



Microwave mediated solvent-free acetylation of deactivated and hindered phenols

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Deactivated and sterically hindered phenols have been acetylated with acetic anhydride under microwave irradiation and using iodine as catalyst in an eco-friendly process. The reaction was carried out under solvent-free conditions and the acetates were obtained in nearly quantitative yields with dramatic reduction of reaction time compared to standard oil-bath heating.

Introduction

Functional group protection strategies are central to target molecule synthesis. The protection of alcohols, phenols and amines as their acetates is one of the most fundamental, useful and widely used transformations in organic synthesis. Although numerous methods are available for the preparation of acetates, an acetic anhydride–pyridine mixture is commonly used.¹ In our ongoing research program dealing with the synthesis and Structure Activity Relationship studies² of 5-hydroxyflavones, we found that acetic anhydride–pyridine is not suitable for acetylation of the 5-OH group (Fig. 1) due to poor yield and long reaction time. The low reactivity of 5-OH is due to the adjacent carbonyl to which it may form a hydrogen bond and thus result in a non-covalent six-membered ring.³ Generally, the acetylation or alkylation of such a proton, requires more drastic conditions, *e.g.* using acetyl chloride with strong bases, or by using phase transfer catalysis; a further drawback is longer reaction times (up to 40 h).¹

Recently, iodine has been used as an efficient catalyst for acetylation of alcohols.⁴ It is likely that the role of iodine is in activation of acetic anhydride as a Lewis acid which promotes the acetylation reaction. Using iodine as a catalyst for the acetylation of 5-hydroxyflavones is not advantageous as the reaction takes a long time at room temperature or under reflux.

In order to generalize the use of iodine as an efficient catalyst for acetylation of phenols and especially those of low reactivity, we now report the coupling of microwave irradiation with the use of iodine for acetylation of deactivated or hindered phenols. The use of microwave energy in organic synthesis is becoming very popular and many reactions are becoming accessible. An advantage of microwave-catalyzed reactions, is that they can take place under solvent-free conditions (eco-friendly process) compared to conventional heating; in addition, lower reaction times and higher yields are generally obtained.⁵

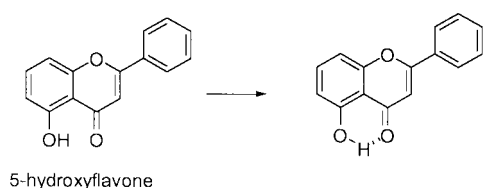


Fig. 1

Results and discussion

In the present article, we report the acetylation of the deactivated and sterically hindered phenols shown in Fig. 2.

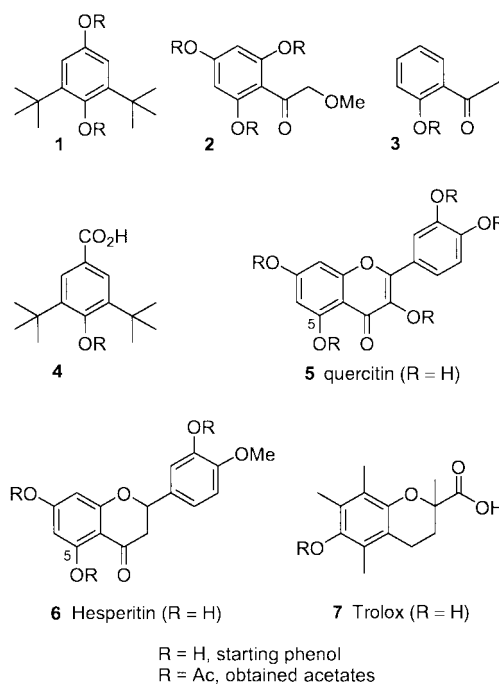
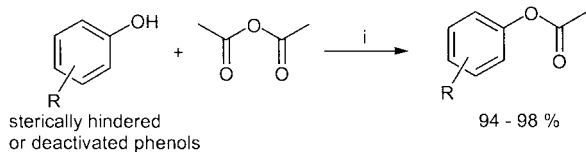


Fig. 2 Phenols acetylated according to the reported method.

Green Context

Functional group protection strategies are fundamental in the synthesis of many target molecules but they are intrinsically wasteful. If they are to be used then it is very important that we utilise the cleanest possible protection methods. Solvents and toxic reagents, as well as very heavy groups (lowering overall process atom efficiency) should be avoided. Here a green procedure for acetylation (relatively small added weight) is described that avoids solvent and uses a widely available safe reagent.

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Scheme 1 Reagents and conditions: i, I₂ (10%), microwaves 2–4 min.

Table 1 Acetylation of phenols shown in Fig. 2. Comparison of microwave and oil-bath heating

Entry ^a	t ^b /min at 500 W (≈65 °C)	Yield (%) ^c (microwave)	Yield (time/h) at 65 °C (oil bath)
1	2	97	70(3)
2	2	95	63(4)
3	2	98	68(3)
4	4	96	63(3)
5	4	94	53(5)
6	4	94	56(5)
7	4	97	50(5)

^a All compounds gave satisfactory NMR and MS analysis. ^b At 500 W power (≈65 °C). ^c Yields are for isolated pure products.

The procedure is easy to perform and the reaction can be conducted in solvent free conditions and leads to quantitative yields of products (Scheme 1, Table 1).

Acetylation does not take place when microwave energy is used in the absence of iodine. When the procedure was tested by simply using iodine (without microwave irradiation), very low yields were obtained and the 5-hydroxy group of quercetin and hesperitin was not acetylated, as deduced by ¹H NMR spectroscopy.

In order to show the usefulness of the microwaves, control experiments were carried out using the same amount of reactants and at the same temperature reached in a microwave oven (65 °C). As shown in Table 1, acetylated derivatives were obtained after a minimum of 3 h heating and the yields were generally lower. In this case, yields can be increased by using chloroform as a solvent.

In conclusion, we have demonstrated that combining iodine with microwave energy is an efficient method for acetylation of deactivated phenols. This eco-friendly method offers scope for the practical synthesis of protected polyphenols and, especially, the biologically active 5-hydroxyflavones.

Experimental

General procedure

In a microwave oven. A catalytic amount of iodine (0.1 mmol) was added to a mixture of the phenolic compound (1 mmol) and acetic anhydride (5 mmol). The mixture, placed in a 100 mL round bottomed flask, was irradiated in a microwave

reactor for 2–4 min at 500 W power. Immediately upon completion, the flask was removed from the oven and the temperature recorded with a thermometer (60–65 °C).⁶ The mixture was poured into water and extracted with CH₂Cl₂. The extract was washed successively with sodium thiosulfate solution, hydrogencarbonate solution and water. The extract was then dried over anhydrous sodium sulfate and evaporated to yield the pure phenol acetate. The reaction was conducted in solvent free conditions except for **5** and **6**, for which dichloromethane (2 mL mmol⁻¹) was added to help solubilization. Even when performed on a large scale (2 or 3 g) the reaction was complete in the same time without affecting the yield (Table 1).

In an oil-bath. The reactants were mixed in the same manner as in the microwave oven and heated in an oil-bath at 65 °C. After cooling to room temperature, dichloromethane was added and the mixture poured into water and the product extracted with dichloromethane and treated as above. The crude product was column chromatographed on silica gel and eluted with cyclohexane–ethyl acetate (8:2).

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- 6 The microwave reactor used was a Normatron® 112 from Normandie Labo S.A. Lintot, France, equipped with magnetic stirring plate and a reflux condenser.