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Towards the rehabilitation of the Mathews' 'dry' hydrolysis reaction using microwave technology

Farid Chemat*

Laboratoire de Chimie des Substances Naturelles et des Sciences des Aliments, Faculté des Sciences et Technologies,
Université de la Réunion, 15 avenue René Cassin, B.P. 7151, F-97715 Saint Denis messag cedex 9, La Réunion, France D.O.M

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Abstract—The Mathews' reaction is a one-pot preparation of carboxylic acids from their corresponding nitriles or amides by a 'dry' hydrolysis with phthalic acid or anhydride in the absence of water and solvent. Excellent isolated yields and selectivity (up to 99%) were attained within short reaction times (typically, 30 minutes) when the reaction was performed under microwave heating. © 2002 Elsevier Science Ltd. All rights reserved.

The Mathews' reaction, a 'dry' hydrolysis procedure of nitriles by phthalic acid or amides by phthalic anhydride to give the corresponding carboxylic acid, is roughly one century old[1,2] and during this period, there have been very few studies.[3–7] The need of a high reaction temperature, expensive co-reagents (tetrachloro and tetrafluoro phthalic acids or anhydrides) and long reaction periods (6–7 days to obtain often only low to moderate yields) have overshadowed its main advantages: simplicity, high yield and selectivity, and also use of inexpensive reagents.

We have found that using microwave technology under solvent- and water-free conditions, the hydrolysis of nitriles with phthalic acid, or of amides with phthalic anhydride, takes place in excellent yields (>98%) and selectivity (>99%) and with short reaction times (<30 min). The reaction allows the presence of some functional groups thanks to the rather mild acidic conditions. The corresponding products are carboxylic acid and phthalimide.

In recent decades microwave technology has taken an undeniable place in chemical laboratory practice as a very effective and non-polluting method of activating reactions.[8,9] Examples of this technology in organic synthesis and to organo-metallic chemistry are numerous.[10] The greater successes achieved have been to perform reactions very efficiently in the absence of any organic solvents (so called dry media conditions) and in closed vessels. The use of microwaves provides fast volumetric heating of the chemicals above their boiling points thus enhancing reaction rates and dramatically shortening preparation times.

A kinetic study, together with a GC/MS (gas chromatography with a mass spectrometer detector) investigation of the crude reaction mixture, allowed the reaction pathway illustrated in Scheme 1 to be established. The reaction mixtures contains initially equimolar quantities of nitrile **1** and phthalic acid **2**. The intermediate compounds **4** and **5**, respectively, the amide corresponding to the starting nitrile **1** and phthalic anhydride, as well as the intermediates **3**, **6** and the expected compounds, carboxylic acid **7** and phthalimide **8**, have been identified by GC/MS technique.[11] The first reaction step is probably protonation of the nitrile followed by a nucleophilic attack giving the identified intermediate **3**. An internal proton shift and substitution give anhydride **5** and the intermediate amide **4**. Reaction of **4** and **5** by a similar pathway gives **6** whose hydrolysis with the water generated in situ gives the expected acid **7** and phthalimide **8**. Furthermore heating **4** and **5** under the same reaction conditions gives also the expected acid **7** and phtalimide **8**. The single water equivalent needed for complete hydrolysis of the nitrile is provided in situ by phthalic acid. Because this hydrolysis reaction is run without addition of water, we call it 'dry' hydrolysis.

Keywords: hydrolysis; microwave; nitrile; amid; carboxylic acid.

* Fax: +262.262.93.81.83; e-mail: chemat@univ-reunion.fr

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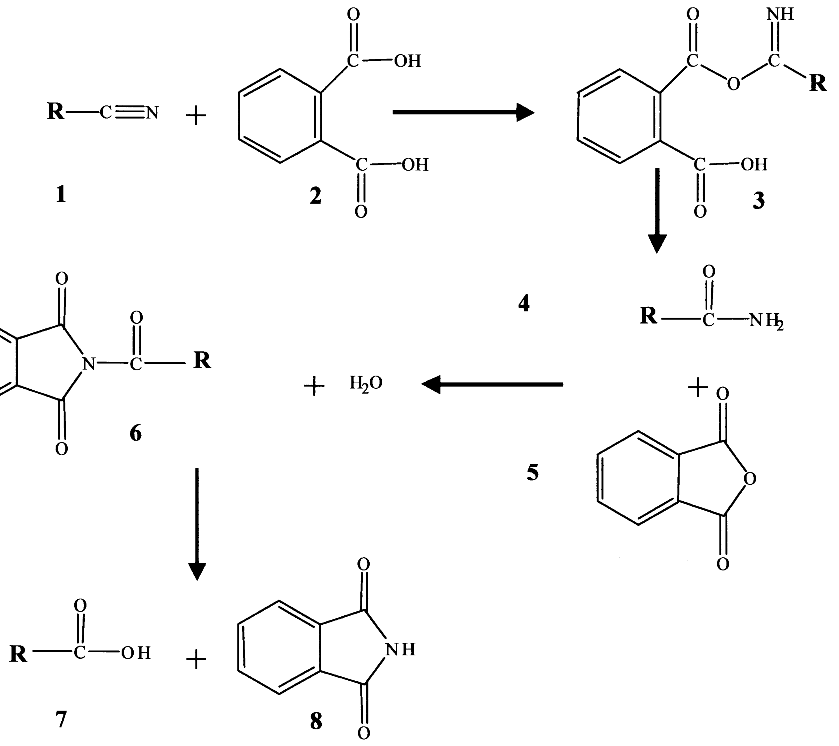

Scheme 1. Mechanism of the Mathews' 'dry' hydrolysis reaction.

