ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Article

Microwave-Assisted Hydrolysis of Ethyl Azolylacetates and Cinnamates with K_2CO_3: Synthesis of Potassium Carboxylates

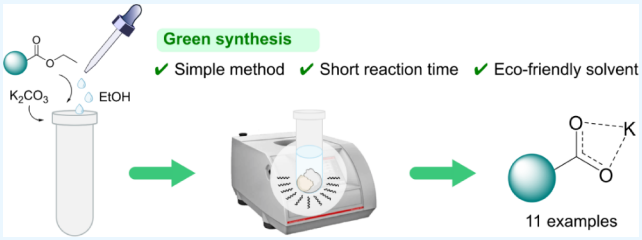
Jorge Hernández-Fernández, Norma Tiempos-Flores, Mario Ordóñez, Verónica M. Rivas-Galindo, Susana López-Cortina, Katia Guadalupe García-Alvarez, and Eugenio Hernández-Fernández*

Cite This: *ACS Omega* 2024, 9, 40783−40789

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: In this study, the hydrolysis of ethyl azolylacetates and ethyl cinnamates using K_2CO_3/ethanol under microwave irradiation was developed. For this purpose, ethyl azolylacetates were first synthesized by nucleophilic substitution between the corresponding azole and ethyl bromoacetate under sonication at 50 °C for 3 h, yielding derivatives with 10−92% chemical yields, while ethyl cinnamates were obtained by a microwave-assisted Horner−Wadsworth−Emmons (HWE) reaction of triethyl phosphonoacetate with a variety of aryl aldehydes at 140 °C for 20 min, yielding derivatives with moderate to high yields (67−98%). Initially, the optimization of the hydrolysis reaction was performed using ethyl pyrazolylacetate as a model starting material while varying the temperature, time, and base equivalents; the best results were achieved by carrying out the reaction at 180 °C for 20 min with 3.0 eq of K_2CO_3. This simple and greener method facilitated the synthesis of potassium carboxylates in moderate to high yields, 80−98% for azolyl derivatives and 73−98% for cinnamate derivatives. The structures of all potassium carboxylates were confirmed by FTIR, ^{1}H, ^{13}C NMR, and HRMS.



1. INTRODUCTION

Organic chemistry has remarkably contributed to the development of novel compounds with unique properties that make them useful for all types of applications and fields, including biology, medicinal chemistry, engineering, materials science, among others.[1] In this context, one of the primary goals of organic synthesis research is the design of more effective synthetic routes and more environmentally friendly methodologies in response to increasing environmental concerns over the last few decades.[2] As such, the discovery of microwave-assisted organic synthesis (MAOS) has led to enhanced chemical reactions under milder conditions, achieving drastic acceleration of reaction rates, lower energy costs, cleaner reactions, improved yields, and has even opened the opportunity to conduct solvent-free reactions.[3−8]

Surprisingly, ester hydrolysis is a fundamental transformation in organic synthesis whose acid- and base-catalyzed methodology under prolonged reflux has barely changed over the last century. Instead, various studies of enzyme-catalyzed[9,10] and neutral hydrolysis[11] have been developed, and in the previous decades, adapted to microwave-assisted methods leading to enhanced yields and lower reaction times.[12−14] Nonetheless, these methods exhibit substantial challenges; enzyme-catalyzed hydrolysis is restricted by narrow substrate specificity[15] and lack of enzyme stability under working conditions,[16] while neutral hydrolysis is limited to slow reaction rates,[17] lack of general applicability[14] or requires specialized catalysts.[18] In this context, efficiently obtaining carboxylic acids and carboxylates holds significant interest due to their synthetic and practical value. Carboxylic acids are widely used in the production of diverse kinds of compounds, including polymers, pharmaceuticals, solvents, and food additives. Moreover, they frequently serve as key intermediates in the synthesis of several important heterocompounds, such as amides,[19,20] oxadiazoles,[21,22] oxazolines,[23] benzothiazoles,[24] and other derivatives with biological interest.[25] On the other hand, carboxylates are usually used to form complexes. Currently, there is a high level of interest in carboxylate complexes because they are highly promising candidates in organic catalysis[26−28] and mimic metallo-enzymes.[29]

Therefore, achieving a general and effective method for the eco-friendly hydrolysis of esters using alternative energy sources such as microwave irradiation has remained a pressing goal. Currently, base-catalyzed hydrolysis predominates over other methods of hydrolysis for many organic compounds[30] (Table 1). Accordingly, we report a microwave-assisted hydrolysis method of ethyl azolylacetates and ethyl cinnamic esters to obtain their corresponding carboxylates through a very simple procedure using potassium carbonate.

Received: June 14, 2024
Revised: August 30, 2024
Accepted: September 5, 2024
Published: September 17, 2024

Table 1. Examples of Catalysts Used in Acid-, Base-, Neutral-, and Enzyme-Catalyzed Ester Hydrolysis[a]

