SHORT PAPER

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Microwave enhanced acetylation of alcohols†

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Microwave irradiation of alcohols with acetic anhydride in the presence of a catalytic amount of NaOH for a few minutes yielded the corresponding acetylated products in excellent yield.

Keywords: alcohols, acetic anhydride, sodium hydroxide

Acylation of alcohols is a fundamental process in organic chemistry and provides a cheap and efficient means for protecting the hydroxy group during oxidation, peptide coupling, and glycosidation reactions. The acetylation of alcohols by acyl chloride or acid anhydride under basic conditions is a well-established reaction in organic synthesis.[1,2] The commonly employed basic catalysts for this purpose are pyridine, 4-dimethylamino-pyridine, and 4-pyrrolidinopyridine (PPY), *etc*.[3,4] Pyridine which functions as both the solvent and a nucleophilic catalyst is the most widely used catalyst in spite of its well-known acute toxicity and disagreeable odour.[5] Handling of large volumes of pyridine and other homogeneous catalysts is troublesome. Large-scale acylation involving sodium acetate requires special modified apparatus to keep the reaction under control.[6] Recently, heterogeneous catalysts[7,8] and Lewis acids[9] have been reported to affect acetylation reactions. Moreover, using inexpensive and non-corrosive catalysts, chemical transformations occur with better efficiency, high purity of the products, and easier workup, with evident economical and ecological advantages especially in industrial processes.

Currently, there has been increasing interest in the use of microwave irradiation techniques in organic syntheses.[10] A number of simple synthetically useful organic reactions have been carried out in the microwave oven in open vessels. With such microwave irradiation techniques, remarkable rate enhancements have been observed and, in some cases, cleaner reactions with easier workup compared to conventional heating methods. Recently, many groups including our own have described microwave-induced reactions in open vessels in domestic microwave ovens.[11-14] In each case, the reactions proceeded in a highly accelerated manner, and the yields and purity of the final products were comparable to those obtained with the traditional protocol.

In the present paper, we describe acetylation of alcohols employing a commercial microwave oven using a catalytic amount of NaOH. We applied this methodology to various classes of natural products, steroids, triterpenes, monoterpenes, and coumarin (Table 1). The reaction was performed on a small scale‡ in solvent-free conditions for a short period (3 or 4 min) and high yields (> 90%) were observed in all cases. Under the present conditions chiral alcohols can be easily acylated in high yields with complete retention of optical activity. All the products can be purified directly after completion of reaction without workup, using a small filter column.

In summary, we have developed a novel, highly efficient and general methodology for protection of alcohols with acetic anhydride under microwave irradiation using a catalytic amount of NaOH. All products were obtained in excellent yields under the same experimental conditions. The main advantages of our methodology are the use of a catalytic amount of a base, the absence of a solvent, shorter reaction time, simple reaction conditions, no workup after completion of the reaction, an improvement over precedent syntheses using conventional heating, and applicability to a wide range of alcohols.

