

Malic acid as an effective and valuable bioorganocatalyst for one-pot, three-component synthesis of pyrrolidinone derivatives

Hamideh Ahankar,^{*a} Ali Ramazani,^{*b,c} Katarzyna Ślepokura,^d and Vasyl Kinzhybalo^e

^aDepartment of Chemistry, Abhar Branch, Islamic Azad University P O Box 22, Abhar, Iran

^bDepartment of Chemistry, University of Zanjan, 45371-38791, Zanjan, Iran

^cDepartment of Biotechnology, Research Institute of Modern Biological Techniques (RIMBT), University of Zanjan, Zanjan 45371-38791, Iran

^dFaculty of Chemistry, University of Wrocław, 14 Joliot-Curie St., 50-383 Wrocław, Poland

^eInstitute of Low Temperature and Structure Research, PAS, 2 Okólna St., 50-422 Wrocław, Poland

Email: hahankar@gmail.com, aliramazani@gmail.com

Dedicated to Prof. György Keglevich on the occasion of his 65th birthday

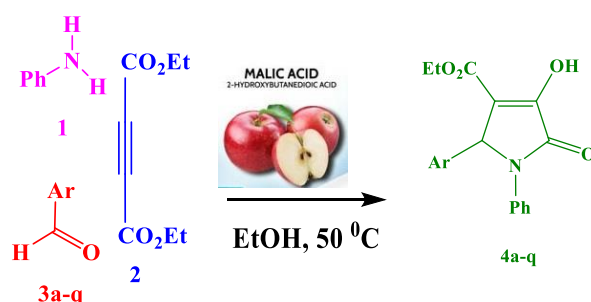
Received 07-11-2021

Accepted Manuscript 11-28-2021

Published on line 12-04-2021

Abstract

Malic acid was used as an effective and valuable bioorganocatalyst for the one-pot, three-component synthesis of important and noteworthy pyrrolidinone derivatives in green solvent at 50°C. Ecofriendly, simplicity in operation, cleaner reaction profile, simple workup procedure, use of non-toxic solvent, and proving vital chemistry principles are some notable features of this method, making it a valuable green alternative to the existing methods. The target products were obtained in good to excellent yields (84-96%). Unequivocal evidence for the structure of ethyl 4-hydroxy-2-[4-(methylthio)phenyl]-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate was obtained from single-crystal X-ray analysis.



Keywords: Pyrrolidinones, malic acid, bioorganocatalysts, green catalysts, green chemistry

Introduction

Recently, multicomponent reactions (MCRs) based on the synthesis of diverse and widespread heterocyclic compounds have received attention in the field of organic synthesis. MCRs are of particular importance from an economic point of view due to their advantages which include the use of one container, variety and high reaction speed, simplicity of reaction conditions, simultaneous addition of all reagents, and high efficiency.¹⁻⁵

Pyrrolidinone derivatives are one of the most important nitrogen-containing heterocyclic compounds synthesized by MCRs. In view of their biological significance, the construction of these frameworks and their structural analogues have attracted much attention.⁶⁻¹⁴ Cotinine,¹⁵ Doxapram,¹⁶ Ethosuximide,¹⁷ and PI-091,¹⁸ are examples of some drugs containing the pyrrolidinone core. Some natural products have a pyrrolidinone scaffold, such as Lactacystin,¹⁹ Holomycin, and Thiolutin,²⁰ Thiomarinol A4,²¹ Oteromycin,²² Pyrrocidine A, B,²³ Quinolactacin C,²⁴ Ypaoamide,²⁵ (-)-Azaspirene,²⁶ and Salinosporamide A.²⁷ Selected natural products with a 2-pyrrolidinone moiety are presented in Figure 1. It should be noted that the 2-pyrrolidinone family has a wide range of pharmacological and biological effects that play an essential role in the treatment of diseases, acting as anticancer,²⁸ antibacterial,²⁹ anti-inflammatory,³⁰ antimicrobial,³¹ antitumor,³² and anticonvulsant³³ agents, and HIV-1 integrase inhibitors.^{34,35}



Figure 1. Selected natural products with a 2-pyrrolidinone moiety.

Although a number of catalysts have been reported for the synthesis of pyrrolidinone derivatives, the use of bioorganocatalysts and green catalysts are very momentous. In this work, we have introduced malic acid

as a green-chemistry bioorganocatalyst for the synthesis of some pyrrolidinone derivatives.^{9-11,14,36} Malic acid is known as a fruit acid that plays a role in creating the sour taste of the fruits. Apples contain a lot of malic acid, called apple extract. This dicarboxylic acid is one of the food additives that serves as a source of extreme tartness in confectionery. It is available in two stereoisomeric [(+) and (-)] forms, although only the (-)-isomer exists naturally.³⁷ (-)-Malic acid was used as the chiral precursor for the synthesis of (-) wikstromol which exhibits several biological activities.³⁸ There are, however, very few reports on the use of malic acid as a catalyst in synthetic chemistry.³⁹⁻⁴¹

Results and Discussion

Using malic acid as a bioorganocatalyst, various reaction conditions were investigated in the reaction of aniline, diethyl acetylenedicarboxylate, and aldehyde derivatives in ethanol solvent to achieve appropriate conditions for the synthesis of pyrrolidinone derivatives (Scheme 1). We tried to make the reaction conditions in such a way that some of the problems of the methods reported in previous articles could be minimized as much as possible. We then optimized the reaction conditions, such as the effect of a suitable solvent, catalyst amount, and the value of temperature.