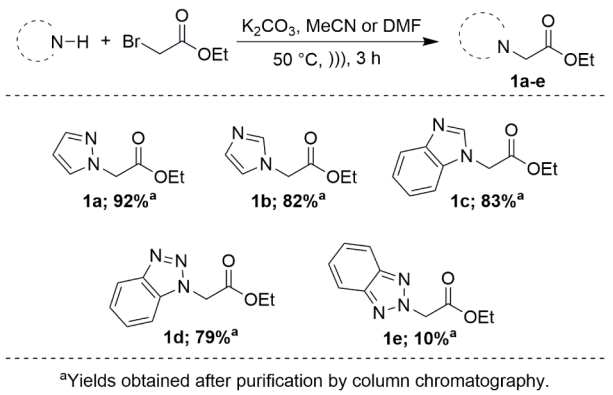
Catalyst	Amount of catalyst	Ester(s)	Reaction conditions	Yield (%)	Ref.
Sulfonated naphthalene-based solid acid	3% (w/w)	Methyl acetate	55 °C, 4 h	37	Fu Z. et al.[31]
KOH	5% (w/v)	Ethyl azolyl esters	Reflux, 1 h	34−35	El-Kardocy A. et al.[32]
KOH	10% (w/v)	Ethyl quinolinyl esters	MW, 90−100 °C, 15 min	ND-97	Malvacio I. *et al.* [33]
LiCl-DMF	5.0 eq.	Methyl esters	MW, 150−160 °C, 10 min	29−99	Wu X. A. *et al.* [13]
Zn-based polymeric NPs	15 μM	Aryl and alkyl esters	40 °C, 4 h	18−99	Arifuzzaman MD. et al.[18]
Carboxylesterase NPs	16 μM	Aryl and alkyl esters	40 °C, 10 min, 28 h	0−95	Smeets J. W. H. et al.[34]
Lipase (Lipozyme RM IM)	3.5 eq.	Methyl phenoxyl ester	MW, 45 °C, 4 h	97	Bevilaqua J. V. et al.[35]
K_2CO_3/EtOH	3.0 eq.	Ethyl azolyl and cinnamic esters	MW, 180 °C, 20 min	73−98	This work

[a]ND = hydrolysis product not detected.

2. RESULTS AND DISCUSSION

In order to have a representative group of ethyl azolylacetates and ethyl cinnamates, initially we prepared the azolylacetates **1a−e** by applying the methodology developed by our research group using ultrasonic energy.[36] For this purpose, ethyl bromoacetate and different azole compounds (pyrazole, imidazole, benzimidazole, and benzotriazole) were reacted in the presence of K_2CO_3 in CH_3CN or DMF, to give the ethyl azolylacetates **1a−c** with moderate to high yields (82−92%). Lower yields were obtained when benzotriazole was used, which afforded a mixture of regioisomers **1d** and **1e** in 79% and 10% yield, respectively (Scheme 1).

Scheme 1. Preparation of Ethyl Azolylacetates 1a−e



[a]Yields obtained after purification by column chromatography.

On the other hand, to obtain ethyl cinnamates **2a−f**, a Horner−Wadsworth−Emmons reaction (HWE) was performed between triethyl phosphonoacetate and commercially available aryl aldehydes such as benzaldehyde, 4-fluorobenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-methoxybenzaldehyde, and 4-nitrobenzaldehyde using K_2CO_3 in ethanol under microwave irradiation at 140 °C for 20 min. After column chromatography purification, ethyl cinnamates **2a−f** were obtained in yields ranging from 67% to 98% (Scheme 2). The highest yields were obtained when benzaldehyde, 4-fluorobenzaldehyde, 4-bromobenzaldehyde, and 4-nitrobenzaldehyde (88−98%) were used; the lowest yields were obtained for compounds **2c** and **2e**, using 4-chloro- and 4-methoxybenzaldehyde, respectively. These results were in agreement with those described in the literature, and spectroscopic data (^{1}H and ^{13}C NMR) of known ethyl azolylacetates[6,36] and ethyl cinnamates[37−39] were further compared to confirm their structures.

After ethyl azolylacetates **1a−e** and ethyl cinnamates **2a−f** were obtained, the next step was to find the optimal reaction conditions for the hydrolysis of these compounds under microwave irradiation. Initially, ethyl pyrazolylacetate **1a** was used as a substrate in the model reaction shown in Table 2. The first five experiments focused on the reaction of **1a** with 3.0 equiv of K_2CO_3 as a base and EtOH as a solvent for 20 min at different temperatures (100−180 °C). The lowest yield (69%) was obtained when the reaction was carried out at 100 °C (Table 2, entry 1). Moreover, the increase in temperature to 120 °C, 140 °C, and 160 °C did not have a significant effect on the yield (Table 2, entries 2, 3, and 4). Interestingly, when the reaction was performed using 3.0 equiv of K_2CO_3 at 180 °C for 20 min, carboxylate **3a** was obtained in a 98% yield (Table 2, entry 5). This result prompted us to evaluate the influence of K_2CO_3 equivalents using 2.0 and 1.0 equiv at 180 °C for 20 min. The yield obtained using 2.0 equiv decreased to 89%, whereas under the same conditions, the yield dramatically dropped to 52% when using only 1.0 equiv (Table 2, entries 6 and 7). Finally, we decided to evaluate the hydrolysis reaction using 3.0 equiv of K_2CO_3 at 180 °C for 10 min, obtaining the carboxylate **3a** with an excellent yield, 97% (Table 2, entry 8).

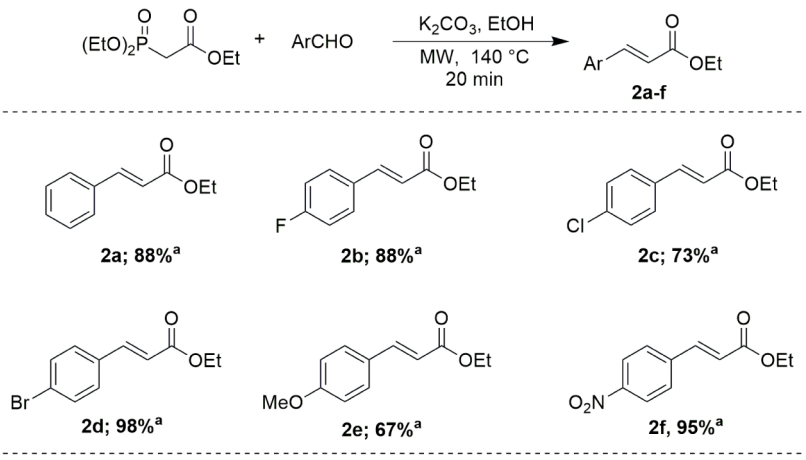
Based on the observed results, we proposed the formation of carboxylate **3a**, which was unequivocally characterized by its low- and high-resolution mass spectrometry analysis. At the same time, the IR data for compound **3a** were compared with the IR data of pirazol-1-yl acetic acid described by Boa et al.[40] (potassium carboxylate vs carboxylic acid), where the pirazol-1-yl acetic acid shows a band at 1733 cm^{-1} which is attributed to the carbonyl group, whereas for compound **3a**, the carboxylate symmetric stretching mode is shifted to lower frequency, 1601 cm^{-1}. These data confirm the presence of the carboxylate group as a resonance hybrid.

