

[e008]



Solvent-free ring opening of ϵ -caprolactone with amines assisted by microwave irradiation

[Julio A. Seijas](#),* [M. Pilar Vázquez-Tato](#),* José Crecente-Campo, Lucía Gil-López, Ismael Roca
Departamento de Química Orgánica. Facultad de Ciencias. Universidad de Santiago de Compostela. Apto. 27080-Lugo. Spain

Abstract: Irradiation of ϵ -caprolactone with microwaves in the presence of secondary or primary amines lead to ϵ -hydroxyamides in good yields.

Introduction

Lactones constitute a widespread class of organic compounds, they are available from natural sources but the most important income is from industrial sources, in particular ϵ -caprolactone is an important industrial product. Most of the use for this lactone is the synthesis of polycaprolactones, which are employed in thermoplastic polyurethanes, resins for surface coatings, adhesives and synthetic leather and fabrics. They also make stiffeners for shoes and orthopedic splints. Other applications include biodegradable bottles and films; controlled release of drugs, pesticides and fertilizers. Their value lies in good water, oil, solvent and chlorine resistance; a particularly low melting point; and good adhesive properties. Their polymers are made by ring opening polymerization of ϵ -caprolactone monomer with alcohol initiators. Products vary in molecular weight from low molecular weight oligomers, for use in the polyurethane industry, up to high molecular weight thermoplastics.

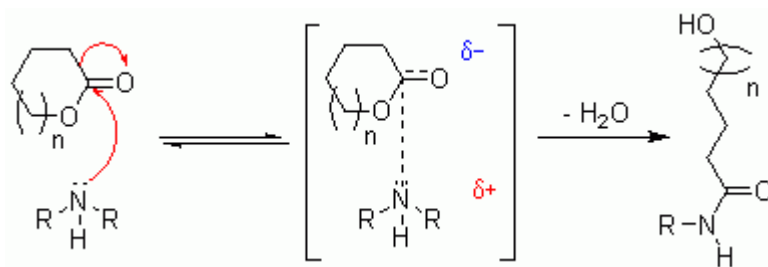
Microwave Assisted Organic Synthesis (MAOS) has shown to be a valuable tool for reducing reaction times, getting cleaner reactions, improving yields, simplifying work-up and designing energy-saving protocols. The increasing demand for clean and efficient "eco-friendly" chemical syntheses has focused general interest on solvent-free reactions which, when combined with microwave irradiation, have advantages from both economic and environmental standpoints.

Microwaves have been used to enhance the synthesis of polycaprolactone derivatives.¹ However to our knowledge, no studies were carried out to open caprolactone with amines assisted by microwaves in order to get simple amides. The aminolysis and alcoholysis of non-cyclic esters assisted by microwaves has been widely studied,^{2,3} meanwhile the opening of its cyclic analogues is an unexplored field that attracted our attention.

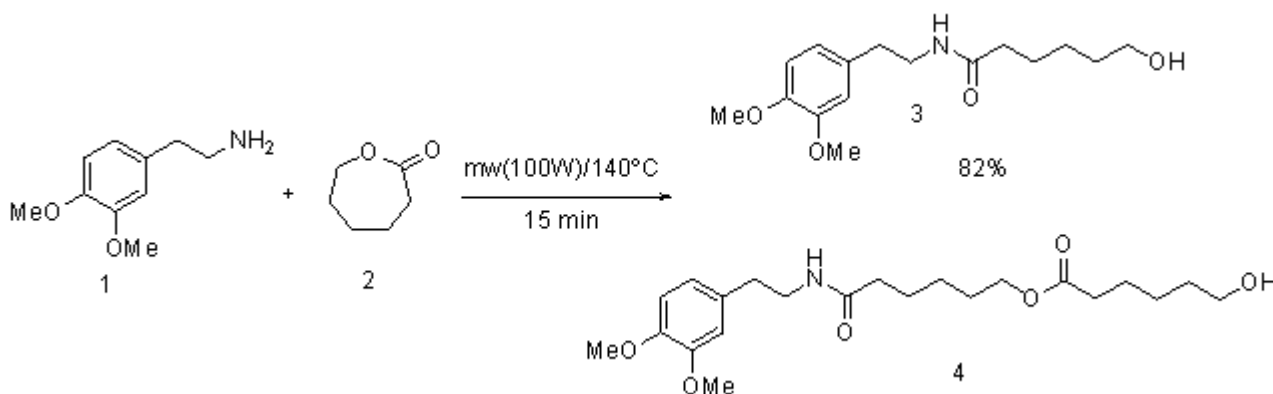
Results

It has been postulated that, the formation of polar transition states in the reaction mechanisms favours the action of microwave specific effects.³ Aminolysis of lactones occur through a polar intermediate (scheme 1), this feature

makes it a good candidate to be enhanced by microwaves.

