

The first example of macrolactonization of ω -hydroxy acids catalyzed by calcined Mg–Al hydrotalcite

Jorge Cárdenas,^{1*} José Antonio Morales-Serna,¹ Ericka Sánchez,¹ Rubén Gaviño,¹
Leticia Lomas,² Nahí Guerra,³ and Guillermo Negrón^{3*}

Instituto de Química, ¹ Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México D. F., México

Departamento de Química ² and Departamento de Ciencias Básicas³, UAM, Av. San Pablo No 180, C.P. 02200, México D. F., México

E-mail: rjcp@servidor.unam.mx and gns@correo.azc.uam.mx

Dedicated to Professor Eusebio Juaristi on the occasion of his 55th birthday

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Abstract

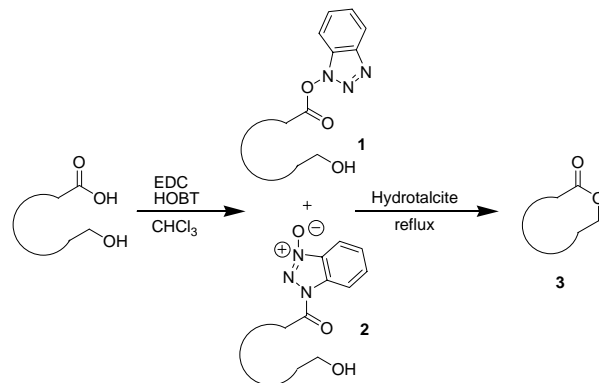
Calcined Mg–Al Hydrotalcites $x = 0.20, 0.27, 0.33$ proved effective catalysts for the lactonization of 10, 12, 15, and 16 hydroxy acid benzotriazole esters to their correspondent macrolactones. This new methodology was used for the lactonization step in the synthesis of Sansalvamide A.

Keywords: Hydrotalcite, macrolactonization, EDC, hydroxybenzotriazole, Sansalvamide A

Introduction

Macrolactones¹ can be prepared indirectly in very good yields by intramolecular condensation of the ω -hydroxy acids.² A very practical method for macrolactonization was described by E. P. Boden and G. E. Keck,³ who used DCC, DMAP, and DMAP·HCl to inhibit the formation of N-acylurea in the Steglich esterification.⁴ Recently, our group developed an efficient macrolactonization protocol using benzotriazole esters and DMAP.⁵ This paper presents a new protocol based on the use of synthetic hydrotalcites $[M^{2+}_{1-x}M^{3+}_x(OH)_2]^{x+}[A^{n-}_{x/n}\cdot mH_2O]^{x-}$, which are hydrated aluminium-magnesium hydroxides of lamellar structure, in which the excess of positive charge, originated from the Mg^{2+} to Al^{3+} substitution, is compensated by carbonate anions in the interlayer space. In these compounds, also known as anionic clays, the layers are built up by condensation of MO_6 ($M = Mg^{2+}$ or Al^{3+}) octahedral as in brucite $[Mg(OH)_2]$. Therefore, hydrotalcite (HT) has OH groups that are shared by three octahedral cations and point to the interlayer space.⁶ Calcinated hydrotalcites induce dehydration, dehydroxylation, and loss of the charge compensating anions, resulting in mixed oxides with MgO-type structures. These

materials have basic properties and can be used instead of the classic base catalysts, needed for the reaction to take place, due to the following advantages: ease of separation of the products, reduction of waste streams, possible regeneration of the catalyst and low cost. These catalysts are very active and have been used for the Knoevenagel condensation of aldehydes,⁷ syntheses of chalcones and flavones,⁸ alkylation of phenol,⁹ condensation of formaldehyde and acetaldehyde,¹⁰ selective methylation of aniline and cathecol,¹¹ cyanosilylation of carbonyl compounds,¹² syntheses of silylated azidohydrins,¹³ etc.

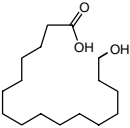

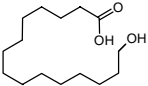
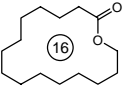
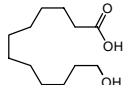
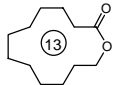
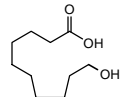
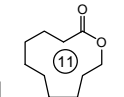


Scheme 1. General macrolactonization reaction.