On the other hand, the ^{1}H NMR data for **3a** were consistent with the ^{1}H NMR data for pirazol-1-yl acetic acid, except for a broad signal (br) at 4.0−4.5 ppm for OH in the carboxylic acid. Another major difference between these two compounds is the ^{13}C NMR signal for carbon C═O, where the pirazol-1-yl acetic acid shows a signal at 172.23 ppm (CO_2H),[41] while **3a** shows a signal shifted to 174.8 ppm (CO_2K) (Figure S2). The $\Delta\delta$ value (2.57 ppm) indicates that the two oxygens from the carboxyl group are coordinated with potassium. These results are consistent with the literature for a bidentate bridge coordination.[42,43]

Once the optimal reaction conditions were found, the next step involved investigating the generality of the hydrolysis reaction of **1a−e** and **2a−f** using K_2CO_3 (3 equiv), ethanol as the solvent, and the reaction running at 180 °C for 20 min.

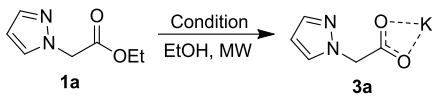
https://doi.org/10.1021/acsomega.4c05596
ACS Omega 2024, 9, 40783−40789

Scheme 2. Preparation of Ethyl Cinnamates 2a−f



[a]Yields obtained after purification by column chromatography.

Table 2. Optimization of Reaction Conditions for the Preparation of Potassium Carboxylate 3a



Entry	K_2CO_3 (eq.)	Temperature (°C)	Time (min.)	Yield (%)[a]
1	3	100	20	69
2	3	120	20	71
3	3	140	20	73
4	3	160	20	74
5	3	180	20	98
6	2	180	20	89
7	1	180	20	52
8	3	180	10	97

[a]The isolated solid was purified by ethanol washing.

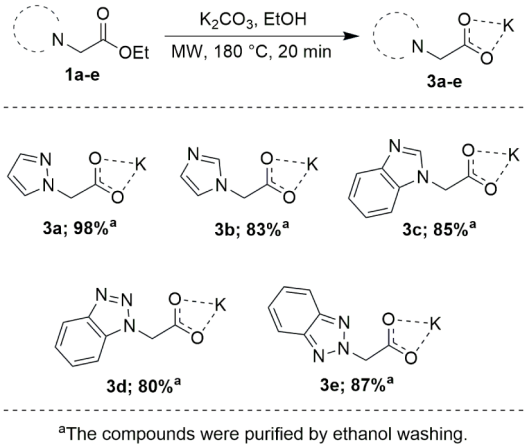
These reaction conditions afforded the target compounds **3a−e** and **4a−f** from good to excellent yields (73 to 98%) as white solids easily separated by filtration from the reaction mixture (Schemes 3 and 4).

The hydrolysis of ethyl imidazolyl **1b**, benzimidazolyl **1c**, and 1-benzotriazolylacetate **1d** generated the corresponding potassium carboxylates **3b**, **3c**, and **3d** in good yields, 83%, 85%, and 80%, respectively. A slight increase in yield was observed for the hydrolysis of **1e** (87%); meanwhile, the hydrolysis of ethyl pyrazolylacetate **1a** gave the best yield (98%).

In the same manner, the hydrolysis reaction of **2a−e** produced the corresponding potassium cinnamates **4a−e** in good to high yields, 87−97%, while a moderate yield (73%) was obtained for compound **4f** (Scheme 4). It is important to mention that the structure of all potassium carboxylates was confirmed by high-resolution mass spectrometry.

The IR and ^{13}C NMR data for the carbonyl group of compounds **3a−e** and **4a−f** are shown in Table 3. For compounds **3a−e**, in the IR spectra, the carbonyl group appears between 1567 and 1641 cm^{-1}, while the carbonyl group in the pirazol-1-yl acetic acid appears at 1773 cm^{-1}. For the carboxylic carbon, in the ^{13}C NMR spectra, the carbons are more deshielded than pirazol-1-yl acetic carbon (172.2−174.8 ppm vs 172.2 ppm). On the other hand, for compounds **4a−f**, all the carboxylic carbons are more shielded than the carboxylic carbon of the cinnamic acid (174.7−176.0 ppm vs 167.6 ppm).[44]

Scheme 3. Preparation of Potassium Azolyl-Carboxylates 3a−e



[a]The compounds were purified by ethanol washing.

3. CONCLUSIONS

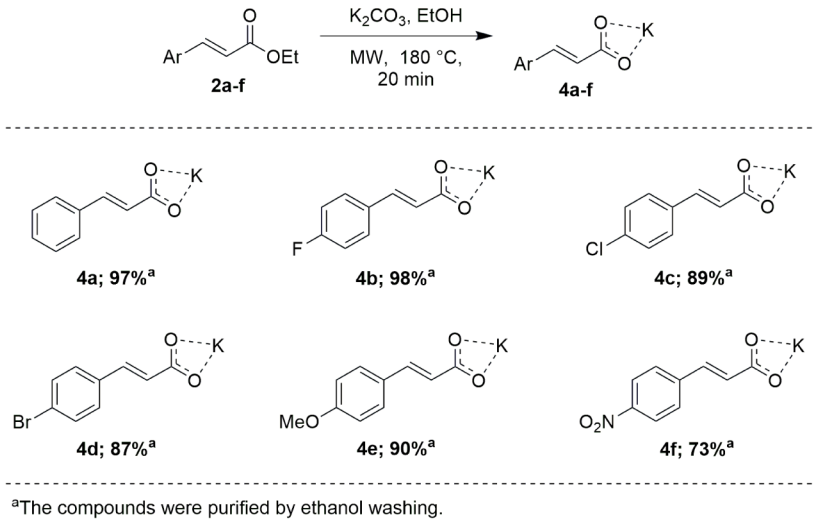
In summary, microwave-assisted organic synthesis has been successfully applied in the preparation of potassium carboxylates, achieving short reaction times and good to high chemical yields compared with traditional synthetic methods. Therefore, we propose this procedure as a fast, practical, and efficient method for synthesizing a variety of carboxylates. It is important to mention that obtaining a crystal suitable for further structural studies by X-ray diffraction and the evaluation of biological activities of these newly synthesized compounds are currently in progress.

