

Microwave-Promoted Ring Opening Reaction of Azalactones

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Abstract: α -Dehydroamino amides are important intermediates for the synthesis of biologically active molecules. A rapid procedure is reported for the synthesis of α -dehydroamino amides from azalactones under MW radiation. Azalactones were produced via Erlenmeyer reaction and submitted to ring opening reactions under MW during 15-30 min. Over 90% yields were obtained.

Keywords: α -Dehydroamino amides, azalactones, ring opening, microwave irradiation.

INTRODUCTION

Cysteine proteases are ubiquitous enzymes in nature. In addition to their role in the metabolism of humans, e. g. as cathepsins [1], they are found in different protozoa and are related to the virulence of these parasites. Besides, they also play an important role in the polyprotein processing of different virus, for example the Corona Virus responsible for the Severe Acute Respiratory Syndrome (SARS) [2].

Cysteine proteases normally present a triad Asp-His-Cys that is responsible for increasing the nucleophilicity of the sulphur atom so playing a fundamental step in the mechanism of protein processing. However, the Corona Virus protease does not include the third catalytic residue, *i.e.*, this enzyme presents a dyad composed by His41 and Cys144. The nucleophilicity of the sulphur atom in cysteine proteases led many groups to try to design enzyme inhibitors containing epoxy [3] or Michael acceptors [4] groups, like α , β -unsaturated compounds. Based on this model, our group has designed and synthesized several dehydroamino acid derivatives in order to obtain peptide mimetics capable to inhibit selectively these enzymes [5].

Production of these compounds that have important pharmacological applications [6], will able us to produce (pseudo) peptides to be tested against corona viruses, *T. cruzi*, *P. falciparum*, *S. mansoni* and *Leishmania spp.* Model cysteine proteases, as papain and human cathepsins will be used to preliminary tests of these inhibitor candidates.

In recent years, the application of microwave-assisted reactions in organic synthesis has received considerable attention. Compared to conventional heating, microwave irradiation often gives enhanced reaction rates and less by products [7,8].

The classic method for azalactones ring opening requires more than 12 hours, in some cases under reflux temperature, to produce the corresponding dehydroamino amide [9,10].

Recently, the synthesis of azalactones [11] and other heterocyclic compounds [12] under MW irradiation has been reported in open vessels using acetic anhydride, which acts both as reagent and organic phase. However, few reports describe the use of this technology in the ring opening [13]. Our main objective was to use the MW technology to obtain some dehydroamino amides in shorter reaction times and with a simple work up procedure.

RESULTS AND DISCUSSION

Several 4-arylidene-2-Z-oxazol-5-ones (Z= CH₃ or Ph) were submitted to react to benzylamine in ethanol using triethylamine (TEA) as co-catalyst under microwave irradiation, as described in Scheme 1.

Preliminary studies of reaction of **1a** with benzylamine under several MW and reflux conditions were carried, Table 1 (entry 1-6), thus showing entry 4 as the best result. The azalactones ring opening tested upon MW irradiation occurred within few minutes, even for the compounds **1a** (entry 4 and 5) which had the reaction time dramatically reduced from more than 12 hours to 35 minutes and the product yield improved from 57 to 88%.

