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MICROWAVE ACCELERATED PREPARATION OF ARYL 2-(N,N-DIETHYLAMINO)ETHYL ETHERS

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Abstract: A simple and expedient method for the preparation of the ubiquitous 2-(N,N-diethylamino)ethyl aryl ether moiety using a conventional microwave oven has been developed. The reactions are performed with pulsed microwave irradiation, to produce gram quantities of ethers in good yields.

The N,N-diethylamminoethylethers derived from phenols are commonly found in compounds of biological interest.[1] Our interest in this moiety is in the preparation of retrograde axonally transported fluorescent imaging agents[2] (RATFIA). The common method for incorporating N,N-diethylaminoethyl ethers onto phenols is alkylation of the phenol using 2-diethylaminoethyl chloride hydrochloride with K_2CO_3 in a polar, aprotic solvent, such as DMF.[3] While effective, we have found the reaction times to be slow (up to two days), the yields variable (dependent upon reagent age) and the use of DMF to be undesirable.

The use of microwave irradiation to accelerate organic reactions has been employed in many laboratories in recent years.[4] Some procedures use sealed vials[5], others use open beakers.[6] All of the microwave reactions offer the advantage of expediency and the use of commercially available ovens makes many methods cost effective. Comparisons of microwave processes to conventional thermal reactions have provided convincing evidence that the reported "microwave effect" that has been ascribed to rate enhancements of some reactions is actually a consequence of superheating the reaction solvent at atmospheric pressure and not the consequence of a special reaction pathway or intermediacy of a high energy vibrational state.[7]

The value of conventional microwave ovens for organic synthesis has been debated. Antagonists state concerns over safety in the use of conventional ovens, *albeit* cited cases involve heating sealed containers. Proponents tout the reduced cost, ease of use, and safety of the conventional oven technique when using open beakers. With the proper combination of reactants, solvent and irradiation time, the use of the conventional microwave oven can be safe and effective.

Preliminary investigations on the alkylation of phenols with 2-diethylaminoethyl chloride hydrochloride were run in several solvent and base combinations on a 100mg scale in lightly capped vials. The best combination was the use of glyme with KOH. If K_2CO_3 were used, with either glyme or ethanol, we obtained no reaction for 4-cyanophenol or phenol. ***If ethanol was used with KOH, we had a fairly regular occurrence of exothermic combustion in the oven at between ten and fifteen seconds.*** None of the reactions were irradiated for longer than 30 seconds to avoid boiling off the solvent. Surprisingly, using phenol, 3-hydroxyphenol or 4-cyanophenol as test compounds, little or no reaction (TLC) occurred if only 2.5 equivalents of KOH was used. In theory, only 2 equivalents of KOH should be required for this reaction.

The use of KOH and glyme works with a variety of phenolic substrates as indicated in the Table. In contrast to our results, a 67% yield was reported for the S_N2 alkylation of sodium phenoxide with 1-chlorobutane at elevated temperatures and pressures dissolved in methanol using a sophisticated microwave flow apparatus designed especially for organic synthesis.[8] The lowest yield we obtained was for the 3-hydroxybenzaldehyde substrate. Based upon GC-MS analysis (crude and purified material have a peak with M^+ m/e = 223 and base peak m/e = 86), this is the result of a competitive Cannizzaro type process. The elaboration of the microwave Cannizzaro reaction is currently under examination in our laboratory.

TABLE: Microwave Alkylation Results.

Substrate	**% Yield**	**% GC Purity**
phenol	92	>99
salicylaldehyde	80	98
3-hydroxybenzaldehyde	39	92
4-hydroxybenzaldehyde	60	98
eugenol	92	>99
4-hydroxyacetophenone	69	>99
3-methoxy-4-hydroxy-benzaldehyde	40	99
trans-4-hydroxystilbene	97	(> 95)
4-cyanophenol	96	>99
2,4,6-tri-*t*-butylphenol	97	98

Interestingly, there was no evidence for the expected isomerization[9] of eugenol to isoeugenol, despite the excess base employed. We compared the microwave process to the conventional reflux procedure for phenol using the same amounts of reagents and solvent. Even after 27 hrs at reflux, the conventional reflux still showed evidence (TLC) of unreacted phenol. Upon work up, the yield of isolated alkylation product (88% yield, 98% purity) was slightly lower than with the microwave procedure. Even if the yield with conventional reflux had been slightly higher, the microwave procedure would be preferable due to its expediency. Microwave-induced organic reaction enhancement (MORE)[6] is manifested in these reactions.

Experimental:[10] Microwave reactions were performed in a conventional microwave oven with a 0.6 ft^3 cavity on a rotating turntable platform at a high power setting (600 W). Reagent chemicals were used without purification and are commercially available. GC analysis was performed on a HP Series II 5890 GC (J&W DB-5 15 m microbore column) HP 5971A MSD and HP 7673 auto injector. Short path distillation was performed under vacuum (0.5 mm Hg) by Kuglehor. Reactions were run in Pyrex media bottles with polypropylene unions and caps. Caps were twisted to hand tight and then loosened by a quarter turn prior to use in the microwave oven. The bottles were **not** sealed. ^{1}H-NMR spectra were obtained on a Varian 400XL 400 MHz FT-NMR, referenced to TMS or residual chloroform in the $CDCl_3$ solvent.

In the typical microwave procedure, the phenol (1.5 g / 15.9 mmol), glyme (25 mL), KOH (3.75 g / 66.8 mmol), and N,N-diethylaminoethyl chloride hydrogen chloride (2.25 g / 13.1 mmol) were all added to a 200 mL bottle. The bottle was lightly capped, but not sealed. The bottle was irradiated at high power for 15 seconds, allowed to cool to room temperature, stirred with a glass rod, and the sample was re-irradiated. The sequence of irradiation, cooling, stirring, and re-irradiation was repeated an average of eight times until no more phenol was detected by TLC. The cooled reaction was worked up by addition of 20 mL of ether and extraction with 1M NaOH (3 x 70 mL). The organic layer was washed with brine (1 x 70 mL), dried with anhydrous K_2CO_3, filtered, and then concentrated. The crude product was purified by short path distillation. The stilbene product was purified by removal of volatile materials under vacuum and the pot residue was isolated and characterized by MP (75-75.5°C) and ^{1}H-NMR. The liquid products were analyzed by GC-MS and ^{1}H-NMR with purities and yields shown in the Table.

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References and Notes:

1. For example: clomiphene (gonad stimulant), diamthazole (antifungal), ethamoxytriphetol (estrogen antagonist), etafenone (vasodilator), halethazole (antiseptic/antifungal), leiopyrrole (antispasmodic), salverine (analgesic).

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10. ***CAUTION*** While we never had an explosion with KOH/glyme, all reactions were run in a hood. The safety problems encountered with using conventional microwave ovens are outlined by Strauss, *et. al,* (see ref. 8). The advantages of using conventional microwave ovens and open containers are outlined by Bose, *et al.*, (see ref. 6). The use of 100 mg scale in development of a microwave oven procedure is advised.

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