4. METHODS

4.1. Chemistry. All commercial materials were used as received, unless noted otherwise. Flash chromatography was performed using 230−400 mesh Silica Flash 60 silica gel. Thin-layer chromatography was done on precoated TLC sheets of silica gel 60 F254 (E. Merck). NMR spectra were recorded on a Varian System instrument (400 MHz for ^1H and 100 MHz for ^{13}C). The spectra were obtained in D_2O, CD_3OD, and

https://doi.org/10.1021/acsomega.4c05596
ACS Omega 2024, 9, 40783−40789

Scheme 4. Preparation of Potassium Cinnamates 4a−f



[a]The compounds were purified by ethanol washing.

Table 3. IR and ^{13}C NMR Spectroscopic Data for the Carbonyl Group in Compounds 3a−e and 4a−f

Compound	Carbonyl group (cm^{-1})	Carboxylic carbon (δ, ppm)	Compound	Carbonyl group (cm^{-1})	Carboxylic carbon (δ, ppm)
3a	1601	174.8	**4a**	1636	175.7
3b	1641	174.8	**4b**	1639	175.6
3c	1567	174.5	**4c**	1634	175.3
3d	1594	172.9	**4d**	1642	175.4
3e	1601	172.2	**4e**	1627	176.0
---	---	---	**4f**	1641	174.7
Pirazol-1-yl acetic acid	1733	172.2	Cinnamic acid	1670	167.6

$CDCl_3$. Chemical shifts (δ) are reported in parts per million. Multiplicities are recorded as follows: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (J) are given in Hz. High-resolution FAB$^+$ mass experiments were done in JEOL HRMStation JHRMS-700. Reactions carried out with stirring under microwave irradiation in closed vessels were all performed by using a microwave synthesis reactor (Anton Paar Monowave 300).

4.2. General Procedure for the Synthesis of Compounds 2a−f. In a capped 10 mL MW-vessel, triethyl phosphonoacetate **1** (1.0 equiv), the corresponding aldehyde (1.0 equiv), K_2CO_3 (1.0 equiv), and EtOH (4 mL) were mixed. The vessel was placed into the irradiation cavity, and the mixture was heated with stirring under microwave irradiation at 140 °C for 20 min. Next, the vessel was cooled to room temperature, and the residue was dissolved in methanol, filtered, and then evaporated under vacuum. The crude product was purified by column chromatography on silica gel using EtOAc:Hex (4:6 v/v) as an eluent. The purity of the final products was determined by ^{1}H NMR. Characterization data for compounds **2a−f** were consistent with those reported in the literature.[37−39]

4.3. General Procedure for the Synthesis of Compounds 3a−e and 4a−f. In a capped 10 mL MW-vessel, the corresponding ester **1a−e** or **2a−f** (1.0 equiv), K_2CO_3 (3.0 equiv), and EtOH (4 mL) were mixed. The vessel was placed into the irradiation cavity, and the mixture was heated with stirring under microwave irradiation at 180 °C for 20 min. Next, the vessel was cooled to room temperature, and the residue was dissolved in methanol, filtered, and then evaporated under vacuum. The solid product was purified by crystallization using cold ethanol. The synthesized compounds were characterized by FTIR, ^{1}H NMR, ^{13}C NMR spectroscopy, and high-resolution mass spectrometry.

4.3.1. Potassium 2-(1H-Pyrazol-1-yl)acetate ***3a.*** 258 mg (98%), white solid, mp >200 °C dec. ^{1}H NMR (400 MHz, CD_3OD): δ 4.69 (s, 2H, $CH_2C{=}O$), 6.26 (t, J = 2.1 Hz, 1H, H_{arom}), 7.43 (d, J = 1.8 Hz, 1H, H_{arom}), 7.57 (d, J = 2.2 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, CD_3OD): δ 56.3, 106.5, 132.3, 139.7, 174.8 (C═O). FTIR: ν = 3453, 3107, 1601, 1394, 1311, 757 cm^{-1}. HRMS (FAB$^+$): calculated for $C_5H_5O_2N_2K_2$ $[M + 2K]^+$, m/z 202.9625; found for $[M + 2K]^+$, m/z 202.9630.

4.3.2. Potassium 2-(1H-Imidazol-1-yl)acetate ***3b.*** 220 mg (83%), white solid, mp >200 °C dec. ^{1}H NMR (400 MHz, CD_3OD): δ 4.47 (s, 2H, $CH_2C{=}O$), 6.86 (br, 1H, H_{arom}), 6.98 (br, 1H, H_{arom}), 7.52 (br, 1H, H_{arom}). ^{13}C NMR (100 MHz, CD_3OD): δ 51.6, 122.1, 128.4, 139.4, 174.8 (C═O). FTIR: ν = 3161, 1647, 1360, 844 cm^{-1}. HRMS (ESI$^+$): calculated for $C_5H_5O_2N_2K_2$ $[M + 2K]^+$, m/z 202.9625; found for $[M + 2K]^+$, m/z 202.9593.