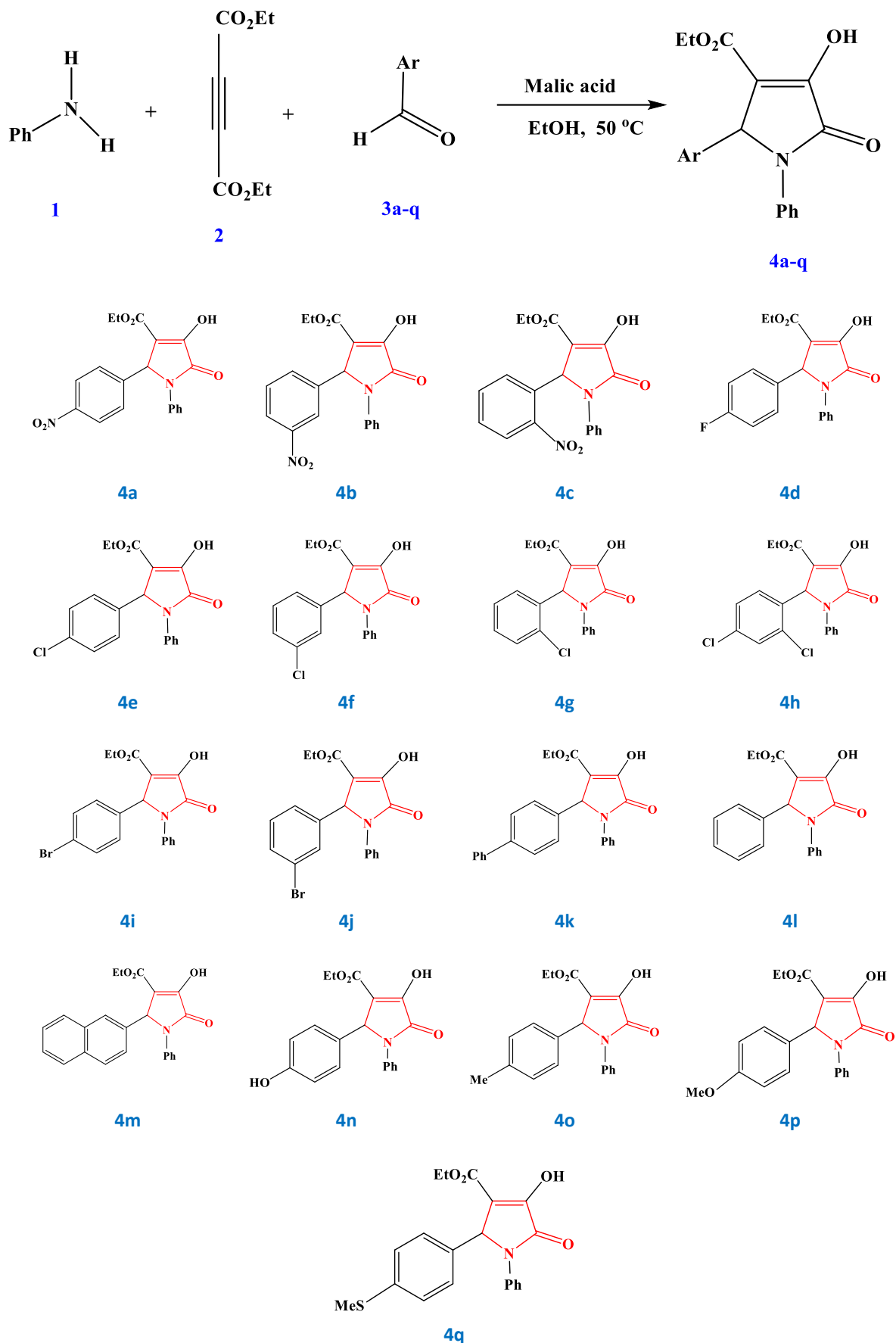
At the beginning of the optimization of reaction conditions, different solvents such as H₂O, C₂H₅OH, and C₂H₅OH-H₂O (50-50) were compared in the synthesis of **4a** as a template compound. The best result was obtained by the reaction of aniline, diethyl acetylenedicarboxylate, 4-nitrobenzaldehyde in ethanol over 90 min with 92% yield (Table 1, entry 3). Water and water-ethanol afforded moderate yields of the desired products, however, they had longer reaction times (Table 1; entries 1 and 2). Thus, ethanol was selected as the most suitable solvent.

Table 1. The effect of solvent on the synthesis of pyrrolidinone derivatives^a

Entry	Solvent	Time (min.)	Yield ^b (%)
1	H ₂ O	150	41
2	C ₂ H ₅ OH- H ₂ O	120	67
3	C ₂ H ₅ OH	90	92

^a Reaction conditions: aniline **1** (1 mmol), diethyl acetylenedicarboxylate **2** (1 mmol), 4-nitrobenzaldehyde **3a** (1 mmol), and malic acid (2 mmol) as a bioorganocatalyst in various solvents at 50 °C.

^b Isolated yield.



Scheme 1. One-pot, three-component syntheses of pyrrolidinone derivatives in the presence of malic acid.

Thereupon, we performed the template reaction at different temperatures, including room temperature (RT), 30, 40, 50, and 60 °C for model reaction as shown in Table 2. At room temperature, a mixture of starting materials was seen during the reaction. By increasing the temperature to 30 °C, after 180 min the reaction was complete with 91% yield (Table 2, entry 2). Raising the temperature to 40 °C reduced the reaction time to 120 min. Raising the temperature to 50 °C did not have any great impact on the yield of the reaction, however, the reaction time was reduced. Increasing the temperature to 60 °C had no significant effect on the yield of product or the reaction time. Therefore, the temperature of 50 °C was chosen as the appropriate temperature for the reactions.