Results and Discussion

As a part of our on going research program on the utilization of hydrotalcites for organic syntheses, we describe a novel and efficient lactonization procedure for ω -hydroxy acid benzotriazole esters using AlMgCO₃-HT with different Mg²⁺/Al³⁺ ratios. It is well known that the use of hydroxybenzotriazole (HOBT) avoids N-acylurea formation and generates active esters **1** and **2** (Scheme 1) *in situ*. Hydrotalcite is used taking into consideration that the basicity of the calcined product can be modified changing the ratio Al:(Al+Mg) ratios (x) of 0.20, 0.27 and 0.33. Hydrotalcites with these ratios were individually prepared, characterized, calcined and used. When the Aldrich Hydrotalcite was used, the lactonization was not fully accomplished. Mg-Al hydrotalcites substituted the classic DMAP base commonly used to form the corresponding macrolactone **3** and the dimer from benzotriazole esters **1** and **2**. This is the first time a macrolactonization has been catalyzed by modified Mg-Al hydrotalcites. The corresponding macrolactones were formed in good yields. GC-MS analyses showed that intramolecular reactions predominated over the intermolecular ones, avoiding the formation of dimers (Table 1).

Table 1. Isolated yield of lactones from ω -hydroxy acid, calcined Mg-Al Hydrotalcite $x = 0.33$

Acid	Ring Size	Macrolide yield ^a (%)	Diolide yield ^a (%)	Macrolide yield ^b (%)	Diolide yield ^b (%)
	3a 	94	-	93	-
	3b 	96	-	96	-
	3c 	76	-	38	12
	3d 	73	9	29	13

^a High dilution. Isolated yield.

^b Low dilution. Yields of a variety of macrolactones and dimers were determined by GC-MS (C. I.), compared with authentic samples prepared in the laboratory or obtained as commercial products.

The M^{2+}/M^{3+} ions ratio can be varied within a limited range. In the case of Mg-Al HT, the lower limit is an atomic ratio of 2/1. Under this value, Al^{3+} is present in a neighboring octahedral structure resulting in the formation of $Al(OH)_3$. Over a ratio of 3/1, the high population of Mg in this octahedral structure can act as the nucleus in the formation of brucite.

The x values do not influence the chemical yield since the same percentages are obtained using $x = 0.20$, 0.27 , and 0.33 . Recognizing the potential utility of this mild method for the synthesis of macrolactones, we decided to study the scope of this reaction. Thus, we used our calcined hydrotalcite Mg-Al, $x = 0.33$, as the basic catalyst, instead of DMAP in the crucial last step of the cyclization of ω -hydroxyacid¹⁴ (**4**) for the total synthesis of cyclodepsipeptide¹⁵ Sansalvamide A, described by our group⁵ with similar yields and a more simplified work-up (Scheme 2). When the reaction was carried out using commercial hydrotalcite no lactones were obtained. The cyclization did not take place and the only products obtained were intermediaries **1** and **2**. The end product, **5**, was characterized by spectroscopic means. The data obtained is in agreement with those described in literature. There is no presence of epimers, acylureas or dimers.