4.3.3. Potassium 2-(1H-Benzimidazol-1-yl)acetate ***3c.*** 211 mg (85%), white solid, mp >200 °C dec. ^{1}H NMR (400 MHz, CD_3OD): δ 4.78 (s, 2H, $CH_2C{=}O$), 7.22−7.30 (m, 2H, H_{arom}), 7.44−7.46 (m, 1H, H_{arom}), 7.65−7.67 (m, 1H, H_{arom}), 8.10 (s, 1H, NCH═N). ^{13}C NMR (100 MHz, CD_3OD): δ 49.4, 111.4, 119.8, 123.2, 124.1, 135.6, 143.7, 145.6, 174.5 (C═O). FTIR: ν = 3316, 3055, 1570, 1397, 741 cm^{-1}. HRMS (FAB$^+$): calculated for $C_9H_7O_2N_2K_2$ $[M + 2K]^+$, m/z 252.9782; found for $[M + 2K]^+$, m/z 252.9781.

4.3.4. Potassium 2-(1H-Benzotriazol-1-yl)acetate ***3d.*** 492 mg (80%), white solid, mp >200 °C dec. ^{1}H NMR (400 MHz,

https://doi.org/10.1021/acsomega.4c05596
ACS Omega 2024, 9, 40783−40789

$CD_3OD/CDCl_3$): δ 5.25 (s, 2H, $CH_2C{=}O$), 7.38−7.42 (m, 1H, H_{arom}), 7.50−7.54 (m, 1H, H_{arom}), 7.66−7.68 (m, 1H, H_{arom}), 7.94−7.96 (m, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$): δ 52.5, 111.9, 119.6, 125.3, 128.4, 135.0, 146.6, 172.9 (C═O). FTIR: ν = 3303, 3060, 1594, 1384, 741 cm^{-1}. HRMS (FAB^+): calculated for $C_8H_6O_2N_3K_2$ $[M + 2K]^+$, m/z 253.9734; found for $[M + 2K]^+$, m/z 253.9732.

4.3.5. Potassium 2-(2H-Benzotriazol-2-yl)acetate ***3e.*** 325 mg (87%), white solid, mp >200 °C dec. ^1H NMR (400 MHz, $CD_3OD/CDCl_3$): δ 5.36 (s, 2H, $CH_2C{=}O$), 7.41−7.46 (m, 2H, H_{arom}), 7.87−7.91 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$): δ 60.5, 118.6, 127.1, 145.3, 172.2 (C═O). FTIR: ν = 3366, 2964, 1601, 1384, 747 cm^{-1}. HRMS (FAB^+): calculated for $C_8H_6O_2N_3K_2$ $[M + 2K]^+$, m/z 253.9734; found for $[M + 2K]^+$, m/z 253.9727.

4.3.6. Potassium Cinnamate ***4a.*** 194 mg (97%), white solid, mp >200 °C dec. ^1H NMR (400 MHz, D_2O): δ 6.44 (d, J = 16.0 Hz, 1H, CHC═O), 7.31 (d, J = 16.0 Hz, 1H, $C_6H_5CH{=}CH$), 7.35−7.40 (m, 3H, H_{arom}), 7.53−7.55 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, D_2O): δ 124.2, 127.7, 129.0, 129.6, 135.2, 140.7, 175.7 (C═O). FTIR: ν = 3022, 1636, 1555, 1383, 966 cm^{-1}. HRMS (FAB^+): calculated for $C_9H_7O_2K_2$ $[M + 2K]^+$, m/z 224.9720; found for $[M + 2K]^+$, m/z 224.9740.

4.3.7. Potassium 3-(4-Fluorophenyl)acrylate ***4b.*** 250 mg (98%), white solid, mp >200 °C dec. ^1H NMR (400 MHz, CD_3OD): δ 6.46 (d, J = 16.0 Hz, 1H, CHC═O), 7.07−7.12 (m, 2H, H_{arom}), 7.37 (d, J = 16.0 Hz, 1H, C_6H_4CH), 7.55−7.58 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, CD_3OD): δ 116.5 (d, J_{C-F} = 22 Hz), 126.6, 130.4 (d, J_{C-F} = 8.3 Hz), 133.7 (d, J_{C-F} = 3.3 Hz), 139.5, 164.5 (d, J_{C-F} = 247.1 Hz), 175.6 (C═O). FTIR: ν = 3392, 3033, 1639, 1556, 1380, 1240 cm^{-1}. HRMS (FAB^+): calculated for $C_9H_6FO_2K_2$ $[M + 2K]^+$, m/z 242.9626; found for $[M + 2K]^+$, m/z 242.9621.

4.3.8. Potassium 3-(4-Chlorophenyl)acrylate ***4c.*** 223 mg (89%), white solid, mp >200 °C dec. ^1H NMR (400 MHz, CD_3OD): δ 6.44 (d, J = 16.0 Hz, 1H, CHC═O), 7.28 (d, J = 16.0 Hz, 1H, C_6H_4CH), 7.29 (d, J = 8.5 Hz, 2H, H_{arom}), 7.44 (d, J = 8.5 Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, CD_3OD): δ 127.7, 129.9, 135.5, 136.2, 139.1, 175.3 (C═O). FTIR: ν = 3029, 1634, 1553, 1377, 966, 827 cm^{-1}. HRMS (FAB^+): calculated for $C_9H_6ClO_2K_2$ $[M + 2K]^+$, m/z 258.9330; found for $[M + 2K]^+$, m/z 258.9334.

4.3.9. Potassium 3-(4-Bromophenyl)acrylate ***4d.*** 207 mg (87%), white solid, mp >200 °C dec. ^1H NMR (400 MHz, CD_3OD): δ 6.53 (d, J = 16.0 Hz, 1H, CHC═O), 7.34 (d, J = 16.0 Hz, 1H, C_6H_4CH), 7.47 (d, J = 8.6 Hz, 2H, H_{arom}), 7.52 (d, J = 8.6 Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, CD_3OD): δ 123.6, 127.6, 130.2, 132.9, 136.5, 139.3, 175.4 (C═O). FTIR: ν = 3407, 3029, 1642, 1553, 1386, 966, 823 cm^{-1}. HRMS (FAB^+): calculated for $C_9H_7BrO_2K_2$ $[M + 2K]^+$, m/z 303.8904; found for $[M + 2K]^+$, m/z 303.8917.

