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Microwave oven synthesis of esters promoted by imidazole

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Abstract—Using imidazole as promotion agent, primary, secondary and phenolic alcohol compounds were esterified with aliphatic and aromatic carboxylic acid anhydrides. Heating a ternary mixture of alcohol, anhydride and imidazole in an unmodified microwave oven produced esters in low to high yields, depending on the steric bulk of the alcohol. © 2003 Elsevier Science Ltd. All rights reserved.

Esterification between alcohol and acid is a most important organic reaction and a large number of reactions have been developed. In these days, catalyzed esterification is a currently active area of research. Among them, the stoichiometric reactions between alcohol and acid reported by Yamamoto¹ et al. and Tanabe² et al. are superior especially from atom economical viewpoint. On the other hand, microwave activation of a large number of organic synthetic³ and metal catalyzed⁴ reactions have recently appeared, attracting attention due time economy. Lidström et al., conveniently reviewed microwave assisted experiments reported between 1994 and 2000.⁵ Although these reports include a number of esterification reactions, the scope of the individual reactions is rather narrow. This report further expands the microwave oven assisted synthesis of esters,⁶ preparing them from a wide range of alcohol and carboxylic acid residues using imidazole as promotion agent, a proven microwave oven amidation⁷ and imidation⁸ agent.

The reagents used have relatively low toxicity and are environmentally friendly. Although there are microwave oven esterification reports that use carboxylic acid and alcohol, silica gel, a persistent waste material, is necessary as a solid support.⁹ Carboxylic acid anhydrides are less reactive than the widely used carboxylic acid chlorides and easily break down into

carboxylic acids and are therefore less toxic and less persistent than either acid chlorides or silica gel support. The promotion agent used here, imidazole, is also lower in toxicity than some esterification catalysts like 4-dimethylaminopyridine (DMAP). This lowers the risk to the individual experimentalist and reduces the toxicity of the waste stream from these experiments. The side-products of this reaction method are relatively benign, imidazole and a carboxylic acid. In contrast to esterification with carboxylic acid chlorides, which produce HCl and SO₂ in their preparation as well as HCl in their use, anhydride/imidazole provides an attractive alternative. This method allows a wide range of alcohol and carboxylic acid moieties to be incorporated into the industrially important chemical class of esters.

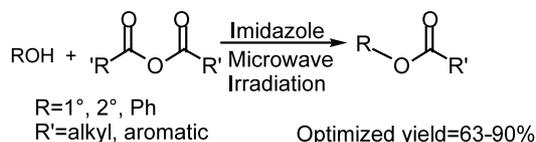
Another area requiring new experiments easily carried out in undergraduate laboratories is chemical education.¹⁰ Using environmentally friendly reagents protects the students and reduces the amount of waste generated. Undergraduate students easily carry out the microwave oven esterification technique reported here.¹¹

Using a ternary mixture of alcohol, anhydride and imidazole, a wide range of compounds were conveniently and efficiently esterified (Scheme 1). The ternary mixture was simply measured into a test tube and irradiated in the microwave oven at full power for three

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Scheme 1.

minutes. The work-up was accomplished by washing the diethyl ether diluted mixture successively with aqueous Na_2CO_3 , water, aqueous 2% citric acid and water. Further purification was unnecessary as indicated by FTIR and NMR (^1H and ^{13}C) spectra.

A wide range of alcohol functional groups were esterified (Fig. 1). Primary, secondary and phenolic groups were esterified in good to excellent yield (Table 1). The compounds chosen for these experiments are

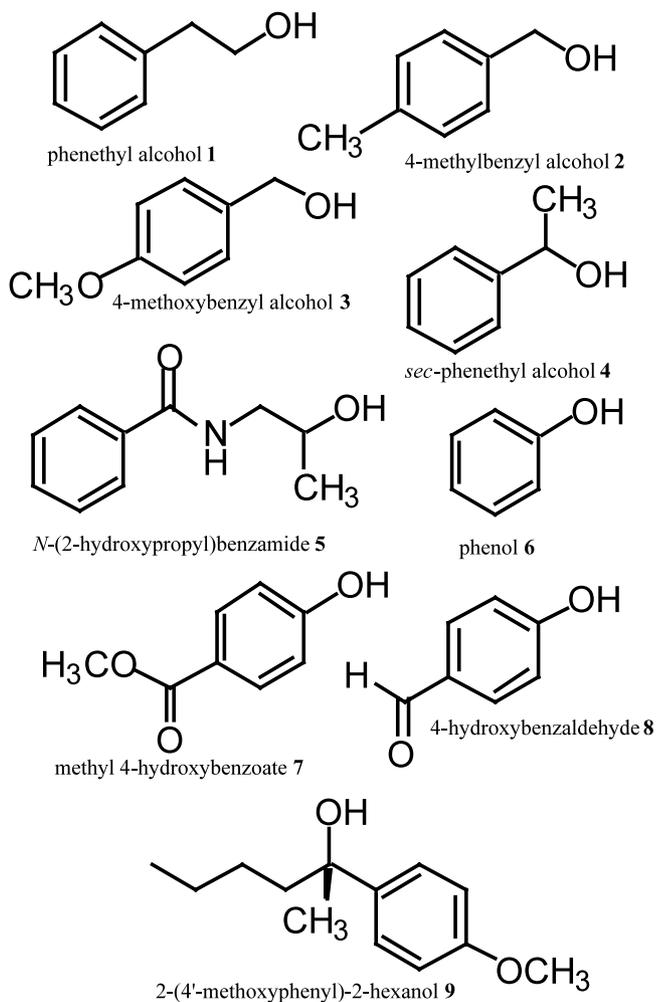


Figure 1. Alcohol compounds used in this study.

