehydrogenation of the alkyl to alkenyl groups and their reaction with olefins to form indanols, etc.^[13]

Ortho- and para-alkyl phenols are also produced by thermal rearrangements of alkyl phenyl ethers in the presence of Lewis acids similar to Hofman-Martius rearrangement of N-alkyl anilines^[14]. But this reaction is usually accompanied by dealkylation product. This reaction is fairly facile for tertiary alkyl ethers only. Secondary and primary groups do not migrate at all. Formation of other by-products like olefins, phenols, dialkylphenol, etc., are also seen. All together make this rearrangement unpopular^[15].

Thus the available reaction methods usually have limitations like long reaction time, poor yields, high reaction temperatures, often encountered with two or more isomers with side products, etc. Moreover, these reactions are carried out in organic solvents that are generally toxic to living being.

EXPERIMENTAL

Melting points were recorded on sulphuric acid bath and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer using KBr pellet. ¹HNMR spectra were recorded on a Bruker WH 400 instrument using TMS as internal standard. The reactions were carried out in a domestic microwave oven (LG 800W) operating at 2450MHz frequency.

General procedure

To a solution of reactant (1mmole) in 20mL of appropriate solvent taken in a 400mL beaker, fused catalyst (1mmole) and dried solid support (10g) were mixed well and the solvent was evaporated in vacuo. This dry mixture was transferred to a 100mL standard flask, which was kept inside a microwave oven operating at high power level, and irradiated for about 4-7 minutes with intermittent cooling at every 0.5 minutes interval. The cooling was necessary to avoid

TABLE 1: Results of rearrangement of alkyl phenyl ethers

Starting material	Product	Reaction Period (min)	Yield (%)	m.p.(°C) (lit) ^[19,20]
Anizole	p-Cresol	5.0	84	35(36)
Phenetole	4 -Ethyl phenol	4.5	86	46(47)
Isopropyl phenyl ether	4 -Isopropyl Phenol	3.5	91	59(59-61)
tert-Butyl phenyl ether	4 -tertButyl Phenol	4.0	88	98(100-101)
Pentyl phenyl ether	4 -Pentyl Phenol	4.0	92	49(49-51)
tertPentyl phenyl ether	4 -tert-Pentyl Phenol	3.0	91	22(23)
3-Methyl anizole	3,4 -Xylenol	6.5	81	61(62.5)
2-Methyl anizole	3,4 -Xylenol	6.5	87	27(27)
Benzyl phenyl ether	4 -Benzyl Phenol	6.0	79	83(83-85)

loss of product by evaporation from the solid support as the temperature attained was very high. The completion of the reaction was confirmed by TLC and products were extracted by appropriate solvents (5*10mL), filtered, dried over anhydrous sodium sulphate and evaporated. Finally the pure products were obtained by column chromatography over silica gel. All products obtained were characterized by ¹HNMR spectra, and by comparison of their IR spectra, melting points and TLC spots with authentic samples. (TABLE 1)

The microwave oven used in these reactions was of domestic type MS 194A supplied by LG Electronics India Ltd. Its technical specification is given below.

RESULTS AND DISCUSSION

Power input	230 V AC 50Hz
Power output	800 (IEC 705 rating standard)
Microwave frequency	2450 MHz
Outside dimension	485 mm(W)x280mm(H)x355 (D)
Power consumption	1200 watts

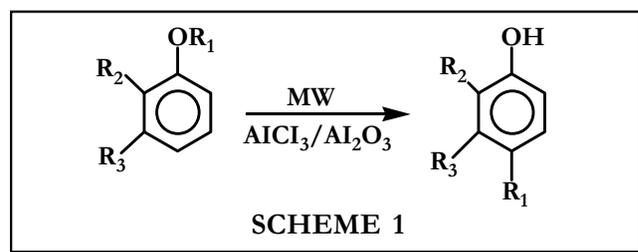
We have sought to develop a general method of rearrangement reactions which should be much faster and ecofriendly in nature and should be free from such limitations encountered with conventional methods. Therefore, the use of microwave heating under solvent free conditions is chosen.

It has been reported from our laboratory that amino aryl ketones could be prepared by thermal Fries rearrangement of anilides in the presence of Lewis acids such as TiCl₄, ZrOCl₂, BiCl₃, etc^[16]. We further developed the same reactions by microwave

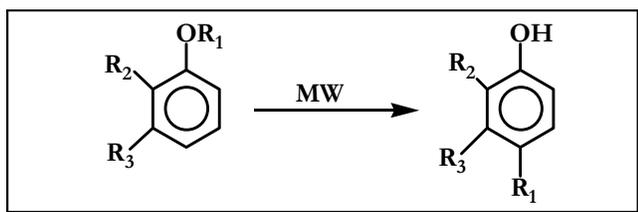
irradiation under solvent free conditions which produced exclusive para product in excellent yields^[17]. We extended this work to new and pharmaceutically very important synthesis of pure para amino benzamides from phenyl ureas^[17]. We also reported a very clean, rapid and very high yielding method for the preparation of exclusive para alkyl anilines under solvent free conditions^[18].

In continuation of our work with rearrangement reactions by microwave irradiation, we herein report a similar high yielding method for the preparation of exclusive para alkyl phenols under solvent free conditions. Rearrangement of alkyl phenyl ethers in the presence of Lewis acid (AlCl₃) adsorbed on an inert solid support (neutral alumina) under microwave irradiation afforded the exclusive products (SCHEME 1).

The reactions were completed within 4-7 minutes at 100% power (800W) and complete conversion of reactants into single para product was noted even in the presence of a deactivating group in the ring (TABLE 1). The reaction is of general applicability and various substituted phenols were synthesized. It is noteworthy that these reactions did not proceed at all if the para position of aniline is blocked.



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Compound	R ₁	R ₂	R ₃
1	CH ₃	H	H
2	C ₂ H ₅	H	H
3	CH(CH ₃) ₂	H	H
4	C(CH ₃) ₃	H	H
5	(CH ₂) ₄ CH ₃	H	H
6	C(C ₂ H ₅)(CH ₃) ₂	H	H
7	CH ₃	H	CH ₃
8	CH ₃	CH ₃	H
9	CH ₂ C ₆ H ₅	H	H

CONCLUSION

In conclusion, we report that we have demonstrated a solvent free, rapid, cleaner, cost effective and ecofriendly synthesis of exclusive para alkyl phenols under microwave irradiation with excellent yields.

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