Table 2. The effect of temperature on the synthesis of pyrrolidinone derivatives^a

Entry	Temperature (°C)	Time (min.)	Yield (%) ^b
1	RT	180	68
2	30	180	91
3	40	120	90
4	50	90	92

Reaction conditions: aniline **1** (1 mmol), diethyl acetylenedicarboxylate **2** (1 mmol), 4-nitrobenzaldehyde **3a** (1 mmol), and malic acid (2 mmol) as a bioorganocatalyst in different temperatures.

^a Isolated yield.

Determination of the optimized amount of catalyst for the synthesis of compound **4a** was carried out by varying the quantity of catalyst, as shown in Table 3. Since there was only a modest yield improvement (2%) with an increase of 0.5 mmol of catalyst, we chose 1 mmol of catalyst as our ideal amount in order to use less catalyst.

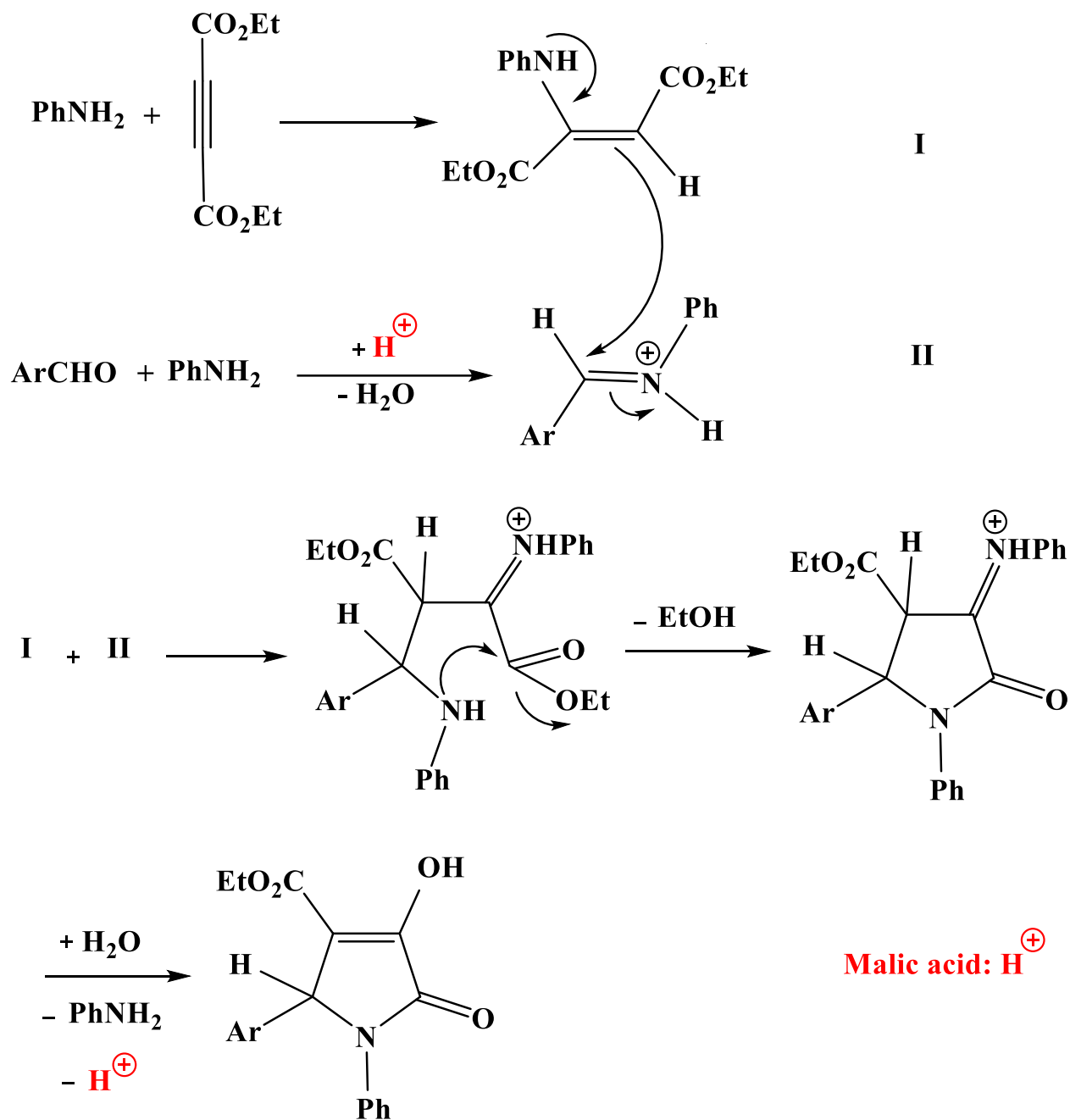
Table 3. The effect of the catalyst amount on the synthesis of pyrrolidinone derivatives^a

Entry	Catalyst (mmol)	Time (min.)	Yield (%) ^b
1	-	240	40
2	0.5	150	67
3	1.0	90	92
4	1.5	90	94

Reaction conditions: aniline **1** (1 mmol), diethyl acetylenedicarboxylate **2** (1 mmol), 4-nitrobenzaldehyde **3a** (1 mmol), various amounts of malic acid in ethanol solvent (2 mL) at 50 °C.