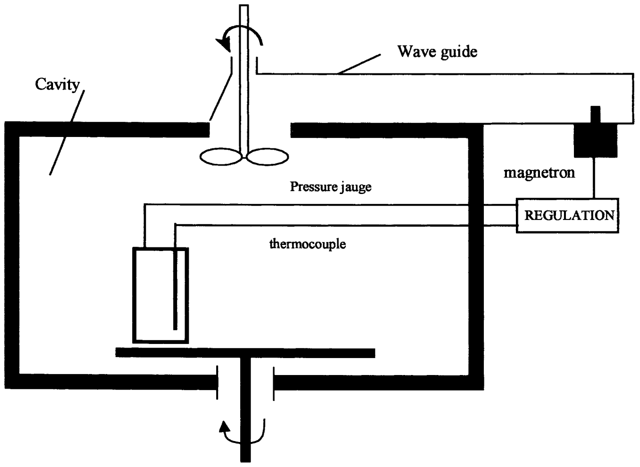

Figure 1. Microwave reactor suitable for organic preparations.

In order to gain more insight into this reaction, kinetic studies have been carried out. Our results fit with a second order kinetic equation: first partial order for both nitrile and phthalic acid. Activation energy and pre-exponential factor have been determined using the Arrhenius equation: $E_a = 35.6$ kJ/mole and $\ln A = 9.1$. 'Dry' hydrolysis of benzonitrile with phthalic acid is complete after 7 days at 140°C. The same reaction can be achieved after only 30 minutes at 250°C and 10 atm using microwave heating.

Microwave heating is used as a useful tool for preparative organic synthesis: reactions can be carried out in a closed Teflon vessel under monitored pressure and temperature. Higher temperatures could be attained with microwave heating which reduce reaction times in comparison with conventional reflux reaction conditions. Degradation reactions do not occur using microwave technology, enhancing yields and selectivity.[12,13]

The generally drastic conventional conditions of nitrile and amide hydrolysis lead to severe drawbacks with compounds containing sensitive functional groups. The method described here was tested as a possible alternative.[14–16] Since nitriles or amides are more difficult to hydrolyze than esters, chemo-selective hydrolysis of the former functionality is an attractive objective. Therefore an investigation was initiated with a series of bi-functional compounds (see Table 1). Fairly good yields are obtained simply by using microwave under mild reaction conditions.

In summary, an extremely simple method for the preparation of carboxylic acids and phthalimides has been rediscovered using microwave technology. The Mathews reaction allows the general, efficient, and chemo-selective hydrolysis of primary and secondary nitriles or amides to carboxylic acids. The reaction can be carried out in the absence of water, solvent, added acid or base even in the presence of an ester functionality.

Table 1. 'Dry' hydrolysis of nitriles **1** and amides **4** to carboxylic acids **7** (MW, 250°C; 10 atm)

R (name)	Reaction time (min)	Yield (%)	Selectivity (%)
Nitrile with phthalic acid			
PhCN (benzonitrile)	15	99	99
$PhCH_2CN$ (phenylacetonitrile)	30	99	99
$C_2H_5OOCCH_2CONH_2$ (ethyl cyanoacetate)	15	53	70
$HOPhCH_2CONH_2$ (*p*-hydroxyphenylacetonitrile)	30	92	96
$(C_3H_7)_2CHCN$ (valeronitrile)	30	98	99
Amide with phthalic anhydride			
$PhCONH_2$ (benzamide)	15	99	99
$PhCH_2CONH_2$ (phenylacetamide)	20	97	98
$PhOCH_2CONH_2$ (phenoxyacetamide)	30	79	90
$(C_3H_7)_2CHCONH_2$ (valeramide)	15	95	98
$(CH_3)_3CCONH_2$ (pivalamide)	15	96	98

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11. The intermediates **3** ($C_{15}H_{11}O_4N$; *m*/*z* 269) and **6** ($C_{15}H_9O_3N$; *m*/*z* 251) were detected by GC (HP 3690) with mass spectrometer detector (HP 1090). All the carboxylic acids prepared were compared with authentic samples.
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14. In a typical run, the nitrile (30 mmol) and phthalic acid (30 mmol) were introduced in the microwave reactor (Fig. 1), and heated under stirring. At the desired reaction time, the reactor was rapidly cooled down in a water/ice mixture, and chloroform (30 mL) is added. The mixture is stirred for 5 min, and the solid filtered off. The chloroform solution contains unreacted nitrile, amide and carboxylic acid. The residual solid contains unchanged phthalic acid, phthalic anhydride and phthalimide. The volume of the chloroform solution is adjusted to 50 mL and naphthalene is added as internal standard. The resulting solution is analyzed by GC/MS (Hewlett Packard 3690; QC BP20 capillary column, 25 m).
15. Milestone ETHOS 1600 batch reactor. The multimode microwave reactor has a twin magnetron (2×800 W, 2455 MHz) with a maximum delivered power of 1000 W in 10 W increments. A rotating microwave diffuser ensures homogeneous microwave distribution throughout the plasma coated PTFE cavity (35×35×35 cm). For experiments carried out in sealed vessels a 100 mL PFA reaction vessel contained in a single high-pressure HPR1000 rotor block segment was employed. During experiments, time, temperature, pressure, and power were monitored/controlled with the 'easy-WAVE' software package. Temperature was monitored with the aid of a shielded thermocouple (ATC-300) inserted directly into the corresponding reaction container. For experiments in sealed vessels a pressure sensor (APC-55) was additionally employed.
16. Nitriles, amides and their corresponding carboxylic acids were purchased from Janssen and Aldrich (99% purity) except for valeronitrile and valeramide, which were given by Sanofi.