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Hydrolysis of amides to carboxylic acids using phthalic anhydride under microwave irradiation and solvent-free conditions

Majid. M. Heravi*, Dordaneh Zargarani, Rahim Hekmat Shoar and Shahnaz Khaleghi

Department of Chemistry, School of Science, Azzahra University, Vanak, Tehran, Iran

Amides efficiently and rapidly give carboxylic acids in high yields upon reaction with phthalic anhydride under microwave irradiation in the absence of solvent.

Keywords: amide, carboxylic acid, phthalic anhydride

Hydrolysis is an important transformation in organic chemistry and because of its significant role, the development of new reagents and the modification of existing methods are still important.[1] Many reagents are now available for almost every conceivable type of hydrolysis.[2] Since amides are more difficult to hydrolyse than esters chemoselective hydrolysis of them is an attractive objective. Tetrahalophthalic anhydride[4] and sodium perborate along with copper salts[5] have been reported as effective for this hydrolysis.

Phthalic anhydride is a potentially useful agent for the conversion of aldehydes into nitriles and nitriles into carboxylic acids[6] and is one century old.[7] It has been recently used as a mild and convenient reagent for the hydrolysis of amides to carboxylic acids under moderate pressure.[8]

The use of supported reagents[9] has attracted much attention because of the selectively, reactivity and associated ease of manipulation. Microwave-enhanced chemical reactions[10] especially on solid supports and those conducted in solventless systems,[11] have gained popularity.

They have several advantages over the conventional homogeneous and heterogeneous reactions in view of the fast reactions and higher yields of pure products. Solvent-free organic reactions using dry media techniques under microwave irradiation are a main topic of interest in our laboratory.[12] In continution of these efforts, we report herein a facile and mild hydrolysis of amides to carboxylic acids using phthalic anhydride with silica gel under microwave irradiation in a solvent-free system.

First we examined the reaction in different solvents under classical heating which was unsuccessful. We then contemplated the hydrolysis of amides to carboxylic acids in the presence of phthalic anhydride with a solid support under microwave irradiation (MW). We examined various minerals such as clay, zeolites, alumina and silica gel and found that silica gel provides the best results in term of formation of pure products and high yields. Microwave irradiation accelerates the reaction drastically. The procedure involves a simple mixing of amide with silica gel and phthalic anhydride and irradiating the mixture in a domestic microwave oven for a short time in the solid state. Our results on this rapid protocol for the hydrolysis of amides to carboxylic acids are summarised in Table 1.

The hydrolysis of benzamide to benzoic acid is a representation of the general procedure employed. Phthalic anhydride and dried silica gel {0.14 g, 1 mmol, 0.2 g silica gel (60 mesh)} was thoroughly mixed with benzamide (0.12 g, 1 mmol,) in a beaker using a spatula. The beaker was placed on a domestic microwave oven for 5 minutes. The progress of reaction was monitored by TLC.

The water equivalent needed to complete hydrolysis of the amide is provided by phthalic anhydride which is converted into phthalimide and water in the first stage. (Scheme **1**). Although we were not able to isolate the malemide intermediate, the isolation of phthalimide at the end of reaction gives no alternative route.

Upon completion of the reaction, the mixture was added to $CHCl_3$ (20 ml) and filtered . The filtrate was evaporated to dryness to afford pure benzoic acid. (Yield, 92%, mp 121°C. lit[13] 121. 4°C)**.** The solid remaining on the filter paper was dissolved in hot methanol (20 ml) and filtered. The filtrate was evaporated at reduced pressure to give pure phthalimide(Yield, 90%, m.p. 231–232°C. lit[13]233–234°C)

In conclusion, the present method for dry hydrolysis of amides to carboxylic acids has some advantages over existing methodologies. The notable advantages of this procedure are its mild conditions, absence of solvent, speed,

Table 1 Hydrolysis of amides to carboxylic acids using phthalic anhydride under microwave irradiation in a solvent-free system

Entry	Substrate	Reaction time/min	Product	Yield /%[a]	M.p./ °C found (reported[13])
1	Benzamide	6	Benzoic acid	92	121 (122.4)
2	3-Nitrobenzamide	7	3-Nitrobenzoic acid	93	140–141 (142)
3	4-Chlorobenzamide	7	4-Chlorobenzoic acid	92	239–241 (243)
4	4-Methoxybenzamide	6	4-Methoxybenzoic acid	90	182– 183 (185)
5	4-Methylbenzamide	7	4-Methylbenzoic acid	90	179–180 (181)
6	4-Nitrobenzamide	7	4-Nitrobenzoic acid	85	238–241 (242.2)
7	2-Ethoxybenzamide	6	2-Ethoxybenzoic acid	75	196– 198 (198.50)
8	Acetamide	5	Acetic acid	90	(16.7)
9	Cyanoacetamide	4	Cyanoacetic acid	85	64–65 (66)
10	Trifluroacetamide	5	Trifluroacetic acid	80	(–15.4)
11	Trichloroacetamide	6	Trichloroacetic acid	75	54–56 (57–58)
12	Propionamide	5	Propionic acid	95	(–21.5)
13	Acrylamide	6	Acrylic acid	60	(14)
14	L (-)Lactamide	5	L (-)Lactic acid	90	51–53 (53)

[a]Yields refer to isolated product. Product identities were confirmed by comparison of physical and spectroscopic data with those of authentic samples.

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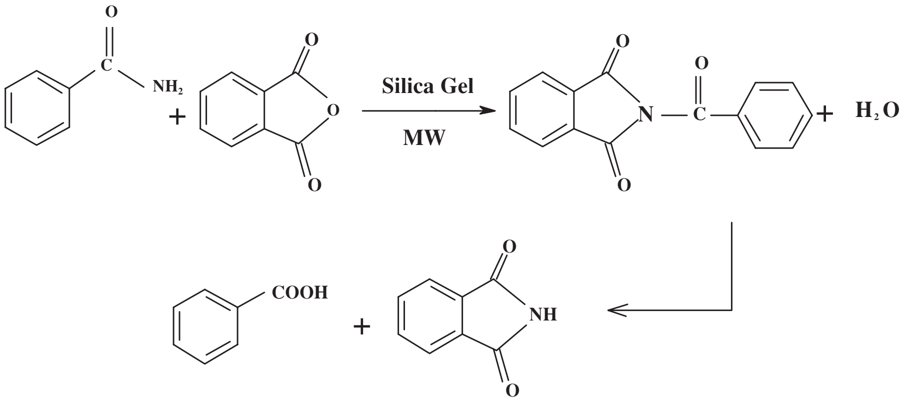
* Correspondent. E-mail: mmheravi@azzahra.ac.ir



Scheme 1

excellent yields, absence of aqueous work up, low cost using inexpensive phthalic anhydride and silica gel and safe and green conditions. We believe this procedure is a useful addition to modern organic synthetic methodologies.

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