^a Isolated yield.

After finding the most suitable reaction solvent (C₂H₅OH), temperature (50 °C), and amount of the catalyst, this method was examined by the reactions of aniline, diethyl acetylenedicarboxylate, and several substituted aldehydes **3a-q** in the presence of malic acid. To check the behavior of different types of aldehydes in the synthesis of pyrrolidinones, we tested numerous, diverse aldehydes, including aromatic aldehydes with different groups in the *ortho*-, *meta*-, and *para*- positions under the reaction conditions. As shown in Table 4, we discovered that aromatic aldehydes with electron-withdrawing groups reacted faster. The structures of all of the synthesized products **4a-q** were defined by their FT-IR, ¹H-NMR, and ¹³C-NMR spectra.



Scheme 2. Mechanism of the acid-catalyzed one-pot, three-component reaction.

The possible mechanism for the one-pot, three-component synthesis of pyrrolidinone derivatives (**4a-q**) in the presence of malic acid is shown in Scheme 2. First, Aniline is added to diethyl acetylenedicarboxylate (I). An imine is then formed from the aldehyde and aniline via the acid-catalysed reaction (II). The resulting 1,3-dipolar intermediate adds to the imine, eventually yielding the target products following cyclization and elimination of aniline and ethanol.

Table 4. Reaction conditions and yields of the synthesis of pyrrolidinone derivatives

Entry	Ar	Product	Time (min)	Yield (%) ^a	mp (°C)	mp ^{Ref} (°C)
1	4-NO ₂ -C ₆ H ₄	4a	90	92	182-183	180-182 ¹⁴
2	3-NO ₂ -C ₆ H ₄	4b	65	89	224-227	225-227 ⁹
3	2-NO ₂ -C ₆ H ₄	4c	75	84	204-206	203-205 ⁹
4	4-F-C ₆ H ₄	4d	45	92	194-196	192-195 ¹⁰
5	4-Cl-C ₆ H ₄	4e	50	96	197-199	190-192 ¹³
6	3-Cl-C ₆ H ₄	4f	50	90	184-187	184-186 ¹⁰
7	2-Cl-C ₆ H ₄	4g	35	90	205-206	200-202 ¹⁴
8	2,4-(Cl) ₂ -C ₆ H ₃	4h	50	90	211-213	-
9	4-Br-C ₆ H ₄	4i	60	93	189-192	190-192 ¹⁴
10	3-Br-C ₆ H ₄	4j	40	89	192-194	191-194 ¹⁰
11	4-Ph-C ₆ H ₄	4k	75	84	222-225	222-225 ⁹
12	Ph	4l	75	88	175-177	174-176 ¹⁴
13	2-Naphthal	4m	80	92	226-228	225-228 ⁹
14	4-OH-C ₆ H ₄	4n	100	84	243-246	240-242 ¹⁴
15	4-Me-C ₆ H ₄	4o	110	91	202-205	201-204 ¹⁰
16	4-MeO-C ₆ H ₄	4p	135	85	150-152	150-153 ⁹
17	4-MeS-C ₆ H ₄	4q	125	85	160-162	159-161 ⁹

Reaction conditions: aniline **1** (1mmol), diethyl acetylenedicarboxylate **2** (1 mmol), aldehyde **3a-q** (1mmol), and malic acid (1 mmol) in ethanol solvent (2 mL) at 50 °C.

^a Isolated yield.

Single-crystal X-ray diffraction studies were used to confirm the structure of the compound **4q**. It crystallizes in the centrosymmetric monoclinic space group; therefore, the compound is racemic. The central pyrrolidinone ring is planar with substituents twisted with respect to it. The N-bound phenyl ring is twisted by 46.82(4)°, whereas the methylthiophenyl ring is twisted by 84.75(1)°. The main building block of the crystal packing is the centrosymmetric dimer (Figure 2).