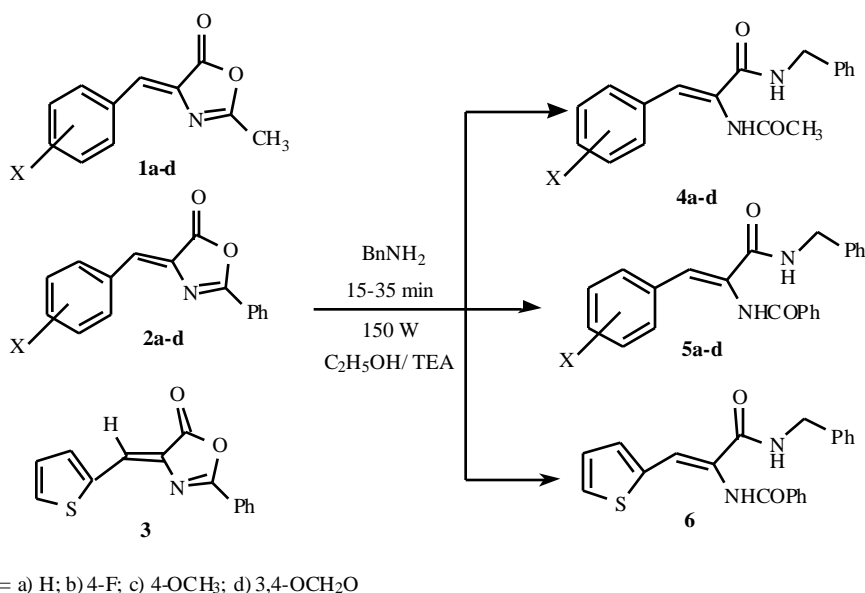
Then, optimal condition (entry 4) were evaluated for several azalactones, entries 7-15. The reaction media was selected based on the solubility of the azalactones. Although some azalactones are more soluble in methyl alcohol than ethanol, and other one only in dioxane, the use of ethanol and triethylamine was approved as a general reaction medium.

The discussion on the so-called microwave effect is now an old one. Microwave (MW) irradiation is a rapid way of achieving a desired temperature [14]. The reduction on reaction times are attributed to be a result of both temperature and pressure effects and possible modifications of activation parameters H and S [15].

CONCLUSION

The present methodology shows several advantages to those previously published mainly due to shorter reaction

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Scheme 1. Reaction path of ring opening by microwave irradiation.

times (entries 1-4; 7-10 and 12-15, comparing to those obtained by conventional method entries 5, 6 and 11) and an excellent approach for the safety and simple preparation of dehydroamino amides. Also, we observed that the product yields were higher than those reported using conventional methods. The present method is an important addition to microwave-assisted synthetic methodologies.

EXPERIMENTAL

Reactions were carried out with a single mode cavity Discover Microwave synthesizer (CEM Corporation, NC, USA) producing continuous irradiation at 2455 MHz and

infrared temperature control system. Microwave experiments were carried out in open vessels with an efficient magnetic stirring and reflux (which avoids all problems of non-homogeneity in temperature). Several catalyst were tested in order to achieve the best product yields and selectivity. The ratio support/substrate was previously optimized. A single-mode focused MW reactor was used to ensure reproducibility and a better control of the reaction parameters (power, temperature) and experiments were duplicated. Reactions were monitored by thin-layer chromatography (TLC; E. Merck, Type 5554 plates). FTIR spectra were acquired with Nicolet Magna-IR 760 equipment. Samples were analyzed using the KBr pellets, and frequencies are expressed in cm^{-1} .

Table 1. Azalactone Ring Opening

Entry	Method used	t (min)	T ($^{\circ}\text{C}$)	Product	Yield (%)
1	MW Al_2O_3 (0,5g)	30	110	4a	46
2	MW HTC (0,5g)	30	140	4a	21
3	MW $\text{C}_2\text{H}_5\text{OH}$ (5ml)	40	92	4a	81
4	MW $\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	35	84	4a	88
5	$\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	720	82	4a	57
6	$\text{C}_2\text{H}_5\text{OH}$	720	81	4a	45
7	MW $\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	30	85	4b	91
8	MW $\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	40	90	4c	86
9	MW $\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	35	85	4d	90
10	MW $\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	15	85	5a	97
11	$\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	1200	85	5a	77
12	MW $\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	15	85	5b	86
13	MW $\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	20	87	5c	80
14	MW $\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	20	84	5d	84
15	MW $\text{C}_2\text{H}_5\text{OH}/\text{NEt}_3$	15	81	6	98

Molar ratio substrate: BnNH_2 = 0.65:0.75; Power= 150W, HTC= hidrotalcite, (5mL/100 μL), decomposition

NMR spectra were recorded on a Fourier Transform Bruker AMX-200 spectrometer operating at 200 MHz (^1H) and 50 MHz (^{13}C), in specified solvents. Chemical shifts are reported in ppm () relative to tetramethylsilane. Proton and carbon spectra were typically obtained at room temperature. The two dimensional experiments were acquired using standard Bruker automated programs for data acquisition and processing. Yields were determined from isolated products.

