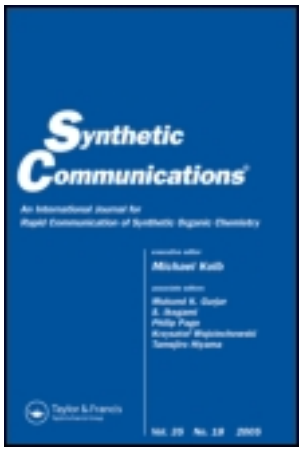

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CHEMOSELECTIVE ACETYLATION OF ALCOHOLS, AMINES, AND THIOLS WITHOUT CATALYST AND SOLVENT

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CHEMOSELECTIVE ACETYLATION OF ALCOHOLS, AMINES, AND THIOLS WITHOUT CATALYST AND SOLVENT

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ABSTRACT

Microwave induced rapid and selective acetylation of alcohols, amines and thiols with acetic anhydride was carried out under non-catalytic and solvent free conditions.

Hydroxyl groups are present in a number of compounds of biological and synthetic interest including nucleosides, carbohydrates, steroids and the side chain of some amino acids. During oxidation, acylation, halogenation with phosphorus or hydrogen halides or dehydration reactions of these compounds, a hydroxyl group must be protected. The protection of hydroxyl, amino and thiol groups is of great importance in synthetic organic chemistry.[1] Though several methods are available for transesterification,[2] routinely acetylation of alcohols, phenols, amines and thiols is carried out with acetic anhydride or acetyl chloride in the presence of either acid or base catalyst.[1] The reaction is generally carried out using tertiary amine catalyst such as triethylamine or pyridine.[3] 4-(Dimethylamino)pyridine, (DMAP) is

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known to increase the rate of acetylation when used as co-catalyst.[4] Vedejs et al reported tributylphosphine as less basic catalyst for acetylation of alcohols.[5] Recently, iodine was used as an acetyl transfer catalyst.[6] In addition to the above catalysts, protonic acids such as toluene-p-sulfonic acid,[7] Lewis acids such as zinc chloride,[8] cobalt chloride[9] and scandium trifluoromethanesulfonate[10] were also applied to catalyse the acylation of alcohols and phenols. More recently montmorillonite K-10 and KSF,[11] expansive graphite,[12] sulfamic acid,[13] chlorotrimethylsilane[14] and lithium chloride[15] were also used as catalysts for this purpose. Each of the above methods has its merit and shortcomings. These methods are not entirely satisfactory. Triethylamine and pyridine[3] have unpleasant odour and are not so easy to remove from the reaction mixture. DMAP is expensive and not easily obtained whereas tributylphosphine is irritant, highly flammable and still expensive. But to the best of our knowledge, there is no report available in the literature for acetylation of alcohols, phenols, amines and thiols without catalyst under solvent-free condition.

There is an increasing interest in the use of environmentally benign reagents and conditions particularly to solvent-free procedures.[16] Microwave heating has been used for a wide variety of applications including the rapid synthesis of organic compounds.[16] 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 can be used. Reactivities and sometimes selectivities are enhanced. We wish to report herein first non-catalytic acetylation of alcohols, amines and thiols using microwaves under solvent-free condition.

As shown in table 1, primary, secondary, benzylic and allylic alcohols, primary amines and thiols are acetylated with acetic anhydride under non-catalytic and solvent-free conditions using microwaves. Diols were also converted into the corresponding diacetates (entries 2,3). It is worth commenting that tertiary alcohols give different results or do not undergo acetylation using acid catalyst.[13] But under this non-catalytic condition using microwaves even tertiary alcohols underwent smooth acetylation (entries 13, 14). Furthermore, α,β-unsaturated alcohol is also acetylated without interfering carbon-carbon double bond (entry 4).