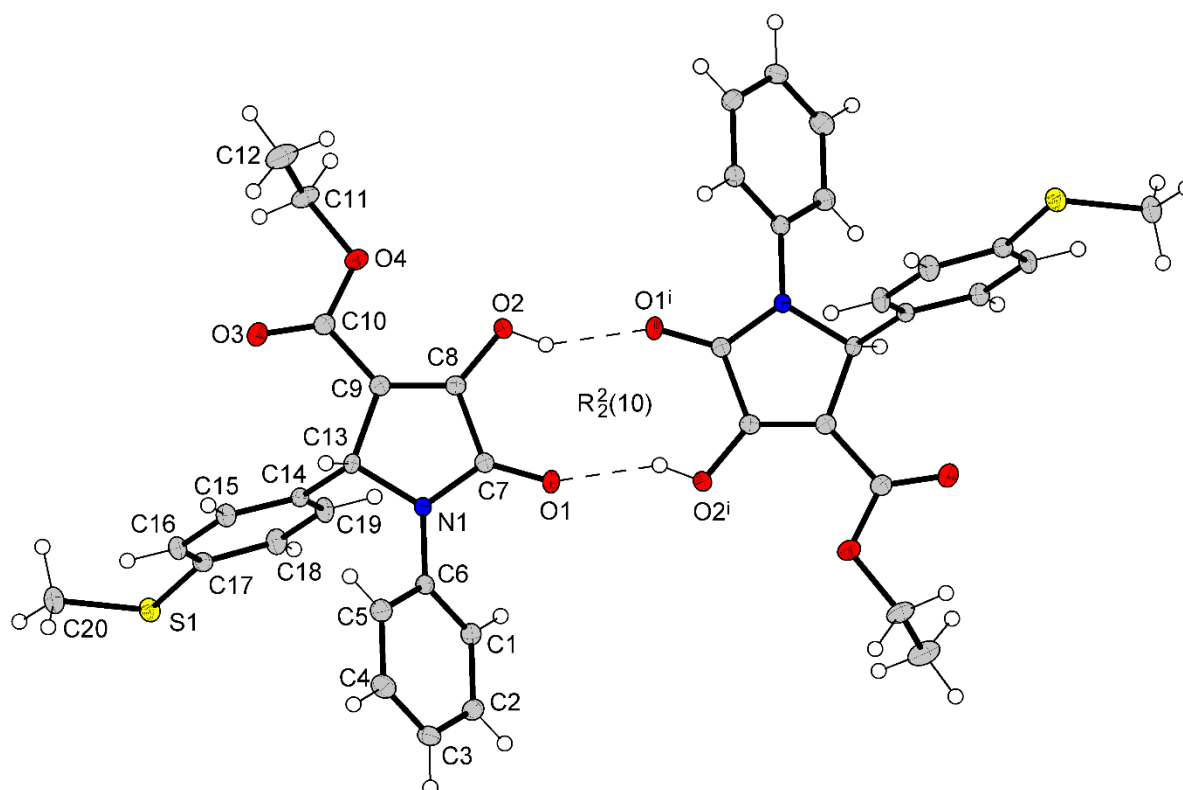


Figure 2. The centrosymmetric dimer in compound **4q** crystal structure along with numbering scheme. Displacement ellipsoids are drawn at 50% probability level. Symmetry code: (i) $1-x, -y, 1-z$.

These dimers are further connected into chains along the *b*-axis direction through C–H⋯O type hydrogen bond (Table 5). The chains are further stabilized by weak interactions of the C–H⋯ π type.

Table 5. Hydrogen-bond geometry (\AA , $^\circ$) for **4q**

<i>D</i> –H⋯ <i>A</i>	<i>D</i> –H	H⋯ <i>A</i>	<i>D</i> ⋯ <i>A</i>	<i>D</i> –H⋯ <i>A</i>
O2–H2⋯O1 ⁱ	0.81(2)	1.97(2)	2.7011(15)	149(2)
C13–H13⋯O1 ⁱⁱ	1.00	2.46	3.4573(18)	172

Symmetry codes: (i) $1-x, -y, 1-z$; (ii) $x, y+1, z$.

It should be noted that we tested several other aromatic aldehydes. Their respective related product **4** could not be generated when we used trans-cinnamaldehyde, salicylaldehyde, 2-hydroxy-1-naphthaldehyde, and 4-(dimethylamino)benzaldehyde under the reaction conditions. In all cases, a mixture of several products and starting materials were observed, based on TLC. The yields of the products of these substrates were poor. Due to electronic effects, forming the imine from aniline and electron-rich aldehydes is very difficult.

We also decided to investigate the behavior of ketones in these reactions. To do this, we tested a reaction with the simplest ketone, acetone. As we suspected, acetone did not respond to the reaction conditions for steric and electronic reasons. Prolonging the reaction time did not affect the reaction results.

Conclusions

We have provided a straightforward, practical, and convenient one-pot, three-component synthesis of pyrrolidinone derivatives in the presence of malic acid as a bioorganocatalyst and green catalyst, and ethanol solvent. The single-crystal X-ray analysis of one of the products, ethyl 4-hydroxy-2-[4-(methylthio)phenyl]-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate was analyzed, confirming its structure. Easy workup, use of green catalyst and solvent, good-to-excellent yields, and short reaction times are among the benefits of this unique procedure.

Experimental Section

General. Chemical materials were provided by Merck, Aldrich, and Fluka. TLC was used to follow the progress of the reactions. Melting points were measured on an Electrothermal 9100 apparatus (LABEQUIP LTD., Markham, Ontario, Canada). FT-IR spectra were measured on a Jasco 6300 FTIR spectrometer. ^1H , and ^{13}C NMR spectra (CDCl_3 and $\text{DMSO}-d_6$) were recorded on a Bruker DRX-250 Avance spectrometer at 250.13, and 62.90 MHz, respectively.

Procedure for the synthesis of pyrrolidinone derivatives. A mixture of aniline **1** (1 mmol), acetylenedicarboxylate **2** (1 mmol), aldehyde **3a-q** (1 mmol), malic acid (1 mmol), and ethanol (2 mL) was magnetically stirred at room temperature. Then, the solution content was stirred at 50°C. To follow the progress of the reaction, TLC was used (n-Hexane: EtOAc, 10:7). The pure products were provided after filtering and recrystallization from hot ethanol.

Ethyl 4-hydroxy-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4a). Yellow solid (339 mg, 92%); mp 182–183°C; FT-IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3299, 3073, 2983, 1732, 1498, 1025; ^1H NMR (250.13 MHz, $\text{DMSO}-d_6$) δ 7.06–8.05 (m, 9H), 6.25 (s, 1H), 4.00 (q, J 7.0 Hz, 2H), 3.97 (br s, 1H), 1.05 (t, J 7.0 Hz, 3H); ^{13}C NMR (62.90 MHz, $\text{DMSO}-d_6$) δ 14.39, 60.17, 60.26, 111.53, 122.85, 123.77, 126.03, 129.48, 130.66, 136.42, 145.21, 147.53, 153.98, 162.31, 164.45.