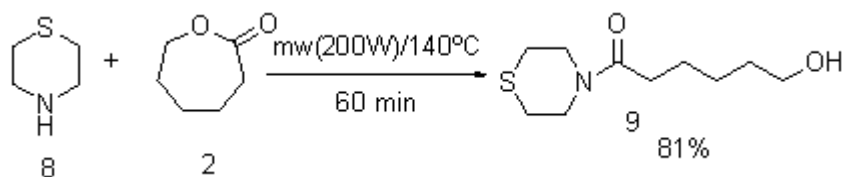


The presence of solvent in reactions irradiated by microwaves can mask the microwave effect. This together with the concern in green chemistry about avoiding waste generation and energy saving, led us to try the microwave assisted solvent-free organic synthesis (MASFOS) of amides by lactone ring opening. The established conditions to open ϵ -caprolactone with the primary amine homoveratrylamine (1:1 ratio) were heating at 140°C with an irradiation power of 100W, during 15 minutes to achieve 82% yield of amide **3**. The presence of a minority product **4** was detected, which after isolation showed to be the product of the reaction of the desired hydroxyamide with a second molecule of caprolactone (scheme 2)



The reactivity of secondary amines was studied by using morpholine. This amine was chosen because the expected reaction product was reported to have antimicrobial activity against *Microsporum canis*, *Microsporum gypseum*, *Trichophyton concentricum*, *Trichophyton mentagrophytes* var. *interdigitales*, *Trichophyton gallinae*, *Trichophyton rubrum*, and *Trichophyton tonsurans*,⁴ fungi of the group dermatophytes causing several kind of ringworm (*tinea*). The reaction of morpholine with ϵ -caprolactone, required a 2:1 ratio of amine:lactone to minimize the amount the secondary product: 6-morpholino-6-oxo-hexyl-6-hydroxyhexanoate (**7**). Under the same irradiation conditions than those used for primary amine and after 60 minutes of irradiation, the yield of **6** was 59% (scheme 3).

When thiomorpholine was used instead of morpholine the reaction yielded 81% of the desired hydroxyamide **9** (scheme 4).



In summary we present a method for aminolysis of ϵ -caprolactone, affording monomeric hydroxyamides in good yields. Currently we are studying the extension of this reaction to different lactones to achieve a simple and direct method for the synthesis of potential antimicrobials.

General procedure: In a closed vessel a mixture of ϵ -caprolactone (361 mg, 3.16 mmol) and homoveratrylamine (555 mg, 3.06 mmol) was irradiated for 15 minutes (CEM-Discover, 100W, 160°C, with a ramp-time of 1.5 minutes). The crude was purified by column chromatography (silica gel, CH₂Cl₂/MeOH 95:05) obtaining N-(3,4-dimethoxyphenethyl)-6-hydroxyhexanamide (**3**, 709 mg) in a 82% yield.

¹H-RMN (300 MHz, CDCl₃), δ : 6.70-6.56 (m, 3H, CH₃OCCHCH, CH₃OCCH), 6.31 (t, 1H, NH, J=5.5 Hz), 3.69 (s, 3H, OCH₃), 3.68 (s, 3H, OCH₃), 3.44 (t, 2H, CH₂NH, J=7.0 Hz), 3.31 (c, 3H, CH₂OH, J=7.0 Hz), 2.61 (t, 2H, PhCH₂, J=7.3 Hz), 2.01 (t, 2H, COCH₂, J=7.5 Hz), 1.50-1.38 (m, 4H, COCH₂CH₂CH₂CH₂), 1.25-1.18 (m, 2H, COCH₂CH₂CH₂).

¹³C-RMN (75 MHz, CDCl₃), δ : 173.7 (NHCO), 149.1 (COCH₃), 147.8 (COCH₃), 131.9 (CCH₂CH₂NH), 120.9 (CHCHCOCH₃), 112.4 (CHCOCH₃), 111.8 (CHCOCH₃), 62.1 (CH₂OH), 56.0 (CH₃O), 55.9 (CH₃O), 40.9 (NHCH₂), 36.0 (CH₂Ph), 35.2 (COCH₂), 32.1 (CH₂CH₂OH), 25.6 (COCH₂CH₂), 25.5 (OHCH₂CH₂).

EM m/z (%): 69 (7), 107 (6), 149 (13), 151 (21), 164 (M⁺, -NHCOCH₂CH₂CHOHCH₂CH₃, 100), 165 (14), 295 (M⁺, 1.5).

IR ν_{\max} (KBr, film): 3279 (OH), 2933, 2860, 1649 (OC-N), 1560, 1518, 1466, 1419, 1259, 1240, 1159, 1144, 1078, 1039, 1024.

Acknowledgements.

XUNTA DE GALICIA for financial support: PGIDIT05PXIB26201PR, PR405 A 098/59-0. USC for a predoctoral fellowship to JCC.

References

- 1 Li Liu, Yu Li, Yue-e Fang*, Liuxi Chen Carbohydrate Polymers 60 (2005) 351–356. L. Q. Liao, L. J. Liu, C. Zhang, F. He, R. X. Zhuo Journal of Applied Polymer Science, Vol. 90, 2657–2664 (2003). Hao Li, Liqiong Liao, Lijian Liu Macromol. Rapid Commun. 2007, 28, 411–416.
- 2.- Aaron B. Beeler,[†] Dayle E. Acquilano,[†] Qibin Su,[†] Feng Yan,[‡] Bryan L. Roth,[‡] James S. Panek, and John A. Porco, Jr. J. Comb. Chem. 2005, 7, 673-681. Carlo Mazzocchia a, Giovanni Modica a, Akim Kaddouri b,* , Roberto Nannicini c C. R. Chimie 7 (2004) 601–605.
- 3.-Laurence Perreux, Andre Loupy, and Michel Delmotte Tetrahedron 59 (2003) 2185–2189.
- 4.-Mod, R. R.; Skau, E.L.;Fore, S. P.; Magne, F. C. US patent 3285812, 1966.