Different azalactones (**1a-d**; **2a-d**; **3**) were prepared by known procedures [9] and used without any purification process for prepare the corresponding dehydroamino amides.

General Procedure for Preparation of α,β -Dehydroamino Amides (**4a-d**; **5a-d**; **6**) Under MW Irradiation

In a general manner, azalactone (2 mmol) was dissolved in ethanol/ NEt_3 (5mL/100 μL). This mixture was subjected to focused microwave irradiation at 150 W for the time and final temperature as indicated in Table 1. After that the solvent was evaporated at reduced pressure and all products were characterized by NMR, IR techniques and were measured the melting point to compare with those obtained by conventional methods. Configuration of ring opening products is the same of the parent azalactone, Z, as previously reported [16].

Z-2-Acetylamino-*N*-benzyl-3-phenyl-acrylamide (**4a**)

Yield: 57%, m.p. 139-140°C; $^1\text{H-NMR}$ (CDCl_3), $\delta(\text{ppm})$: 8,1 (1H, d, $J=8,0\text{Hz}$); 7,3 (10H, m); 4,8 (2H, s, CH_2); 2,2 (3H, s, CH_3); IR (KBr), $\nu(\text{cm}^{-1})$: 3407; 3086; 3051; 3032; 2999; 2980; 2917; 1717; 1645; 1557; 1494; 1405; 1242; 1138.

Z-2-Acetylamino-*N*-benzyl-3-(4-fluorophenyl-acrylamide) (**4b**)

Yield: 68 %, m.p.: 145-146°C; $^1\text{H-NMR}$ (DMSO-d_6), $\delta(\text{ppm})$: 8,6 (1H, d, $J=8,2\text{Hz}$); 9,4 (1H, s, NH); 7,7 (2H, q); 7,2 (3H, t); 2,0 (3H, s, CH_3); IV (KBr), $\nu(\text{cm}^{-1})$: 3290; 3070; 3043; 2991; 1643; 1603; 1589; 1502; 1409; 1226; 1196.

Z-2-Acetylamino-*N*-benzyl-3-(4-methoxyphenyl-acrylamide) (**4c**)

Yield: 72%, m.p.: 147-149°C; $^1\text{H-NMR}$ (DMSO-d_6), $\delta(\text{ppm})$: 9,3 (1H, s, NH); 8,3 (1H, d, NH); 7,6 (2H, d, $J=8,00\text{Hz}$); 7,2 (1H, s); 7,0 (2H, d, $J=8,00\text{Hz}$); 3,7 (3H, s, OCH_3); 2,0 (3H, s, CH_3); IV (KBr), $\nu(\text{cm}^{-1})$: 3286; 3068; 3008; 2979; 2941; 2910; 2844; 2586; 1637; 1603; 1530; 1508; 1259; 1178; 1028.

Z-2-Acetylamino-*N*-benzyl-3-(4-methylenedioxyphenyl-acrylamide) (**4d**)

Yield: 80%, m.p.: 192-193°C; $^1\text{H-NMR}$ (DMSO-d_6), $\delta(\text{ppm})$: 9,3 (1H, s, NH); 7,2 (3H, m); 6,9 (1H, d, $J=8,0\text{Hz}$); 6,0 (2H, s, CH_2); 2,0 (3H, s, CH_3); IV (KBr), $\nu(\text{cm}^{-1})$: 3500-2500; 3246; 2790; 1691; 1659; 1500; 1491; 1450; 1250-1033; 933.