Ethyl 4-hydroxy-2-(3-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4b). Yellow crystals (328 mg, 89%); mp 224–227°C; FT-IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3329, 3023, 2982, 1721, 1501, 1024; ^1H NMR (250.13 MHz, CDCl_3) δ 1.19 (t, 3H, J 7.0 Hz, 2H), 4.18 (q, J 7.0 Hz, 2H), 5.79 (s, 1H), 6.37–7.79 (m, 8H), 9.22 (br s, 1H). ^{13}C NMR (62.9 MHz, CDCl_3) δ 13.81, 56.01, 61.50, 112.69, 121.60, 126.05, 127.88, 128.06, 129.16, 129.43, 131.60, 134.81, 135.56, 135.79, 157.37, 162.55, 164.99.

Ethyl 4-hydroxy-2-(2-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4c). Yellow crystals (309 mg, 84%); mp 204–206°C; FT-IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3294, 3080, 2982, 1732, 1499, 1021; ^1H NMR (250.13 MHz, CDCl_3) δ 1.20 (t, J 7.13 Hz, 3H), 4.18 (q, J 7.0 Hz, 2H), 5.65 (s, 1H), 7.08–7.68 (m, 9H), 9.10 (br s, 1H); ^{13}C NMR (62.90 MHz, $\text{DMSO}-d_6$) δ 14.34, 54.98, 60.39, 112.19, 122.58, 125.18, 126.11, 127.84, 129.54, 131.64, 134.21, 136.65, 150.51, 153.85, 160.13, 162.26, 164.83.

Ethyl 2-(4-fluorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4d). White crystals (313 mg, 84%); mp 194–196°C; FT-IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3295, 3066, 2984, 1717, 1499, 1027; ^1H NMR (250.13 MHz, CDCl_3) δ 1.19 (t, J 7.0 Hz, 3H), 4.19 (q, J 7.0 Hz, 2H), 5.72 (s, 1H), 6.90–7.45 (m, 9H), 9.06 (br s, 1H). ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.93, 60.86, 61.28, 112.94, 115.63 (d, $^2J_{\text{CF}}$ 21.89 Hz), 122.39, 125.99, 129.07, 129.29, 129.08 (d, $^3J_{\text{CF}}$ 9.37 Hz), 130.89 (d, $^4J_{\text{CF}}$ 3.08 Hz), 136.03, 156.38, 160.58, 162.72, 164.70 (d, $^1J_{\text{CF}}$ 23.40 Hz).

Ethyl 2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4e). White crystals (343 mg, 96%); mp 197-199°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3307, 3067, 2982, 1733, 1499, 1015. ^1H NMR (250.13 MHz, CDCl_3) δ 1.19 (t, 3H, J 7.0 Hz, 2H), 4.20 (q, J 7.0 Hz, 2H), 5.72 (s, 1H), 7.08–7.74 (m, 9H), 9.07 (br s, 1H). ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.97, 60.83, 61.38, 112.77, 122.26, 126.05, 128.87, 129.08, 133.74, 134.29, 135.93, 156.40, 162.76, 164.81.

Ethyl 2-(3-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4f). White crystals; (322 mg, 90%); mp 184-187°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3302, 3050, 2979, 1725, 1475, 1021; ^1H NMR (250.13 MHz, CDCl_3) δ 1.20 (t, 3H, J 7.0 Hz, 3H), 4.20 (q, 2H, J 7Hz, 2H), 5.71 (s, 1H), 7.10–7.48 (m, 9H), 9.17 (br s, 1H); ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.90, 60.87, 61.39, 112.72, 122.14, 125.49, 126.03, 127.88, 128.77, 129.10, 129.93, 134.37, 135.99, 137.35, 156.56, 162.75, 164.83.

Ethyl 2-(2-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4g). White crystals (322 mg, 90%); mp 205-206°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3300, 3064, 2986, 1728, 1499, 1076; ^1H NMR (250.13 MHz, CDCl_3) δ 1.16 (t, J 7.15 Hz, 3H), 4.16 (q, J 7.15 Hz, 2H), 6.43 (s, 1H), 6.93–7.54 (m, 9H), 9.24 (br s, 1H); ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.73, 56.45, 61.34, 112.5, 119.2, 121.62, 125.82, 126.88, 127.49, 129.03, 129.64, 132.77, 136.05, 157.33, 162.72, 165.22.

Ethyl 2-(2,4-dichlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4h). White solid (352 mg, 90%); mp 211-213°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3293, 3023, 2982, 2935, 1722, 1501, 1035; ^1H NMR (250.13 MHz, CDCl_3) δ 1.21 (t, J 7.15 Hz, 3H), 4.18 (q, J 7.15 Hz, 2H), 5.80 (s, 1H), 6.37–7.79 (m, 8H), 9.22 (br s, 1H); ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.81, 56.01, 61.50, 112.69, 121.60, 126.05, 127.88, 128.06, 129.16, 129.43, 131.60, 134.81, 135.56, 135.79, 157.37, 162.55, 164.99.

Ethyl 2-(4-bromophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4i). White crystals (373 mg, 93%); mp 189-192°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3297, 3052, 2981, 1717, 1499, 1027; ^1H NMR (250.13 MHz, $\text{DMSO}-d_6$) δ 1.06 (t, J 7.0 Hz, 3H), 3.64 (br s, 1H), 4.01 (q, J 7.0 Hz, 2H), 6.05 (s, 1H), 7.07- 7.60 (m, 9H); ^{13}C NMR (62.90 MHz, $\text{DMSO}-d_6$) δ 14.41, 60.23, 60.42, 112.20, 121.46, 122.93, 125.99, 126.70, 129.15, 131.60, 136.03, 142.07, 153.27, 162.36, 164.32.