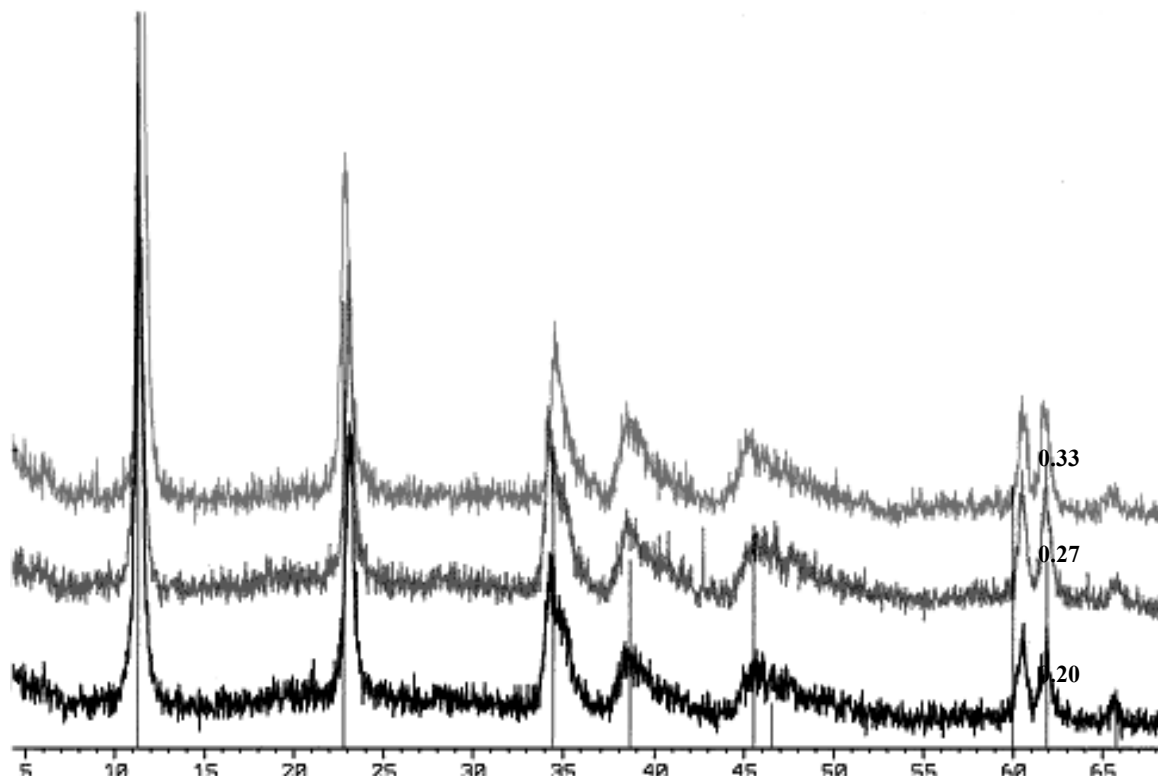
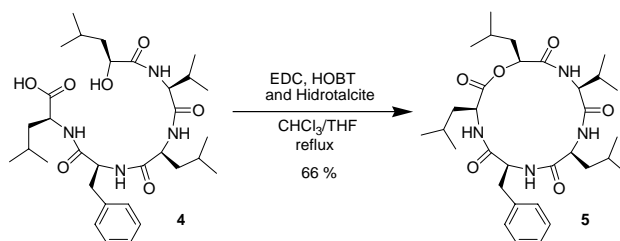


Figure 1. X-ray diffraction patterns of hydrotalcites Mg-Al with $x = \text{Al} / (\text{Al} + \text{Mg}) = 0.20, 0.27$ and 0.33 are shown; these materials show a crystalline hydrotalcite pattern, indicating the formation of these compounds.



Scheme 2. Macrolactonization of Sansalvamide A.

In summary, we have described an efficient method for the preparation of macrolactones from ω -hydroxy acids using EDC, HOBT and Hydrotalcites. This simple and mild methodology could constitute an attractive alternative for the formation of complex molecules such as Sansalvamide A. The macrolactonization protocol described here afforded large size lactones **3a** and **3b** in good yields at high or low dilution procedures. Medium size lactones **3c** and **3d** were obtained with the correspondent dilactones as by products, these dimers were obtained in lower yields than those reported for other methodologies. It can be inferred that these results are due to

the fact that following our methodology the cyclization takes place on the catalyst surface, which favors the intramolecular rather than the intermolecular reaction.

Experimental Section

Preparation of hydrotalcite catalysts. General procedure

Hydrotalcites Mg-Al with $x = \text{Al}/(\text{Al} + \text{Mg})$ ratios of 0.20, 0.27 and 0.33 were prepared by coprecipitation following the procedure described by Reichle.¹⁶ $\text{Mg}_{10}\text{Al}_2(\text{OH})_{24}\text{CO}_3 \cdot 6\text{H}_2\text{O}$: $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (0.01 mol) and $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (0.05 mol) were dissolved in deionized water (70 mL). A second deionized water solution (100 mL) of Na_2CO_3 (0.1 mol) and NaOH (0.35 mol) was prepared. The first solution was slowly added to the second one. The resulting mixture was heated at 338 K with vigorous stirring for 18 h. After the heating period, the slurry was cooled to room temperature, washed with deionized water until $\text{pH} \approx 9$ and dried at 383 K for 18 h. Hydrotalcites were activated by calcination at a rate of 2 °C/min up to 773 K and maintained for 2 h in a flow of air. Samples were then cooled in dry nitrogen and stored.