4.3.10. Potassium 3-(4-Methoxyphenyl)acrylate ***4e.*** 221 mg (90%), white solid, mp >200 °C dec. ^1H NMR (400 MHz, D_2O): δ 3.79 (s, 3H, CH_3O), 6.33 (d, J = 16.0 Hz, 1H, CHC═O) 6.93 (d, J = 8.8 Hz, 2H, H_{arom}), 7.29 (d, J = 16.0 Hz, 1H, C_6H_4CH), 7.49 (d, J = 8.8 Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, D_2O): δ 55.4 (CH_3O), 114.4, 122.0, 128.2, 129.3, 140.5, 159.9, 176.0 (C═O). FTIR: ν = 2939, 2622, 1627, 1393, 977, 829 cm^{-1}. HRMS (FAB^+): calculated for $C_{10}H_9O_3K_2$ $[M + 2K]^+$, m/z 254.9826; found for $[M + 2K]^+$, m/z 254.9858.

4.3.11. Potassium 3-(4-Nitrophenyl)acrylate ***4f.*** 178 mg (73%), white solid, mp >200 °C dec. ^1H NMR (400 MHz, D_2O): δ 6.52 (d, J = 16.1 Hz, 1H, CHC═O), 7.27 (d, J = 16.1 Hz, 1H, CHC_6H_4), 7.63 (d, J = 8.4 Hz, 2H, H_{arom}), 8.13 (d, J = 8.4 Hz, 2H, H_{arom}). ^{13}C NMR (100 MHz, D_2O): δ 124.0, 128.3, 138.0, 142.1, 147.4, 162.5, 174.7 (C═O). FTIR: ν = 3233, 1641, 1373, 1341, 845 cm^{-1}. HRMS (FAB^+): calculated for $C_9H_6O_4NK_2$ $[M + 2K]^+$, m/z 269.9571; found for $[M + 2K]^+$, m/z 269.9578.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c05596.

Copies of ^1H NMR, ^{13}C NMR, FTIR spectra, and HRMS reports of the synthesized compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Eugenio Hernández-Fernández − *Facultad de Ciencias Químicas, Universidad Autónoma de Nuevo León, San Nicolás de los Garza, Nuevo León 66455, México;* orcid.org/0000-0001-6769-9125; Phone: +52 (81) 8329 40 00, ext 6293; Email: eugenio.hernandezfr@uanl.edu.mx; Fax: +52 (81)8329 40 00, ext 6293

Authors

Jorge Hernández-Fernández − *Facultad de Ciencias Químicas, Universidad Autónoma de Nuevo León, San Nicolás de los Garza, Nuevo León 66455, México*

Norma Tiempos-Flores − *Facultad de Ciencias Químicas, Universidad Autónoma de Nuevo León, San Nicolás de los Garza, Nuevo León 66455, México*

Mario Ordóñez − *Centro de Investigaciones Químicas-IICBA, Universidad Autónoma del Estado de Morelos, Cuernavaca, Morelos 62209, México;* orcid.org/0000-0001-9395-7079

Verónica M. Rivas-Galindo − *Facultad de Medicina, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León 64460, México;* orcid.org/0000-0002-7981-3674

Susana López-Cortina − *Facultad de Ciencias Químicas, Universidad Autónoma de Nuevo León, San Nicolás de los Garza, Nuevo León 66455, México*

Katia Guadalupe García-Alvarez − *Facultad de Ciencias Químicas, Universidad Autónoma de Nuevo León, San Nicolás de los Garza, Nuevo León 66455, México*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c05596

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank to CONAHCYT and PAICYT-UANL of México for their financial support via projects CF-2023-I-1693, 286614, 140607, and 326-CN-2022. J.H.F. thanks CONAHCYT for the Graduate Scholarship.

■ REFERENCES

(1) de Almeida, A. F.; Moreira, R.; Rodrigues, T. Synthetic Organic Chemistry Driven by Artificial Intelligence. *Nat. Rev. Chem.* **2019**, *3* (10), 589−604.