Ethyl 2-(3-bromophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4j). White crystals (357 mg, 89%); mp 192-194°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3304, 3048, 2980, 1727, 1499, 1023; ^1H NMR (250.13 MHz, CDCl_3) δ 1.22 (t, J 7.13 Hz, 3H), 4.21 (q, J 7.13 Hz, 2H), 5.68 (s, 1H), 7.09–7.48 (m, 9H), 9.16 (br s, 1H); ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.92, 60.80, 61.41, 112.73, 122.13, 122.44, 125.90, 126.04, 129.12, 130.22, 130.80, 131.68, 135.97, 137.58, 156.57, 162.74, 164.84.

Ethyl 2-([1,1'-biphenyl]-4-yl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4k). White solid (335 mg, 84%); mp 222-225°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3238, 3030, 2976, 1702, 1485, 1018; ^1H NMR (250.13 MHz, CDCl_3) δ 1.20 (t, J 7.13 Hz, 3H), 4.21 (q, J 7.17 Hz, 2H), 5.79 (s, 1H), 7.08–7.5 (m, 12H), 9.10 (br s, 1H); ^{13}C NMR (62.90 MHz, CDCl_3) δ 14.0, 61.23, 61.31, 113.12, 122.23, 125.85, 126.21, 126.94, 127.38, 127.92, 128.76, 129.01, 1334.04, 136.30, 140.18, 141.28, 156.46, 162.88, 165.09.

Ethyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4l). White crystals (284 mg, 88%); mp 175-177°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3250, 3077, 2970, 1710, 1458, 1090; ^1H NMR (250.13 MHz, CDCl_3) δ 1.16 (t, 3H, J 7.0 Hz, 3H), 4.17 (q, J 7.0 Hz, 2H), 5.74 (s, 1H), 7.05–7.50 (m, 9H), 9.14 (br s, 1H); ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.91, 61.23, 61.56, 113.19, 122.27, 125.81, 127.53, 128.50, 128.57, 128.94, 135.07, 136.24, 156.36, 162.94, 165.05.

Ethyl 4-hydroxy-2-(naphthalen-1-yl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4m). White crystal (343 mg, 92%); mp 226-228°C; FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3250, 3077, 2970, 1710, 1458, 1090; ^1H NMR (250.13 MHz, CDCl_3) δ 1.13 (t, 3H, J 7.0 Hz, 3H), 4.14 (q, 2H, J 7.0 Hz, 2H), 5.91 (s, 1H), 7.02–7.47 (m, 12H),

9.18 (br s, 1H); ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.89, 61.26, 61.69, 113.13, 122.24, 123.83, 125.87, 126.38, 127.71, 127.77, 127.89, 128.67, 128.98, 132.46, 133.06, 133.26, 136.27, 156.59, 162.93, 164.11.

Ethyl 4-hydroxy-2-(4-hydroxyphenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4n). White solid (284 mg, 84%); mp 243-246°C; FT-IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3311, 3027, 2990, 1698, 1451, 1071; ^1H NMR (250.13 MHz, $\text{DMSO}-d_6$) δ 1.10 (t, J 7.0 Hz, 3H), 3.55 (br s, 1H), 3.99 (q, J 7.00 Hz, 2H), 5.93 (s, 1H), 6.55–7.69 (m, 9H), 9.34 (br s, 1H); ^{13}C NMR (62.90 MHz, $\text{DMSO}-d_6$) δ 14.44, 60.08, 60.78, 112.94, 115.41, 123.03, 125.67, 126.66, 129.03, 129.24, 136.79, 152.57, 157.24, 162.48, 164.27.

Ethyl 4-hydroxy-5-oxo-1-phenyl-2-(p-tolyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (4o). White crystal (307 mg, 91%); mp 202-205°C; FT-IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3250, 3077, 2970, 1710, 1458, 1090; ^1H NMR (250.13 MHz, CDCl_3) δ 1.19 (t, J 7.0 Hz, 3H), 2.25 (s, 3H), 4.18 (q, J 7.0 Hz, 2H), 5.71 (s, 1H), 7.02–7.50 (m, 9H), 9.00 (br s, 1H); ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.93, 21.11, 61.21, 61.32, 113.24, 122.24, 125.73, 127.36, 128.90, 128.27, 131.93, 136.33, 138.24, 156.30, 162.90, 165.11.

Ethyl 4-hydroxy-2-(4-methoxyphenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4p). White crystal (300 mg, 85%); mp 150-152°C; FT-IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3250, 3029, 2929, 1706, 1458, 1107, 1032; ^1H NMR (250.13 MHz, CDCl_3) δ 1.20 (t, J 7.25 Hz, 3H), 3.73 (s, 3H), 4.19 (q, J 7.08 Hz, 2H), 5.69 (s, 1H), 6.74–7.46 (m, 9H), 9.15. (br s, 1H); ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.98, 55.16, 61.03, 61.25, 113.21, 113.97, 122.37, 125.80, 126.71, 128.66, 128.94, 136.23, 156.38, 159.52, 162.00, 165.00.