Experimental

Steroids (entry 1 and 2), triterpene (entry 3) and coumarin (entry 6) were natural products; they were isolated from *Hydrangea chinenses*.[15] All products are known compounds; they were identified by comparison of their physical and spectral data with those of authentic samples.[16-24] *Stigmaste-5-ene-3β-ol* acetate, the major product of entry 1, was purified from the reaction mixture by column chromatography (Si-Gel, solvent system=$CHCl_3$/hexane, 80/20); IR (neat): 2945 cm^{-1} and 1730 cm^{-1}; ^1H NMR: δ 5.38 (1H, d, *J*=4.6 Hz, HC=C), δ 4.57 (1H, m, OAc-C<u>H</u>), δ 2.03 (3H, s, OAc), δ 1.02 and δ 0.68 (each 3H, s, CH_3), δ 0.79–0.80 (9H, m, 3×CH_3). *(22E)-Stigmasta-5,22-dien-3β-ol acetate*, the major product of entry 2, was purified from the reaction mixture by column chromatography (Si-Gel, solvent system=$CHCl_3$); IR (neat): 2950 cm^{-1} and 1725 cm^{-1}; ^1H NMR: δ 5.35 (1H, d, *J*=5.2 Hz, HC=C), δ 5.10 (2H, m, HC=CH), δ 4.60 (1H, m, OAc-C<u>H</u>), δ 2.03, (3H, s, OAc), δ 1.02 and δ 0.69 (each 3H, s, 2×CH_3), δ 0.76–0.86 (9H, m, 3×CH_3). *Fern-9(11)-en-3β-yl acetate*, the major product of entry 3, was purified from the reaction mixture by column chromatography (Si-Gel, solvent system=$CHCl_3$/hexane, 50/50); IR (neat): 2900 cm^{-1} and 1735 cm^{-1}; ^1H NMR: δ 5.21 (1H, d, *J*=5.6 Hz, HC=C), δ 4.50 (1H, dd, *J*=4.5, 11.4 Hz, OAc-C<u>H</u>), δ 2.05 (3H, s, OAc), δ 1.08, δ 0.94, δ 0.84, δ 0.80, δ 0.75, and δ 0.72 (each 3H, s, 6×CH3). *Bornyl acetate*, the major product of entry 4, was purified from the reaction mixture by column chromatography (Si-Gel, solvent system= $CHCl_3$/acetone, 95/5); IR (neat): 1725 cm^{-1} and 1250 cm^{-1}; ^1H NMR: δ 4.86 (1H, m, OAc-C<u>H</u>), δ 2.03 (3H, s, OAc), δ 0.87, δ 0.84, and δ 0.80 (each 3H, s, CH_3). *Isobornyl acetate*, the major product of entry 5, was purified from the reaction mixture by column chromatography (Si-Gel, solvent system= $CHCl_3$/acetone, 95/5); IR (neat): 1725 cm^{-1} and 1240 cm^{-1}; ^1H NMR: δ 4.62 (1H, m, OAc-C<u>H</u>), δ 1.98 (3H, s, OAc), δ 0.98, δ 0.94 and δ 0.80 (each 3H, s, CH_3). *7-Acetoxycoumarin*, the major product of entry 6, was purified from the reaction mixture by column chromatography (Si-Gel, solvent system=EtOAc/hexane, 50/50 ~ 60/40); IR (neat): 1750 cm^{-1} and 1735 cm^{-1}; ^1H NMR: δ 7.67 (1H, d, *J*=7.6 Hz, Ar-H), δ 7.49 (1H, d, *J*=7.6 Hz, Ar-H), δ 7.11 (1H, d, *J*=1.2 Hz, Ar-H), δ 7.04 (1H, dd, *J*=1.2, 7.6 Hz, Ar-H), δ 6.38 (1H, d, *J*=7.6 Hz, Ar-H), δ 2.32 (3H, s, OAc). *3,4-Diacetoxycinnamic acid*, the major product of entry 7, was purified from the reaction mixture by column chromatography (Si-Gel, solvent system=$CHCl_3$/hexane, 60/40~50/50); IR (neat): 1763 cm^{-1}, 1683 cm^{-1}, and 1682 cm^{-1}; ^1H NMR: δ 7.70 (1H, d, *J*=16.0 Hz, HC=C), δ 7.40 (1H, d, *J*=1.0 Hz, Ar-H), δ 7.38 (1H, dd, *J*=1.0, 7.6 Hz, Ar-H), δ 7.23 (1H, d, *J*=7.6 Hz, Ar-H), δ 6.37 (1H, d, *J*=16.0 Hz, HC=C), δ 2.30 and δ 2.08 (each 3H, s, OAc). *4-Acetoxybenzoic acid*, the major product of entry 8, was purified from the reaction mixture by column chromatography (Si-Gel, solvent system=$CHCl_3$); IR (neat): 2800 cm^{-1} and 1773 cm^{-1}; ^1H NMR: δ 7.95 and δ 7.14 (each 2H, d, *J*=8.0 Hz, Ar-H), 2.11 (3H, s, OAc). *Acetic acid trans-cinnamyl ester*, the major product of entry 9, was purified from the reaction mixture by column chromatography (Si-Gel, solvent system=$CHCl_3$/hexane, 80/20); IR (neat): 1730 cm^{-1}; ^1H NMR: δ 7.21–7.41 (5H, m, Ar-H), δ 6.66 (1H, d, *J*=15.6 Hz, HC=C), δ 6.30 (1H, dt, *J*=6.4, 15.6 Hz, HC=C), δ 4.72 (2H,

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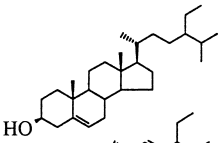
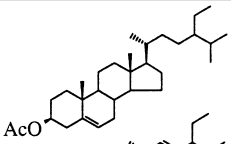
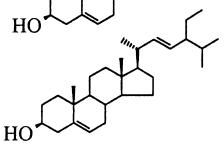
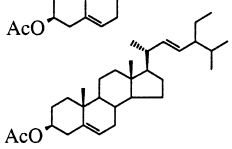
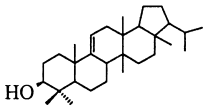
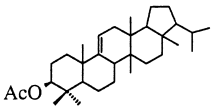
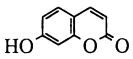
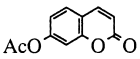
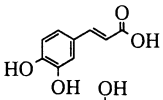
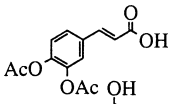
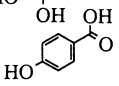
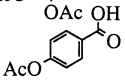
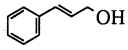
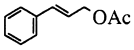
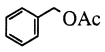
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

‡See Caution

Table 1 Acetylation of alcohols with acetic anhydride under microwave irradiation using catalytic amount of NaOH

Entry	Alcohol	Time/min	Product	Yield/%[a]	Ref.
1		3		95	15
2		3		93	15
3		4		94	16
4		3		94	17
5		3		90	18
6		3		93	19
7		3		92	20
8		3		94	21
9		3		93	22
10		3		96	23

[a]Isolated yield.

d, *J*=6.4 Hz C<u>H</u>$_2$OAc), δ 2.10 (3H, s, OAc). *Acetic acid benzyl ester*, the major product of entry 10, was purified from the reaction mixture by column chromatography (Si-Gel, solvent system=$CHCl_3$/hexane, 80/20); IR (neat): 2000 cm^{-1} and 1725 cm^{-1}; ^{1}H NMR: δ 7.20–7.42 (5H, m, Ar-H), δ 5.18 (2H, s, CH_2), δ 2.11 (3H, s, OAc).

General procedure for acylation of alcohols: A mixture of alcohol (1 mmol), acetic anhydride (2 mmol) and 5 mg of NaOH in a test tube was irradiated in a domestic microwave (530 W) oven for a few minutes (3–4 min). The crude reaction product was purified by column chromatography over silica gel to afford the acetylated product.

‡**Caution**: Reactions were carried out on a small scale. For large-scale preparations the reaction could be quenched with water at low temperature, be made basic (PH~9) and then the product extracted into an organic solvent so that further isolation could be carried out without hazards caused by acetic anhydride.

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