All hydrotalcites samples were characterized by powder XRD with Cu- K_α radiation, using a Siemens diffractometer in the range from 4 to 70° (2 Theta). FT-IR spectra were recorded on a Nicolet Magna 750 spectrometer, data collection was performed using DRIFT and KBr disc techniques. DTA and TGA analyses were carried out in a Dupont thermobalance, using He flow at a heating rate of 10°C/min. Specific surface areas were calculated by N_2 adsorption at 75.25 K (BET method) using a Micromeritics ASAP 2000 instrument, the samples were first out gassed at 523 K. Methyl 10-hydroxydecanoate, 12-hydroxydodecanoic acid, pentadecanolide and 16-hydroxyhexadecanoic acid were purchased from Aldrich Chemical Company. Hydrolysis of the esters with KOH in methanol afforded 10-hydroxydecanoic acid and 15-hydroxypentadecanoic acid. The products of the macrolactonization reactions were determined and analyzed by means of a Hewlett Packard GC/MS system 5890 / 5972 gas chromatograph with an HP-5 column, 70 - 270°C (5°C / min), Inj. 250°C, Det. 280°C. These products were determined by comparison with the standard mass spectrometry of organic compounds, and fragmentation patterns. ¹H NMR spectra were measured on a Varian UNITY-300 spectrometer. Chemical shifts are reported in parts per million (δ) with tetramethylsilane as the internal standard, coupling constants in Hz. Infrared (IR) spectra were recorded on a Nicolet 5-SX FT IR spectrophotometer. High resolution mass spectra were obtained in a JEOL JMS-SX102A mass spectrometer.

Preparation of macrolactones, low dilution procedure

A solution of HOBT (90 mg, 0.59 mmol), EDC (105 mg, 0.55 mmol), 16-hydroxyhexadecanoic acid (136 mg, 0.5 mmol) and Hydrotalcite (200 mg) in ethanol-free chloroform (20 mL) was brought to reflux for 18 h. The reaction mixture was cooled to room temperature. The mixture was concentrated and diluted with ether (30 mL), the hydrotalcite and urea were separated by filtration. The filtrate was concentrated under reduced pressure, diluted with ethyl acetate

(75 mL), washed with 10% citric acid solution (25 mL), 10% K₂CO₃ solution (1X25 mL), brine, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified through a silica gel column chromatography (25X1.5 cm). Elution was carried out with hexane and then with 3% THF-hexane. In this way, hexadecalactone was obtained (**3a**). mp 48 °C: IR (KBr) 2920, 2849, 1733 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.31 (m, 22H), 1.62 (m, 4H), 2.33 (t, J= 6.4 Hz, 2H), 4.12 (t, J= 5.6 Hz, 2H). CIMS: m/z 283 [M+29] (20), 255 [M+1] (100), 253 (36), 237 (50), 219 (13), 171 (9), 157 (8), 143 (6).

3b. mp 34 °C: IR (KBr) 2923, 2850, 1732, 1457, 1164 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.32 (br s, 20H), 1.66 (m, 4H), 2.33 (t, J= 6.6 Hz, 2H), 4.13 (dd, J= 5.6, 5.2 Hz, 2H). CIMS: m/z 269 [M+29] (16), 241 [M+1] (100), 223 (54), 205 (18), 185 (5), 171 (6), 157 (7), 143 (7), 139 (7).

3c mp 40 °C: IR (KBr) 2916, 2846, 1727, 1272, 1107 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.28 (m, 14H), 1.58 (m, 4H), 2.31 (t, J= 6.8 Hz, 2H), 4.12 (t, J= 5.8 Hz, 2H). CIMS: m/z 227 [M+29] (65), 199 [M+1] (71), 181 (100), 163 (37), 143 (6) 143 (5), 139 (5), 97 (10).

3c dimer. CIMS: m/z 425 [M+29] (7), 397 [M+1] (100), 379 (40), 361 (5), 199 (9), 181 (15).

3d. mp 47 °C: IR (KBr) 2916, 2846, 1726, 1271, 1107 cm⁻¹. ¹H NMR (200 MHz, CDCl₃): δ 1.30 (s, 10H), 1.57 (m, 4H), 2.31 (t, J= 6.8 Hz, 2H), 4.13 (t, J= 5.6 Hz, 2H). CIMS: m/z 199 [M+29] (49), 171 [M+1] (45), 153 (100), 135 (29), 111 (7), 171 (9), 157 (8), 143 (6).

3d dimer. CIMS: m/z 369 [M+29] (7), 341 [M+1] (100), 323 (83), 305 (7), 199 (4), 171 (16), 153 (22), 135 (5).