Using an alternative heating mode (oil bath) at temperature of 120°C, the reaction of benzyl alcohol with acetic anhydride could not even proceed after 7 hours. In order to know whether there is any effect of acetic acid formed on acetylation or not, attempt was made to carry out acetylation in the presence of sodium bicarbonate (acid scavenger) and it was observed that acetylation proceeded equally well in the presence or absence of sodium bicarbonate. It is important to noteworthy that alcohol (entry 17), amine

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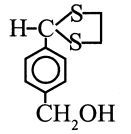
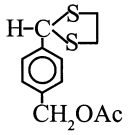
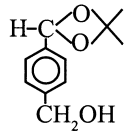
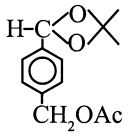
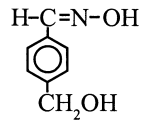
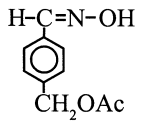
Table 1. Acetylation of Alcohols, Amines and Thiols Using Microwaves Without Solvent

Entry	Substrate	Product[17]	Time (min)	Yield[a,b] (%)
1	Octadecanol	Octadecyl acetate	6	91
2	1,7-Heptane diol	1,7-Heptane diacetate	6	85
3.	1,8-Octanediol	1,8-Octane diacetate	7	85
4.	Cinnamyl alcohol	Cinnamyl acetate	8	80
5.	Benzyl alcohol	Benzyl acetate	8	80
6.	2,4-Dichlorobenzyl alcohol	2,4-Dichlorobenzyl acetate	10	85
7.	4-Methoxybenzyl alcohol	4-Methoxybenzyl acetate	6	95
8.	3,4-Methylenedioxy-benzyl alcohol	3,4-Methylenedioxy-benzyl acetate	10	91
9.	2-Nitrobenzyl alcohol	2-Nitrobenzyl acetate	7	90
10.	Cyclohexanol	Cyclohexyl acetate	6	84
11	Menthol	Menthyl acetate	8	89
12.	Benzoin	Benzoin acetate	9	86
13.	t-Butyl alcohol	t-Butyl acetate	4	82
14.	Triphenyl methyl alcohol	Triphenyl methyl acetate	9	87
15	4-Chlorothiophenol	4-Chlorophenyl thioacetate	6	83
16.	4-Bromothiophenol	4-Bromophenyl thioacetate	5	88
17.	4-Hydroxybenzyl alcohol	4-Hydroxybenzyl acetate	7	90
18.	4-Hydroxy aniline	4-Hydroxy acetanilide	2	83
19.	4-Hydroxy benzyl thioalcohol	4-Hydroxy benzyl thioacetate	4	89
20.			6	84
21.			7	81
22.			8	82

[a]Yields are of pure isolated products. [b]Products are characterised by their physical constants,[17] spectral characteristics (IR, ^{1}H NMR) and comparison with authentic samples.[17]

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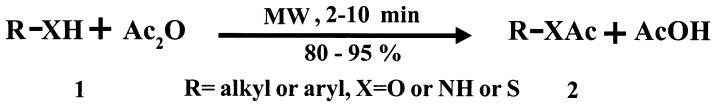

(entries 18) and thiol (entry 19) were chemoselectively acetylated in the presence of phenol. Though acetic acid is generated during the reaction, benzyl alcohols are selectively acetylated without touching other acid sensitive functional groups such as methoxy (entry 7), methylenedioxy (entry 8), thioacetal (entry 20), acetal (entry 21) and oxime (entry 22). Thus tolerance of different sensitive functional groups to these reaction conditions depicits the flexibility and generality of the protocol.

EXPERIMENTAL

Microwave oven (Kelvinator T-37 model) was used with its 100% power at 2450 MHz.

Typical Procedure

A mixture of 4-methoxybenzyl alcohol (5 mmol) and acetic anhydride (5 mmol) in a beaker covered with watch glass was irradiated by microwaves for 10 min. (heating and cooling at the interval of 1 min.). After completion of the reaction (TLC), the product was extracted with ether (3×15 ml). The ether layer was washed with 10% NaOH and then dried with anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 4-methoxybenzyl acetate in excellent yield (95%).

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