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# Microwave-Assisted Acetylation of Phenols without Catalyst Under Solvent Free Condition

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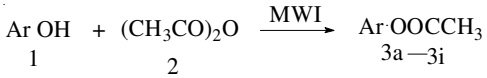
Etherification between phenols with acetic anhydride was tested under different conditions. Phenols were efficiently acylated with acetic anhydride to give phenol acetate derivatives in good high yields without catalyst and solventless conditions under microwave irradiation.

**Keywords: Acetylation, Phenols, Microwave irradiation.**

## INTRODUCTION

The acylation of hydroxyl groups is one of the most frequently used transformations in organic synthesis. Among the various protecting groups used for the hydroxyl function, acetyl is the most common group in view of its easy introduction, being stable to the acidic reaction conditions and also easily removable by mild alkaline hydrolysis[1]. Typically, acylation of alcohols and phenols is performed under homogeneous catalysis with acetic acid or acetyl chloride or anhydride, in the presence of a convenient basic catalyst such as triethylamine or pyridine[2]. In addition, 4-(dimethylamino)pyridine, 4-pyrrolidinopyridine[3]. Tetramethylethylenediamine[4], tertiary phosphines[5], carbon tetrabromide in ethyl acetate[6], *p*-toluenesulfonic acid[7], zinc chloride[8], iodine[9], sulfamic acid[10], magnesium bromide[11], cobalt chloride[12], tantalum chloride[13], La(OPr-i)$_3$[14], silica gel-supported sodium hydrogen sulfate[15], montmorillonite K-10 and KSF[16], alumina[17], yttria zirconia with acetic acid[18], $Ac_2O$-pyridine/basic alumina under microwave irradiation[19], KF-$Al_2O_3$ with $Ac_2O$/AcCl[20], vanadyl(V) acetate[21], distannoxane[22], zeolite HSZ-360[23], Pseudo-monas cepacia PS lipase adsorbed on Celite[24], and twisted amides[25] have also been applied for the acetylation of alcohols and phenols. Another important development has been the introduction of trifluorme-thanesulfonate derivatives, such as TMSOTf[26], Yb-(OTf)$_3$[27], Cu(OTf)$_2$[28], Sc(OTf)$_3$[29], In(OTf)$_3$[30], Bi(OTf)$_3$[31], cerium(III)[32] and (IV)[33] salts as efficient catalysts in acetylation with acetic acid, or anhydride or acetyl chloride. All these ways lead to wastes as well as some reactions involving solvents, often toxic, polluting and longer time.

There is an increasing interest in the use of environmentally benign reagents and conditions. Particularly to solvent free procedures. Avoiding organic solvent during the reactions in organic synthesis leads to a clean, efficient and economical technology: safety is largely increased. Working is considerably simplified, cost is reduced increased amount of reactants,which can be used[34]. Microwave irradiation has become increasingly popular in recent years to improve the yield and shorten reaction times in a variety of reactions[35-37]. Reactive and selective sometimes are enhanced. Some microwave irradiation assisted solventless acetylation were described using catalyses[38]. Here we report acetylation of phenols using acetic anhydride as acetylating agent without catalyst and solventless conditions under microwave irradiation, as shown in **Scheme-I**:




**Scheme-I**

## EXPERIMENTAL

All the reagents employed in the synthesis were of analytical reagent grade. The materials were used as purchased and used directly without any additional purification. Melting points were determined on an XT-4 electro thermal micro melting point apparatus and are uncorrected. Infrared spectra were measured as KBr discs (or liquid film) using an Alpha centaurispectrometer. $^1$H NMR spectra (200 MHz) were recorded in $CDCl_3$ using a BRUKER PT 200 spectrometer. Mass spectra were obtained on a Qp-1000A GC-MS spectrometer using the electron impact mode (70 or 20 eV). Microwave irradiation was carried out with a domestic microwave oven GlanzWP 750B at 2450 Hz. Sonication was performed in Shanghai SK-250LH ultrasonic cleaner with the frequency of

59 kHz. $KF/Al_2O_3$ was prepared according to reference[20].The remaining chemicals were obtained from commercial sources.

**General procedure:** To a mixture of phenols (5 mmol) and acetic anhydride (6 mmol) were added in a bottle (50 mL) and irradiated at 675 W for 10 min in microwave oven. After cooling to room temperature, then reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was washed with satd $NH_4Cl$ solution (30 mL) and $NaHCO_3$ solution (25 mL) and brine (40 mL), respectively. The organic layer dried over $MgSO_4$ and concentrated to give the product.

## RESULTS AND DISCUSSION

The results for a variety of esterifcation compounds are summarized in the Table-1, various types of phenols with electron donating and withdrawing groups were rapidly acylated with acetic anhydride and afforded the corresponding phenol acetate in excellent yields under microwave irradiation without catalyst and solventless conditions.

