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Microwave-assisted methylation of phenols with DMF-DMA

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ABSTRACT

We evaluated the potential of *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) as a methylating agent for a library of *para*-substituted phenols under microwave irradiation. The rate of reaction was dictated by the electronic nature of the *para*-substituent. With an electron-withdrawing group the reaction was completed within 30 min. For electron-donating groups, the reaction times were 60 min. Esterification and enamino-ketone formation was also observed with carboxylic acid and ketone functional groups, respectively.

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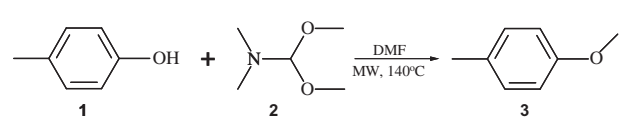
The use of microwave chemistry to accelerate the rates of organic chemistry reactions has become exceedingly popular from the mid 1980's onwards. In 1990, there were approximately 125 journal articles describing microwave-assisted chemistry. This rose to over 550 by 2000, and in 2010, just under 2400 articles were published. The exact method by which microwaves actually accelerate reactions has been debated, and thus is still occasionally referred to as the 'specific microwave effect.' The two most common thoughts of how rates of reactions (k) are accelerated with microwaves are (1) by lowering the free energy of activation (E_a),[1] or (2) by increasing the pre-exponential factor A (Eq. 1).[2] The latter of the two has received the most attention and can be best described at the dipolar polarization mechanism. When an applied microwave radiation is introduced to a sample, the molecules that possess a dipole will rotate in phase with the oscillating electric field. However, the frequency is such that the field has already changed prior to the dipole having been fully orientated. This produces a phase difference between the dipole and the field. Energy is thus lost by the dipole via molecular friction and collision, producing the dielectric heating.

$$k = Ae^{-Ea/RT} \quad (1)$$

As mentioned, much discussion has been focused on the 'specific microwave effect', however a critical review by de la Hoz et al. lent strong support for the improvement of reaction rate being purely a thermal evident.[3] The debate was finally quelled in 2009 with work by Kappe and co-workers with the use of a silicon carbide reaction vial.[4] They clearly demonstrated that even though the SiC vial absorbed all of the microwave irradiation, reaction rates and yields were identical to those done within Pyrex vials. This clearly showed that the enhanced rates of reactions observed under microwave irradiation are a thermal and not a specific effect.

Numerous types of reactions have been performed using microwaves to accelerated reaction rates. These include, and are by no means limited to; Suzuki cross-coupling,[5] alkylation,[6] acylation,[7] cyclization,[8] and synthesis of chiral oxazolinones.[9] In addition, *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) has been utilized in synthesis of arylpyrazoles,[10] benzofurans,[11] pyridones,[12] and quinolinecarbonitiles,[13] under microwave irradiation. All the aforementioned structural moieties utilize DMF-DMA's ability to form enamines via enolate-type chemistry. We recently, employed DMF-DMA in the synthesis of various isoflavones,[14,15] via conventional heating. We noticed that some phenols were methylated under these conditions.[15] The use of DMF-DMA as a methylating agent for phenols has received very little attention even though it was initially introduced by Abdulla and Brinkmeyer over 30 years ago.[16] Numerous other techniques exist for the methylation of phenols, many of which can be done under microwave irradiation. Some are with the use of dimethyl sulphate,[17] dimethyl carbonate,[18] tetramethylammonium chloride,[19] and recently methyl iodide with a phase-transfer catalysis.[20] Herein, we report our work on the methylation of *para*-substituted phenol using DMF-DMA under microwave irradiation.

We initially examined cresol (**1**) with 2 equiv of DMF-DMA (**2**) in DMF under microwave irradiation to obtain 4-methylanisole (**3**) (Scheme 1). The reaction is quite sensitive to rate of warming and irradiation wattage used. If the rate by which maximum temperature and wattage reacted is too high, pressure has a tendency



Scheme 1. Synthesis of 4-methylanisole (**3**) from cresol (**1**) and DMF-DMA (**2**) under microwave irradiation.

