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# Selective Dealkylations of Alkyl Aryl Ethers in Heterogeneous Basic Media under Microwave Irradiation.

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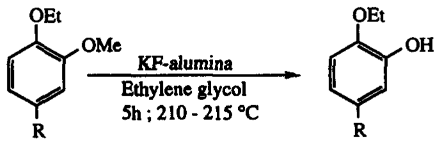
***Abstract:*** Ethyl isoeugenol and 2-ethoxyanisole could be selectively deethylated using potassium t-butoxide in the presence of crown ether under solvent-free conditions. By addition of ethylene glycol, selectivity was reversed to demethylation. In both cases, strong enhancements were observed under focused microwaves. © 1997 Published by Elsevier Science Ltd.

Dealkylation of alkyl aryl ethers is a synthetically very useful reaction as it constitutes an important method for deprotection of hydroxyl groups from substituted phenols [2]. A wide variety of systems has been proposed in homogeneous phase using more generally Lewis acids such as $AlCl_3$ [3] and $BX_3$ [4] or strong bases such as alkaline hydroxides [5] or amides [6] and lithium diphenyl phosphide [7]. These conditions suffer from harsh reaction conditions and present a lot of inconvenience connected to their handling, removal and toxicity of catalysts.

Heterogeneous conditions were thus developed with significant advantages. Potassium fluoride coated on alumina, previously widely described as a strong base [8], was shown by Singh et al. to be also an effective reagent for the selective O-demethylation of aromatic methyl ethers [9].



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**a** R= -CH=CH-$CH_3$ **b** R= H

In connection with our interest for mild heterogeneous solvent-free conditions [10], we checked the behaviour of ethyl isoeugenol **1a** using different basic systems. We especially examined phase transfer catalysis (PTC) conditions in the absence of solvent under microwave irradiation as it was shown of great efficiency in a lot of cases including Krapcho decarbethoxylation [11]. A system potassium t-butoxide/transfer agent was selected as it behaves at the same time as a strong base (H-nucleophilicity) [12] or a strong nucleophile (C-nucleophilicity) [13].

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Ethyl isoeugenol **1a** is able to lead to either propenylguaethol **2a** by O-demethylation or isoeugenol **3a** by O-deethylation. The main results are given in Table I.

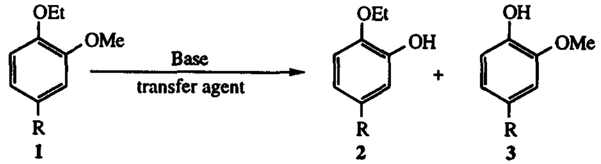


Table I: Dealkylation of ethyl isoeugenol **1a** (5 mmoles) using a base (2 eq, 10 mmoles) in the presence of a phase transfer agent (10%) under monomode microwave activation [14].

| Base | Phase transfer agent | Exp. cdts | | | Yields [a] | | |
|---|---|---|---|---|---|---|---|
| | | $P_W$ | $t_{mn}$ | $T_{°C}$ [b] | % **1a** | % **2a** | % **3a** |
| KF | Aliquat 336 | 270 | 120 | 177 | 95 | 2 | - |
| LiF | " | 90 | 60 | 116 | 99 | - | - |
| " | 12-crown-4 | 90 | 60 | 123 | 97 | 2 | - |
| KOtBu | - | 60 | 20 | 93 | 92 | - | - |
| " | Aliquat 336 | 90 | 20 | 175 | 20 | - | 60 |
| " | Kryptofix [2.2.2] | 90 | 10 | 135 | 15 | - | 68 |
| " | 18-crown-6 | 60 | 20 | 139 | 9 | - | 82 |

a) g. c. yields using a standard; b) maximum in temperature during microwave irradiation measured by infrared detection [15] using a monomode Synthewave 402 reactor (Prolabo)

It was noteworthy that we obtained selective deethylation under these conditions, whereas KF-alumina in ethylene glycol leads to selective demethylation. The two methods seem to be complementary. The effect of this solvent was thus checked under PTC conditions. The more significant results are indicated in Table II.