Table 1. Alcohol esterification using carboxylic anhydrides with imidazole promoter under economical conditions^a

Entry	Alcohol	Anhydrides yield (%)		
		Ac	Pr	Bz
1	Phenethyl	65	86	72
2	<i>p</i> -Methoxybenzyl	25	45	0
3	<i>sec</i> -Phenethyl	58	79	1
4	<i>N</i> -(2-Hydroxypropyl)benzamide	5	43	2
5	Phenol	12	52	87
6	Methyl 4-hydroxybenzoate	–	6	–

Irradiation was for three minutes at full power (500 watts).

^a Alcohol:anhydride:imidazole molar ratios were 1:1:1.

important in a wide range of applications. The propionate of phenethyl alcohol **1** is a proven octopominergic compound.¹² Such compounds are useful in developing more environmentally friendly insecticides. The esters of chiral secondary alcohols **4** and **5** are very useful for studying enzyme catalyzed kinetic resolutions¹³ and as chiral building blocks. Simple and efficient esterification methods are needed to facilitate this area of study, important in pharmaceutical chemistry.

At least eleven synthetically significant carboxylic acid esters were made under conservative conditions as defined by an equimolar ternary mixture of alcohol, anhydride and imidazole (Table 1). This finding appears to be in opposition to reports of excellent yield of phenolic esters without catalyst by Kwon et al.¹⁴ We found the use of imidazole was essential to obtain significant yields of any ester. When benzoic anhydride was used, a less reactive anhydride, only phenol and phenethyl alcohol yielded significant esterification product under these conditions.

Although some of the esterifications worked well with stoichiometric amounts of reagents, significant yield enhancement was observed when using alcohol:anhydride:imidazole molar ratios of 1:3:1 (Table 2). Part of these enhanced results were due to imidazole promotion (Table 2, entries 1 and 2). Using three equivalents of anhydride allowed synthetically useful yields for most of the acetylations. Acetate esters are very useful intermediates. This result compares favorably with the microwave oven acetylation of sugars described by Limousin et al.¹⁵ While increasing the anhydride ratio we also observed the lack of influence on reaction yield of microwave oven wattage (Table 2).

Table 2. Esterification using alcohol:anhydride:imidazole molar ratio of 1:3:1

Entry	Alcohol	Anhydrides yield (%)	
		Ac	Pr
1	Phenethyl	86 ^a	92
2 ^b	Phenethyl	29	44
3 ^c	<i>p</i> -Methoxybenzyl	87	74
4	<i>p</i> -Methylbenzyl	83 ^a	74 ^a
5	<i>sec</i> -Phenethyl	73	84
6	<i>N</i> -(2-Hydroxypropyl)benzamide	63	89
7 ^d	(+)- <i>N</i> -(2-Hydroxypropyl)-benzamide	–	90
8	Phenol	74	66
9	Methyl 4-hydroxybenzoate	–	84
10	4-Hydroxybenzaldehyde	–	48
11 ^e	2-(4'-Methoxyphenyl)-2-hexanol	0	0

Irradiation was for three minutes at full power (500 watts).

^a Full power was 1,000 watts for these experiments.

^b There was no imidazole promoter in these reactions.

^c These were irradiated for only two minutes at full power.

^d No racemization was observed in esterification or subsequent hydrolysis. Acetylation was assumed to be similar.

^e Approximately 20% olefin and 40% recovered alcohol.

Table 3. Phenethyl alcohol esterification using propionic anhydride with various promoters under identical conditions with Table 2

Entry	Promoter	Yield (%)
1	Imidazole	92
2	4-Dimethylaminopyridine (DMAP)	95
3	1,4-Diazabicyclo[2.2.2]octane (DABCO)	88
4	1,4-Diazabicyclo[5.4.0]undec-7-ene (DBU)	2

Even when the wattage was doubled for the allotted time, little change in yield was observed. Additionally, the tolerance of the method for reactive ester and aldehyde groups was demonstrated (Table 2, entries 9 and 10). One caveat to the success of imidazole promotion was that tertiary alcohols could not be esterified. Evidence of alkene side-products in the IR and proton NMR spectra pointed to the likelihood of elimination under the conditions necessary for esterification.

Finally, a selection of catalytic bases was used (Table 3). Imidazole performed comparably well to DMAP and DABCO (1,4-diazabicyclo[2.2.2]octane), common catalytic bases. Imidazole's chief advantage was cost. It was also a very conveniently measured solid material, contrasted with the more expensive and less effective liquid DBU (1,4-diazabicyclo[5.4.0]undec-7-ene) catalyst.

The simple and quick microwave oven method described here for esterification of alcohol compounds adds a new procedure to the organic synthetic tool box. Imidazole promotion extended the method over previous reports by allowing primary, secondary and phenolic alcohol compounds to be esterified with a useful range of carboxylic acid residues. This method should be of use in research, education, and industry.

Acknowledgements

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