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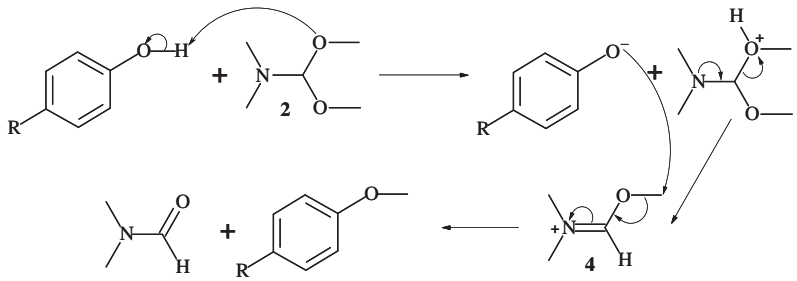
Table 1
Influence of wattage and reaction times on the methylation of cresol

Entry #	Wattage	Time (min)	Yield[a] (%)
1	750	>1	NA[b]
2	600	>1	NA[b]
3	500	30	43
4	500	60	78
5	500	90	79
6	250	30	12
7	250	60	27
8	250	90	51
9	250	120	59

[a] Isolated yields are given.
[b] Reaction vessel exploded.

to accumulate. Explosions of the reaction vessel within the microwave were observed. [Note: Although the explosion was relegated within the microwave, extra precautions should be taken when performing this reaction, such as laboratory coat, gloves, and splash goggles should be worn.] At 700 W (Table 1: entry 1) and 600 W (Table 1: entry 2) the reaction flasks exploded in less than 1 min. When the wattage was lowered to 500 W, a 43% yield was obtained after 30 min of irradiation (Table 1: entry 3). Extending to 60 min (Table 1: entry 4) afforded an isolated yield of 78% of the desired 4-methylanisole. Further extension to 90 min (Table 1: entry 5) gave no makeable increase in yield. At 250 W, the yield was inferior, even at 120 min (Table 1: entries 6–9). Thus, we focused on 500 W for 1 h for the remainder of the phenolic derivatives.



Scheme 2. Proposed mechanism of methylation of phenols with DMF-DMA (**2**).

Table 2
Methylation of *para*-substituted phenols with DMF-DMA under microwave irradiation[21]

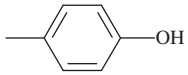
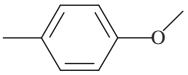
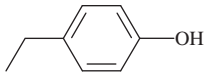
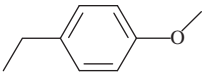
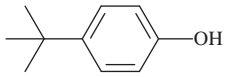
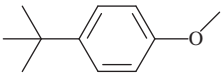
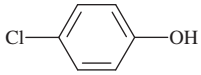
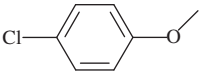
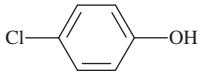
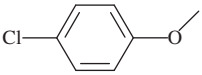
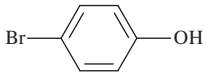
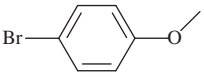
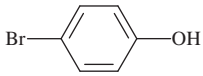
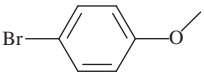
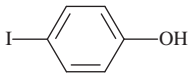
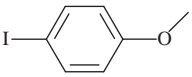
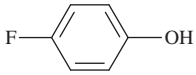
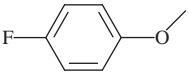
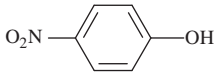
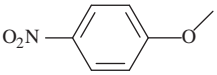
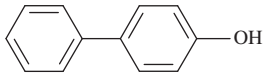
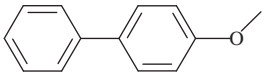
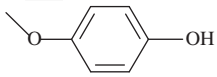
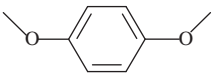
Entry #	Substrate	Time (min)	Product	Yield[a] (%)
1		60		78
2		60		75
3		60		67
4		60		91
5		30		90
6		60		89
7		30		89
8		30		83
9		30		85
10		30		84
11		60		81
12		60		87

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Table 2 (*continued*)