Table II: Effect of ethylene glycol (EG) on the dealkylation of **1a** (5 mmoles) induced by base (10 mmoles) and 18-crown-6 (10%) under microwave (MW) irradiation or under conventional heating (Δ) using a thermoregulated oil or sand bath. ,

| Base | E G (Volume / ml) | Exp. cdts | | | | Yields | | |
|---|---|---|---|---|---|---|---|---|
| | | mode | $P_W$ | $t_{mn}$ | $T_{°C}$ | % **1a** | % **2a** | % **3a** |
| KOtBu | - | MW | 60 | 20 | 139 | 9 | - | **82** |
| " | - | Δ | | 20 | 139 | 32 | - | 52 |
| " | 2 | MW | 60 | 60 | 228 | 6 | **56** | 3 |
| " | 2 | Δ | | 60 | 228 | 70 | 2 | - |
| NaOH | 5 | MW | 60 | 180 | 200 | 5 | **70** | 2 |
| " | 5 | Δ | | 180 | 200 | 70 | - | - |

The addition of ethylene glycol was determinant from selectivity point of view in the case of KOtBu and crown ether reaction. This is at the origin of a total reversal in selectivity, allowing O-demethylation.

To avoid the possible influence of the double bond on aromatic ring and check the generality of our observation, same conditions were extrapolated to 2-ethoxyanisole **1b** (Table III).

Table III: Dealkylation of 2-ethoxyanisole **1b** (5 mmoles) using base (10 mmoles, 2 eq.) in the presence of a phase transfer agent (10%) with or without ethylene glycol (E G) under microwave irradiation [14] (MW) or using a thermoregulated oil bath (Δ).

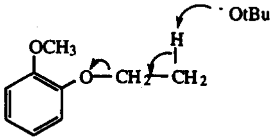
| Base | Phase transfer | E G | | Exp. cdts | | | | Yields | |
|---|---|---|---|---|---|---|---|---|---|
| | agent | (ml) | mode | Pw [a] | t mn | T °C | % **1b** | % **2b** | % **3b** |
| KOtBu (2 eq.) | - | - | MW | 60 | 20 | 120 | 39 | - | 60 |
| " | Aliquat 336 | - | MW | 60 | 20 | 120 | 28 | - | 66 |
| " | 18-crown-6 | - | MW | 60 | 20 | 120 | 7 | - | **90** |
| " | P E G 400 | - | MW | 60 | 20 | 120 | 13 | - | 80 |
| " | T D A - 1 | - | MW | 60 | 20 | 120 | 7 | - | **91(90)** |
| " | " | - | Δ | | 20 | 120 | 48 | - | 50 |
| " | " | - | Δ | | 120 | 120 | 28 | - | 60 |
| KOtBu (2 eq.) | Aliquat 336 | 2 | MW | 60 | 60 | 180 | 86 | 10 | 3 |
| " | T D A - 1 | 2 | MW | 60 | 60 | 180 | 93 | 5 | 1 |
| " | 18-crown-6 | 2 | MW | 60 | 60 | 180 | 20 | 58 | 22 |
| " | " | 2 | MW | 60 | 75 | 180 | - | **72** | 23 |
| " | " | 2 | Δ | | 75 | 180 | **98** | - | - |
| " | " | 2 | Δ | | 1200 | 180 | 63 | 26 | 10 |
| NaOH (2 eq.) | 15-crown-5 | - | MW | 60 | 30 | 180 | **93** | - | 2 |
| " | " | - | Δ | | 75 | 180 | **99** | - | - |
| NaOH (4 eq.) | 15-crown-5 | 5 | MW | 20 | 120 | 205 | **5** | **77** | 10 |
| " | " | 5 | Δ | | 120 | 205 | **94** | - | - |

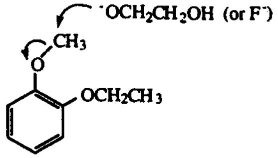
a) maximal in power during microwave irradiation.

The conclusions were rather the same for those two substrates:

- deethylation is the dominant reaction with KOtBu and crown ether (or TDA-1) in the absence of any organic solvent. A strong microwave effect on reactivity was observed as the yield fell to only 50% under conventional heating, instead of 90% under microwave irradiation, without any change on selectivity.
- demethylation became the dominant reaction when ethylene glycol was added. A very strong microwave influence (not purely thermal) was shown as no reaction occurred under conventional heating (same conditions of time and temperature). This observation was in accordance with some results from literature [16].

In terms of mechanism, as KOtBu is known as a very strong base, we can envisage a ß-elimination for deethylation whereas KOtBu and EG (leading probably to $K^+, {}^-OCH_2CH_2OH$ or at least a decrease in basicity of KOtBu due to his solvation by EG) leads to a nucleophilic attack on the less hindered methyl group.





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