Preparation of macrolactones, high dilution procedure

A solution of HOBT (30 mg, 0.20 mmol), EDC (38 mg, 0.20 mmol) and Hydrotalcite (200 mg) in ethanol-free chloroform (50 mL) was brought to reflux. Then a solution of ω-hydroxy acid **4** (100 mg, 0.16 mmol) in 10 mL of THF was infused via syringe pump for 18 h. After addition was completed, the syringe apparatus was removed and the reaction mixture was cooled to room temperature. The mixture was concentrated and diluted with ether (30 mL) and the hydrotalcite and urea were separated by filtration. The filtrate was concentrated under reduced pressure, diluted with ethyl acetate (75 mL), washed with 10% citric acid solution (1X25 mL), 10% K₂CO₃ solution (1X25 mL), brine, dried over Na₂SO₄ and concentrated under vacuum. The crude product was purified through a silica gel column chromatography (25X1.5 cm). Elution was carried out with hexane and then with 70% ethyl acetate-hexane. In this way, Sansalvamide A (**5**) was obtained as white solid, mp 143-145 °C, 64 mg, 66%. IR (Pellet/KBr): 3397, 3277, 2963, 2934, 2873, 1746, 1665, 1533, 1467, 1372, 1276, 1053 cm⁻¹. ¹H NMR (CD₃OD): δ 0.81 (d, J=6.6 Hz, 3H), 0.85 (d, J=6.6 Hz, 3H), 0.86 (d, J=6.6 Hz, 3H), 0.92 (d, J=6.6 Hz, 3H), 0.96 (d, J=6.6 Hz, 6H), 0.99 (d, J=6.6 Hz, 6H), 1.38-1.88 (m, 9H), 2.07 (oct, J=6.6 Hz, 1H), 3.08 (dd, J=13.8, 10.8 Hz, 1H), 3.24 (dd, J=13.8, 4.8 Hz, 1H), 3.72 (dd, J=9, 5.1 Hz, 1H), 4.09 (d, J=8.4 Hz, 1H), 4.55 (dd, J=10.8, 4.8 Hz, 1H), 4.71 (dd, J=9.6, 5.7 Hz, 1H), 5.6 (dd, J=9, 4.8 Hz, 1H), 7.28-7.23 (m, 5H). ¹³C NMR (CD₃OD): δ 18.7, 19.9, 22.1, 22.4, 23.1, 23.3, 23.5, 25.9, 26.1, 26.2, 32.1, 38, 39.6, 41.3, 41.7, 52.5, 56.4, 58.1, 60.6, 76.3, 128, 129.7, 130.2, 138.7, 171.4, 172.8, 173.6, 174.01, 174.09; HRMS (FAB) calcd for C₃₂H₅₁O₆N₄ 587.3809, found 587.3812.

Acknowledgements

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14. **O-LeuValLeuPheLeuOH (4)**. White solid (91 %). IR (Pellet/KBr): 3286, 3084, 2959, 2931, 2872, 1720, 1642, 1549, 697 cm⁻¹. ¹H NMR (CDCl₃): δ 0.70 (d, J=6.6 Hz, 3H), 0.75 (d, J=6.6 Hz, 3H), 0.78 (d, J=6.6 Hz, 3H), 0.82 (d, J=6.6 Hz, 3H), 0.83 (d, J=6.6 Hz, 6H), 0.84 (d, J=6.6 Hz, 6H), 1.32-1.52 (m, 5H), 1.59 (m, 3H), 1.73 (m, 1H), 1.89 (m, 1H), 2.79 (dd, J=14.1, 8.7 Hz, 1H), 3.02 (dd, J=14.1, 4.8 Hz, 1H), 3.85 (td, J=9, 4.2 Hz, 1H), 4.17 (dd, J=9, 2.7 Hz, 1H), 4.26 (ddd, J=7.8, 6.9, 6.6 Hz, 1H), 4.54 (td, J=8.4, 4.8 Hz, 1H), 7.23-7.14 (m, 5H), 7.5 (d, J=9 Hz, 1H), 7.9 (d, J=8.1 Hz, 1H), 8.00 (d, J=7.8 Hz, 1H), 8.12 (d, J=8.4 Hz, 1H) ppm. ¹³C NMR (CDCl₃): δ 17.7, 19.2, 21.5, 21.7, 22.9, 23.4, 24, 24.1, 24.2, 31.3,

- 37.2, 40.6, 40.9, 43.7, 50.7, 51.1, 53.2, 56.4, 69.7, 126.2, 128, 129.2, 137.6, 170.5, 171.5, 174.2, 174.4 ppm. HRMS (FAB) calcd for $C_{32}H_{53}O_7N_4$ 605.3914, found 605.3906.
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