TABLE-1
RESULTS FOR A VARIETY OF ETHERIFICATION COMPOUNDS WITHOUT CATALYSES AND COLVENTFREE CONDITIONS UNDER MICROWAVE IRRADIATION[a]

| Product[b] | Phenols | Yields (%)[c] | m.p. °C/Lit |
|---|---|---|---|
| **3a** | Phenol | 96 | Oil[41] |
| **3b** | 4-Methyl phenol | 95 | Oil[42] |
| **3c** | 3-Nitro phenol | 90 | 52-53(53-54[41]) |
| **3d** | 1,2-Catechol | 94 | 62-63°C (62-63 °C[43]) |
| **3e** | 1,4-Quinol | 94 | 121-122(120-121[43]) |
| **3f** | 1,3,5-Triphenol | 88 | 101-103(102-103[43]) |
| **3g** | 1-Naphthol | 90 | 45-46(44-45[41]) |
| **3h** | 2-Naphthol | 92 | 68-69(67-69[41]) |
| **3i** | 4-Nitro phenol | 93 | 77-79(77-78[41]) |

[a]Conditions: Aryl phenols (5 mmol), acetic anhydride (6 mmol), 675 W for 10 min. [b]All products gave satisfactory $^1H$ NMR, Mass spectra and IR. [c]Yield of isolated product

To expore the scope and versatily of this method, different reaction conditions were investigated. Highlighted in Table-2 for 2-naphthol acetate (**3h**), for example, is the influenece of catalysts, reaction time, mole ratios, ultrasound wave and microwave on the reaction yield.

Since $KF/Al_2O_3$[39] is a new kind of highly active catalytic catalysts that can catalyze many reactions under mild conditions, to give high yields, the high efficacy and ease of product isolation, a large number of ultrasonic reactions[40] can be carried out in higher yield, shorter reaction time or milder conditions, this prompted us to investigate its use for acetylation purposes.

To demonstrate the catalysis of $KF/Al_2O_3$, the reaction was carried out with high speed stirring, ultrasonic irradiation and microwave irradiation conditions in the absence of $KF/Al_2O_3$ catalyst, it was concluded that the acetylation of 2-naphthol with acetic anhydrides could not happen with high speed stirring at 135 °C and under ultrasonic irradiation. However, it was observed that compound **3h** (Table-2 entry 7) was obtained in 92 % yield in 10 min. When $KF/Al_2O_3$ was used to catalyze the reaction of 2-naphthol with acetic anhydrides, the acetylation of 2-naphthol with acetic anhydrides could not happen at 135 °C with high speed stirring and ultrasonic irradiation, while in the presence of $KF\text{-}Al_2O_3$ catalys and microwave, compound **3h** was also obtained in 92 % yields in 10 min (Table-2 entry 2,3,4,5,6), these result revealed that microwave can effectively accelerate the reaction, $KF/Al_2O_3$ was no effective for acetylation of 2-naphthol with acetic anhydrides.

The different mole ratios of esterifcation of 2-naphthol with acetic anhydrides was studied under microwave irradiation, the results show the best mole ratio is 2-naphthol: acetic anhydrides = 1:1.2.

We investigated the effects of irradiation power and time on the reaction. It was found that the highest yield of compounds is obtained at a power level of 675 W for 10 min continuous irradiation.

### Conclusion

In summary, a simple, safe and eco-efficient method for acetylation of phenols has been developed. The method has advantages in terms of yields, short reaction times, ease of operation and compatibility with other protecting groups. We believe that the present methodology could be an important addition to the existing methodologies.

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TABLE-2
OPTIMIZATION OF THE REACTION CONDITION

| Entry | Catalyst (mmol %) $KF/Al_2O_3$ | Method | Time (min) | [b]Yields (%) |
|---|---|---|---|---|
| 1 | 0.3 | MWI | 6 | 60[a] |
| 2 | 0.3 | MWI | 8 | 78[a] |
| 3 | 0.3 | MWI | 10 | 92[a] (0[c]) |
| 4 | 0.3 | MWI | 12 | 89[a] |
| 5 | 0.5 | MWI | 10 | 92[a] |
| 6 | 0.7 | MWI | 10 | 92[a] |
| 7 | 0 | MWI | 10 | 92[a] (0[c]) |
| 8 | 0.3 | Ultrasound | 40 | (0[d]) |
| 9 | 0 | Ultrasound | 40 | (0[d]) |

Conditions: 2-naphthol (5 mmol), acetic anhydride (6 mmol). [a]Microwave irradiation at 675 W. [b]Yield of isolated product. [c]Reaction temperature 135 °C, high speed stirring reaction time 5 h, without microwave irradiation. [d]Reaction temperature 20-25 °C, ultrasound irradiation at 59 kHz

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