(2) Schaub, T. Efficient Industrial Organic Synthesis and the Principles of Green Chemistry. *Chem. - Eur. J.* **2021**, *27* (6), 1865−1869.
(3) Sharma, A.; Appukkuttan, P.; Van der Eycken, E. Microwave-Assisted Synthesis of Medium-Sized Heterocycles. *Chem. Commun.* **2012**, *48* (11), 1623−1637.
(4) Gaba, M.; Dhingra, N. Microwave Chemistry: General Features and Applications. *Indian J. Pharm. Educ. Res.* **2011**, *45* (2), 175−183.
(5) Rana, K. K.; Rana, S. Microwave Reactors: A Brief Review on Its Fundamental Aspects and Applications. *Open Access Library J.* **2014**, *1* (6), 1−20.
(6) Ortega-Villarreal, A. S.; Hernández-Fernández, E.; Jensen, C.; Valdivia-Berroeta, G. A.; Garrard, S.; López, I.; Smith, S. J.; Christensen, K. A.; Reyes-González, M. A.; Michaelis, D. J. Synthesis and Characterization of Ethyl Benzotriazolyl Acrylate-Based D-π-A Fluorophores for Live Cell-Based Imaging Applications. *RSC Adv.* **2019**, *9* (16), 8759−8767.
(7) Polshettiwar, V.; Varma, R. S. Microwave-Assisted Organic Synthesis and Transformations Using Benign Reaction Media. *Acc. Chem. Res.* **2008**, *41* (5), 629−639.
(8) Ortega-Villarreal, A. S.; Hernández-Fernández, E.; López, I. Chapter 9 - Synthesis of Nanomaterials and Compounds via Microwave Irradiation as a Greener Alternative. In *Handbook of Greener Synthesis of Nanomaterials and Compounds*; Elsevier, 2021; Vol. *1*, pp. 315358. DOI: .
(9) Lai, J.; Huang, H.; Lin, M.; Xu, Y.; Li, X.; Sun, B. Enzyme Catalyzes Ester Bond Synthesis and Hydrolysis: The Key Step for Sustainable Usage of Plastics. *Front. Microbiol.* **2023**, *13* (12), 1113705.
(10) Lif, A.; Holmberg, K. Chemical and Enzymatic Ester Hydrolysis in a Winsor I System. *Colloids Surf., A* **1997**, *129−130*, 273−277.
(11) Da Silva, P. L.; Guimarães, L.; Pliego, J. R. Revisiting the Mechanism of Neutral Hydrolysis of Esters: Water Autoionization Mechanisms with Acid or Base Initiation Pathways. *J. Phys. Chem. B* **2013**, *117* (21), 6487−6497.
(12) Khan, N. R.; Rathod, V. K. Microwave Assisted Enzymatic Synthesis of Speciality Esters: A Mini - Review. *Process Biochem.* **2018**, *75*, 89−98.
(13) Wu, X. A.; Ying, P.; Liu, J. Y.; Shen, H. S.; Chen, Y.; He, L. Lithium Chloride-Assisted Selective Hydrolysis of Methyl Esters under Microwave Irradiation. *Synth. Commun.* **2009**, *39* (19), 3459−3470.
(14) Ranu, B. C.; Dutta, P.; Sarkar, A. An Efficient and General Method for Ester Hydrolysis on the Surface of Silica Gel Catalyzed by Indium Triiodide under Microwave Irradiation. *Synth. Commun.* **2000**, *30* (22), 4167−4171.
(15) Wescott, C. R.; Klibanov, A. M. Solvent Variation Inverts Substrate Specificity of an Enzyme. *J. Am. Chem. Soc.* **1993**, *115* (5), 1629−1631.
(16) Reetz, M. T. What Are the Limitations of Enzymes in Synthetic Organic Chemistry? *Chem. Rec.* **2016**, *16* (6), 2449−2459.
(17) Rusydi, F.; Aisyah, N. D.; Fadilla, R. N.; Dipojono, H. K.; Ahmad, F.; Mudasir; Puspitasari, I.; Rusydi, A. The Transition State Conformational Effect on the Activation Energy of Ethyl Acetate Neutral Hydrolysis. *Heliyon* **2019**, *5* (9), No. e02409.
(18) Arifuzzaman, M. D.; Bose, I.; Bahrami, F.; Zhao, Y. Imprinted Polymeric Nanoparticles as Artificial Enzymes for Ester Hydrolysis at Room Temperature and PH 7. *Chem. Catal.* **2022**, *2* (8), 2049−2065.
(19) Lamar, A. A.; Liebeskind, L. S. Carboxyl Activation via Silylthioesterification: One-Pot, Two-Step Amidation of Carboxylic Acids Catalyzed by Non-Metal Ammonium Salts. *Tetrahedron Lett.* **2015**, *56* (44), 6034−6037.
(20) Bahrami, K.; Khodaei, M. M.; Targhan, H.; Sheikh Arabi, M. Preparation of Esters and Amides from Carboxylic Acids and N-Formylation of Amines Promoted by 1,3,5-Triazo-2,4,6-Triphosphorine-2,2,4,4,6,6-Hexachloride (TAPC). *Tetrahedron Lett.* **2013**, *54* (37), 5064−5068.
(21) Nava-Ramirez, J. C.; Santana-Krimskaya, S. E.; Franco-Molina, M. A.; Ortega-Villarreal, A. S.; Lopez, I.; Michaelis, D. J.; Hernandez-Fernandez, E. Synthesis of α,β-Unsaturated Benzotriazolyl-1,3,4-Oxadiazole Derivatives: Anticancer Activity, Cytotoxicity, and Cell Imaging. *IEEE Trans. NanoBiosci.* **2022**, *21* (1), 125−134.
(22) Zarei, M. A Mild and Efficient One-Pot Preparation of 1,2,4-Oxadiazoles from Nitriles and Carboxylic Acids Using Vilsmeier Reagent. *ChemistrySelect* **2018**, *3* (40), 11273−11276.
(23) Wipf, P.; Wang, X. Parallel Synthesis of Oxazolines and Thiazolines by Tandem Condensation - Cyclodehydration of Carboxylic Acids with Amino Alcohols and Aminothiols. *J. Comb. Chem.* **2002**, *4* (6), 656−660.
(24) Meghdadi, S.; Amirnasr, M.; Ford, P. C. A Robust One-Pot Synthesis of Benzothiazoles from Carboxylic Acids Including Examples with Hydroxyl and Amino Substituents. *Tetrahedron Lett.* **2012**, *53* (51), 6950−6953.
(25) De, P.; Yoya, G. K.; Constant, P.; Bedos-Belval, F.; Duran, H.; Saffon, N.; Daffé, M.; Baltas, M. Design, Synthesis, and Biological Evaluation of New Cinnamic Derivatives as Antituberculosis Agents. *J. Med. Chem.* **2011**, *54* (5), 1449−1461.
(26) Saito, T.; Aizawa, Y.; Yamamoto, T.; Tajima, K.; Isono, T.; Satoh, T. Alkali Metal Carboxylate as an Efficient and Simple Catalyst for Ring-Opening Polymerization of Cyclic Esters. *Macromolecules* **2018**, *51* (3), 689−696.
(27) Folkertsma, E.; De Waard, E. F.; Korpershoek, G.; Van Schaik, A. J.; Solozabal Mirón, N.; Borrmann, M.; Nijsse, S.; Moelands, M. A. H.; Lutz, M.; Otte, M.; Moret, M. E.; Klein Gebbink, R. J. M. Mimicry of the 2-His-1-Carboxylate Facial Triad Using Bulky N,N,O-Ligands: Non-Heme Iron Complexes Featuring a Single Facial Ligand and Easily Exchangeable Co-Ligands. *Eur. J. Inorg. Chem.* **2016**, *2016* (9), 1319−1332.
(28) Trant, J. F.; Hudlicky, T. Ring-Opening of Hindered Cyclic Epoxides with Potassium Carboxylates in the Presence of Conjugate Acids. *Can. J. Chem.* **2013**, *91* (12), 1179−1185.
(29) Holm, R. H.; Solomon, E. I. Preface: Biomimetic Inorganic Chemistry. *Chem. Rev.* **2004**, *104* (2), 347−348.
(30) Mitchell, S. M.; Ullman, J. L.; Teel, A. L.; Watts, R. J. PH and Temperature Effects on the Hydrolysis of Three β-Lactam Antibiotics: Ampicillin, Cefalotin and Cefoxitin. *Sci. Total Environ.* **2014**, *466−467*, 547−555.
(31) Fu, Z.; Wan, H.; Cui, Q.; Xie, J.; Tang, Y.; Guan, G. Hydrolysis of Carboxylic Acid Esters Catalyzed by a Carbon-Based Solid Acid. *React. Kinet., Mech. Catal.* **2011**, *104* (2), 313−321.
(32) El-Kardocy, A.; Mostafa, Y. A.; Mohamed, N. G.; Abo-Zeid, M. N.; Hassan, N. A.; Hetta, H. F.; Abdel-Aal, A. B. M. CK2 Inhibition, Lipophilicity and Anticancer Activity of New: N1versus N2-Substituted Tetrabromobenzotriazole Regioisomers. *New J. Chem.* **2020**, *44* (30), 13007−13017.
(33) Malvacio, I.; Vera, D. M. A.; Moyano, E. L. Microwave Assisted Synthesis of Ethyl-Quinolon-4-One-3-Carboxylates and Hydrolysis to Quinolon-4-One-3-Carboxylic Acids. *Curr. Microwave Chem.* **2014**, *1* (1), 52−58.
(34) Smeets, J. W. H.; Kieboom, A. P. G. Enzymatic Enantioselective Ester Hydrolysis by Carboxylesterase NP. *Recl. Trav. Chim. Pays-Bas* **1992**, *111* (11), 490−495.
(35) Bevilaqua, J. V.; Pinto, J. C.; Lima, L. M.; Barreiro, E. J.; Alves, T. L. M.; Freire, D. M. G. Enzymatic Hydrolysis by Immobilized Lipase Applied to a New Prototype Anti-Asthma Drug. *Biochem. Eng. J.* **2004**, *21* (1), 103−110.
(36) Hernández-Fernández, E.; Sánchez-Lara, P. P.; Ordóñez, M.; Ramírez-Marroquín, O. A.; Avalos-Alanís, F. G.; López-Cortina, S.; Jiménez-Pérez, V. M.; Ibarra-Rivera, T. R. Synthesis of β-Hydroxyacetamides from Unactivated Ethyl Acetates under Base-Free Conditions and Microwave Irradiation. *Tetrahedron: asymmetry* **2015**, *26* (1), 73−78.
(37) Kelly, M. J. B.; Fallot, L. B.; Gustafson, J. L.; Bergdahl, B. M. Water Mediated Wittig Reactions of Aldehydes in the Teaching Laboratory: Using Sodium Bicarbonate for the in Situ Formation of Stabilized Ylides. *J. Chem. Educ.* **2016**, *93* (9), 1631−1636.
(38) Rodrigues-Santos, C. E.; Echevarria, A.; Sant'anna, C. M. R.; Bitencourt, T. B.; Nascimento, M. G.; Bauerfeldt, G. F. Quantitative

