

Reaction in water under microwave: rapid and convenient synthesis of N-hydroxymethylimides and N-hydroxymethyl lactams

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ABSTRACT

N-hydroxymethyl imides and N-hydroxymethyl lactams were obtained by the reaction of formaldehyde with imides or lactams in water under microwave irradiation (15 min., 240 W).

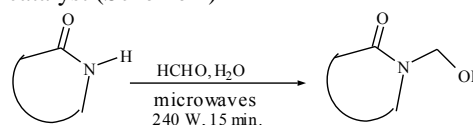
I. Introduction

Actually chemical synthesis employs large amounts of hazardous and toxic solvents. In last decade, there has been an incredible growth in research involving water as a green, environmentally benign replacement for a wide range of organic solvents.¹ The water is a no toxic, non-flammable, non-polluting and inexpensive solvent. It is an ideal solvent for synthesis on condition that the organic compound can be dissolved.² It has also a high dielectric constant so their molecules are very well activated under microwave irradiation.³

We have been interested in the synthesis of a series of related compounds belonging to the following families: the N-hydroxymethyl lactams and N-hydroxymethyl imides

We report herein the reaction of an aqueous formaldehyde solution under microwave irradiation for the transformation of amides into N-

hydroxymethyl lactams without use of any catalyst (Scheme 1)



Scheme 1: Synthesis of N-hydroxymethyl imide or N-hydroxymethyl lactam

Moreover the application of N-hydroxymethyl imides or N-hydroxymethyl lactams has been of great interest in the field of agropharmaceutical manufacturing (potential antipsychotic⁴, agents for modification of textile material⁵, precursor of surface-active ethers, in the synthesis of insecticides (tribenuron)⁶, proteolytic enzyme inhibitors and so on. They are also used in active energy-curable varnishes for coatings⁷, inks and adhesives for protecting wood surface,⁸ as corrosion inhibitors, and as flame-protection agents. Although, a large number of synthesis of these products is described, only few are really effective and generally, the assistance of catalysts is necessary.⁹

Previously, it has been reported the formation of aromatic hydroxymethyl imide by action of the paraformaldehyde on amides in DMF¹⁰, (the use of aqueous formaldehyde leads to very bad results). Unlike of our case, a kitchen microwave oven was used without reflux cooler, in these conditions, the formaldehyde formed escape quickly with the water and can't react sufficiently with the reagent. On the other part, the insufficient coupling with a multimode irradiator does not allow to obtain good and reproducible results with water.

In our case, the aqueous solution formed with formaldehyde and lactam or imide was irradiated under reflux with a microwave monomode irradiator. The main advantage of this procedure is to carry out reactions which would be impossible to do correctly in a kitchen microwave oven.

It is also possible to follow the rise in temperature in the reactor (use an infrared thermometer).

Reactional mixtures were irradiated for 15 minutes, but reaction is generally ended after 4-5 min. The curve of evolution of the temperature shows an inflection point followed by a landing temperature showing the end of the reaction. By cooling the reaction mixture, the products N-hydroxymethyl lactams crystallize. A further crystallization (for the solvent, see table 1) was not always necessary to obtain the pure product. The yield of the reaction was almost quantitative. Results with different imides and lactams are reported in the table 1.

The products obtained were characterised by their ¹H and ¹³CNMR spectra and their quantitative analysis.

In conclusion, the synthesis under focused microwave irradiation of N-hydroxymethyl imides or N-hydroxymethyl lactams is fast and efficient from a commercial available aqueous formaldehyde without the assistance of any catalyst.

II. Experimental part

Reactions were carried out with a monomode microwave irradiator Prolabo Synthwave 402 at 2450 MHz monitored by a microcomputer. The power of irradiation was fixed and the temperature was recorded in direct.

General procedure (N-hydroxymethylimide or N-hydroxymethyl lactam) ex: Phthalimide

In a quartz tube surmounted with a reflux cooler, the phthalimide (100 mmol) and an aqueous solution of formaldehyde (37%, 3 ml) were irradiated for 15 min with power 240 W. A homogeneous solution was obtained and by cooling, crystallised in a heap of colourless crystals. The product was recrystallised in a acetone Mp= 149°C (lit=149).

All N-hydroxymethylimides crystallised spontaneously. In the case of N-hydroxymethyl lactams, liquids were first obtained. The pyrrolidin-2-one derivative was crystallised in ethanol, in the case of the piperidin-2-one derivative, we have not obtained crystallisation.

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Table 1: Synthesis of N-hydroxymethylactams or N-hydroxymethylimides under microwave irradiation (15 min, 240 W).

Product Starting product		Yield (%)	mp °C Solvent	Mol formula	C	Found (required)% H
2a	phthalimide	98	149 (acetone)	C ₉ H ₇ NO ₃	60.97(61.02)	3.96(3.98)
2b	saccharin	97	125 (EtOH)	C ₈ H ₇ NO ₄ S	45.10(45.07)	3.27(3.31)
2c	maleimide	96	104-106 (EtOAc)	C ₅ H ₅ NO ₃	47.34(47.25)	4.03(3.97)
2d	succinimide	98	64-66 (EtOAc)	C ₅ H ₇ NO ₃	46.58(46.51)	5.51(5.46)
2e	pyrrolidin-2-one	88	82 (EtOH)	C ₅ H ₉ NO ₂	52.22(52.16)	7.82(7.88)
2f	piperidin -2-one	85	liquid	C ₆ H ₁₁ NO ₂	55.61(55.8)	8.68(8.58)

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