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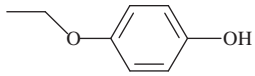
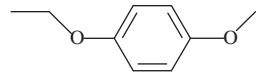
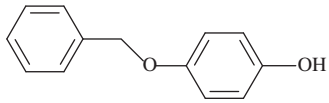
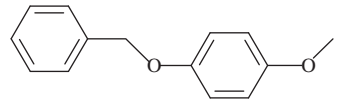
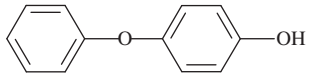
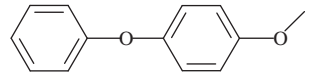
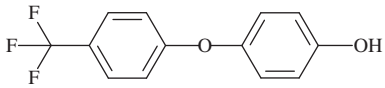
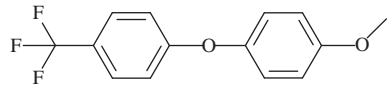
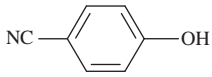
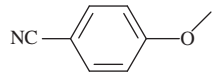
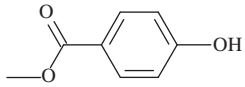
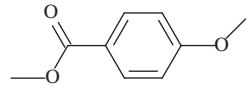
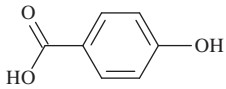
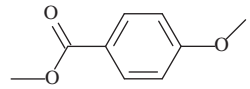
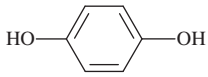
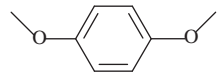
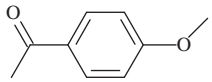
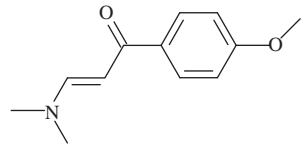
13		60		91
14		60		69
15		60		90
16		30		92
17		30		78
18		30		98
19[b]		30		89
20[b]		60		84
21[b]		30		81

[a] Isolated yields are given.
[b] 4 equiv of DMF-DMA was used.

Early on we observed higher yields for phenolic derivatives the electron-withdrawing functionality in the *para* position. We thus, attempted methylation of these phenols for only 30 min of irradiation at 500 W. Indeed, virtually identical yields were obtained under these conditions. It is hypothesized that the accelerated rate of the reaction is due to the decreased pK_a of the phenolic proton on compounds possessing a *para*-substituted electron-withdrawing group. This would allow for the increased production of the alkoxyimmonium ion (**4**) intermediate (Scheme 2). Therefore, for all the remaining compounds, we selected either 30 or 60 min of irradiation depending on whether the phenol possessed an electron donating, or withdrawing group in the *para* position.

Overall, yields of 67% (Table 2: entry 3) to 91% (Table 2: entry 13), for phenolic compounds possessing *para*-substituted electron donating group were obtained. For electron withdrawing moieties, this was slightly higher, with a range of 78% (Table 2: entry 17) to 98% (Table 2: entry 18). In addition, 4-hydroxybenzoic acid (Table 2: entry 19) and hydroquinone (Table 2: entry 20) both went through double alkylation, with the former producing an ester. The use of DMF-DMA, as well as other formamide acetals, has been previously examined as an esterifying agent and a similar mechanism has been proposed; whereby the attack of the carboxylate ion onto a chiral alkoxyimmonium ion proceeded with an inversion of configuration.[22] Finally, 4′-hydroxyacetophenone (Table 2: entry 21) was not only alkylated as expected, but further reacted to convert the ketone functionality to an enamino-ketone. This latter process has been utilized by others and has been shown to be quite effective under microwave irradiation conditions.[23]

In summary, we examined microwave-assisted methylation of *para*-substituted phenols using *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA). Reactions were performed at 500 W for either 30 or 60 min depending on if there was an electron-withdrawing or donating group attached, respectively. In addition, esterification as well as enamine formation, was accomplished simultaneously with methylation of phenols, if a carboxylic acid or ketone was present.

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References and notes

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21. *General procedure for methylation:* cresol (0.50 g, 4.62 mmol) was added to a solution of DMF-DMA (1.23 mL, 9.24 mmol) in DMF (15 mL) in a 50 mL PTFE lined glass reactor and capped with a plastic releasing valve top. The glass reactor was irradiated in a Milestone START Microwave at 500 W with a slow ramp to 140 °C over 10 min, and then maintained for an addition 50 min. The flask was cooled, H_2O (15 mL) was added, extracted with Et_2O (4 × 30 mL), and the combined organic was washed with H_2O (4 × 30 mL) to remove excess DMF. The ethereal layer was dehydrated with $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography (9:1 hexanes/EtOAc) afforded a 4-methylanisole (0.44 g, 78%) as clear colorless liquid.
The same procedure was followed for *para*-substituted electron withdrawing groups with to only exception being the reaction time was decreased to a total of 30 min.
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