https://doi.org/10.1021/acsomega.4c05596
ACS Omega 2024, 9, 40783−40789

Structure-Property Relationship (QSPR) Models for a Local Quantum Descriptor: Investigation of the 4- and 3-Substituted-Cinnamic Acid Esterification. *Molecules* **2015**, *20* (9), 17493−17510.
(39) Hall, M. I.; Pridmore, S. J.; Williams, J. M. J. Alkenes from Alcohols by Tandem Hydrogen Transfer and Condensation. *Adv. Synth. Catal.* **2008**, *350* (13), 1975−1978.
(40) Boa, A. N.; Crane, J. D.; Kowalczyk, R. M.; Sultana, N. H. Addition of (Pyrazol-1-Yl)Acetyl and (Pyridin-2-Yl)Acetyl Groups to the Terminal Amino Group of a Phe-Gly Dipeptide Affords ATCUN-like Copper(II) Binding Sites. *Eur. J. Inorg. Chem.* **2005**, *2005* (5), 872−878.
(41) Chen, X.-Y.; Goff, G. S.; Scott, B. L.; Runde, W. Comparison of Structural Variations of Ln(III) Compounds with (Pyrazol-1-Yl)-Acetic Acid. *Polyhedron* **2014**, *68*, 80−86.
(42) Nelson, P. N.; Taylor, R. A. Theories and Experimental Investigations of the Structural and Thermotropic Mesomorphic Phase Behaviors of Metal Carboxylates. *Appl. Petrochem. Res.* **2014**, *4* (3), 253−285.
(43) Kalinowska, M.; Świsfocka, R.; Rzązyczyńska, Z.; Sienkiewicz, J.; Lewandowski, W. W. (FT-IR, FT-Raman, UV, 1H, and 13C NMR) and Theoretical Studies of m-Anisic Acid and Lithium, Sodium, Potassium, Rubidium, and Caesium m-Anisates. *J. Phys. Org. Chem.* **2010**, *23* (1), 37−47.
(44) Dávila-Guzmán, N. E.; Medina-Almaguer, Y. B.; Reyes-González, M. A.; Loredo-Cancino, M.; Pioquinto-García, S.; De Haro-Del Rio, D. A.; Garza-Navarro, M. A.; Hernández-Fernández, E. Microwave-Assisted Synthesis of Trans-Cinnamic Acid for Highly Efficient Removal of Copper from Aqueous Solution. *ACS Omega* **2020**, *5* (1), 317−326.

https://doi.org/10.1021/acsomega.4c05596
ACS Omega 2024, 9, 40783−40789