N-((*Z*)-1-Benzylcarbamoyl-2-phenyl-vinyl)-benzamide (**5a**)

Yield: 77%, m.p.: 170-171°C; $^1\text{H-NMR}$ (CDCl_3), $\delta(\text{ppm})$: 8,5 (1H, d, NH); 7,8 (1H, d, NH, $J=6,0\text{Hz}$); 7,3 (14H); 6,90 (1H, s); 4,4 (2H, d, CH_2 , $J=6,0\text{Hz}$); IR (KBr), $\nu(\text{cm}^{-1})$: 3219, 3056, 3029; 2923; 1638; 1603; 1578; 1515; 1479; 1278.

N-[(*Z*)-1-Benzylcarbamoyl-2-(4-fluoro-phenyl)-vinyl]-benzamide (**5b**)

Yield: 45%, m.p.: 175-178°C; $^1\text{H-NMR}$ (CDCl_3), $\delta(\text{ppm})$: 8,4 (1H, s, NH); 7,7 (2H, d, $J=7,2\text{ Hz}$); 7,3 (10H, m); 6,8 (2H, t, $J=8,5\text{ Hz}$); 6,7 (1H, s); 4,3 (2H, d, CH_2 , $J=4,6\text{ Hz}$); IR (KBr), $\nu(\text{cm}^{-1})$: 3251; 3061; 3029; 2955; 2921; 1665; 1642; 1602-1484; 1228; 1156.

N-[(*Z*)-1-Benzylcarbamoyl-2-(4-methoxy-phenyl)-vinyl]-benzamide (**5c**)

Yield: 68%, m.p.: 159-161°C; $^1\text{H-NMR}$ (DMSO-d_6), $\delta(\text{ppm})$: 9,9 (1H, s, NH); 8,0 (2H, d, $J=8,0\text{Hz}$); 7,7 (2H, d, $J=8,0\text{Hz}$); 7,6 (3H, t, $J=8,0\text{Hz}$ e $6,0\text{Hz}$); 7,5 (1H, s); 3,7 (3H, s, CH_3); IV (KBr), $\nu(\text{cm}^{-1})$: 3240, 3033; 1694; 1649; 1254; 1174.

N-[(*Z*)-1-Benzylcarbamoyl-2-(4-methylenedioxy-phenyl)-vinyl]-benzamide (**5d**)

Yield: 76% m.p.: 161-163°C; $^1\text{H-NMR}$ (DMSO-d_6), $\delta(\text{ppm})$: 9,8 (1H, s, NH); 8,0 (2H, d, $J=8,00\text{Hz}$); 7,5 (3H, m); 7,4 (1H, s); 7,3 (1H, s); 7,2 (1H, d, $J=8,00\text{Hz}$); 6,9 (1H, d, $J=8,00\text{Hz}$); 6,0 (2H, s, $\text{O-CH}_2\text{-O}$); IV (KBr), $\nu(\text{cm}^{-1})$: 3074; 3032; 2952; 2908; 2798; 1695; 1641; 1598; 1502; 1447; 1263; 1247; 1155; 1037; 929.

N-((*Z*)-1-Benzylcarbamoyl-2-thiophen-2-yl-vinyl)-benzamide (**6**)

Yield: 76%, m.p.: 130-135°C; $^1\text{H-NMR}$ (DMSO-d_6), $\delta(\text{ppm})$: 8,4 (1H, s, NH); 8,0 (2H, d, $J=6,0\text{Hz}$); 7,5 (3H, m); 7,4 (8H, m); 7,0 (2H, s); 5,1 (1H, q, CH, $J=6,0\text{Hz}$); 4,3 (2H, s, CH_2); IR (KBr), $\nu(\text{cm}^{-1})$: 3230, 3060, 3027, 2976, 2929, 1651, 1619, 1579, 1516, 1477, 1446, 1346, 1280, 1215, 1126, 698.

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