Ethyl 4-hydroxy-2-(4-(methylthio)phenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (4q). Yellow crystal (14mg, 85%); mp 160-162°C; FT-IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3250, 3077, 2970, 1710, 1458, 1090; ^1H NMR (250.13 MHz, CDCl_3) δ 1.18 (t, J 7.00 Hz, 3H), 2.38 (s, 3H), 4.17 (q, J 7.00 Hz, 2H), 5.68 (s, 1H), 7.10–7.47 (m, 9H), 9.15. (br s, 1H); ^{13}C NMR (62.90 MHz, CDCl_3) δ 13.98, 15.26, 61.12, 61.27, 113.07, 122.24, 125.84, 126.13, 127.95, 128.96, 131.58, 136.14, 139.00, 156.00, 163.00, 164.81.

X-Ray crystallography. The yellow powder of **4q** was solved in hot ethanol. Good-quality crystals were prepared in excellent yields by slow evaporation at room temperature. The crystallographic measurements of **4q** were performed on an Agilent Technologies Xcalibur R κ -geometry automated four-circle diffractometer equipped with a Ruby CCD camera and graphite-monochromated $\text{MoK}\alpha$ radiation (λ 0.71073 Å). The data were collected at 100(2) K using the Oxford-Cryosystems cooler. Data were corrected for Lorentz and polarization effects. Data collection, cell refinement, data reduction, and analysis were carried out with CrysAlisPro.^{42,43} The empirical (multi-scan) absorption correction was applied to the data with the use of CrysAlisPro. The structure was solved with direct methods using SHELXS-97,⁴⁴ and refined on F^2 by a full-matrix least squares technique with the anisotropic thermal parameters for non-H atoms with SHELXL-2014/7.⁴⁵ The H atoms were found in different Fourier maps and initially refined isotropically. In the final refinement cycles, the C-bonded H atoms were repositioned in their calculated positions and refined using a riding model, with C–H 0.95-1.00 Å and $U_{\text{iso}}(\text{H})$ 1.2 $U_{\text{eq}}(\text{C})$ for CH and CH_2 and 1.5 $U_{\text{eq}}(\text{C})$ for CH_3 . The hydroxyl H atom was refined freely. Crystal data, data collection, and structure refinement details for **4q** are summarized in Table 1 in Supplementary Material. Figures were made with the DIAMOND program.⁴⁶ The crystallographic information file (CIF) was deposited with the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/; deposition number CCDC-2021152).

Acknowledgements

The authors thank the Department of Chemistry, Abhar Branch, Islamic Azad University for the lab facilities to conduct this work.

Supplementary Material

The spectral data of the products, copies of FT-IR, ^1H and ^{13}C NMR spectra, and X-ray crystallography data are provided in the Supplementary Material file associated with this manuscript.

References

1. Jiang, B.; Rajale, T.; Wever, W.; Tu, S.J.; Li, G. *Chem. Asian J.* **2010**, *5*, 2318.
<https://doi.org/10.1002/asia.201000310>
2. Abdelmoniem, A.M.; Ghozlan, S.A.; Butenschön, H.; Abdelmoniem, D.M.; Elwahy, A.H.; Abdelhamid, I.A. *Arkivoc* **2019**, *2019*, 163.
<https://doi.org/10.24820/ark.5550190.p010.875>
3. Zafari, P.; Saatluo, B.E.; Rashidi, A.; Baradarani, M.M.; Jouleb, J.A. *Arkivoc* **2021**, *9*.
<https://doi.org/10.24820/ark.5550190.p011.225>
4. Mao, J.; Wang, J.; Zhang, W.; Li, Z.; Zhu, J.; Guo, C. *Arkivoc* **2016**, *3*, 171.
<http://doi.org/10.3998/ark.5550190.p009.398>
5. Kazemizadeh, A.R.; Ramazani, A. *Arkivoc* **2008**, *15*, 159.
<https://doi.org/10.3998/ark.5550190.0009.f15>
6. Sun, J.; Wu, Q.; Xia, E.Y.; Yan, C.G. *Eur. J. Org. Chem.* **2011**, *16*, 2981.
<https://doi.org/10.1002/ejoc.201100008>
7. Sarkar, R.; Mukhopadhyay, C. *Tetrahedron lett.* **2013**, *54*, 3706.
<https://doi.org/10.1016/j.tetlet.2013.05.017>
8. Franco, M.S.; Casagrande, G.A.; Raminelli, C.; Moura, S.; Rossatto, M.; Quina, F.H.; Pereira, C.M.; Flores, A.F.; Pizzuti, L. *Synth. Commun.* **2015**, *45*, 692.
<https://doi.org/10.1080/00397911.2014.978504>
9. Ahankar, H.; Ramazani, A.; Ślepokura, K.; Lis, T.; Joo, S.W. *Green Chem.* **2016**, *18*, 3582.
<https://doi.org/10.1039/C6GC00157B>
10. Hosseinzadeh, Z.; Ramazani, A.; Ahankar, H.; Ślepokura, K.; Lis, T. *Silicon* **2019**, *11*, 2933.
<https://doi.org/10.1007/s12633-017-9737-4>
11. Ahankar, H.; Ramazani, A.; Ślepokura, K.; Lis, T.; Kinzhybalov, V. *Res. Chem. Intermed.* **2019**, *45*, 5007.
<https://doi.org/10.1007/s11164-019-03878-1>
12. Vidal, J.D.; Climent Olmedo, M.J.; Corma Canós, A.; Concepción Heydorn, P.; Iborra Chornet, S. *ChemSusChem* **2017**, *10*, 119.
<http://doi.org/10.1002/cssc.201601333>
13. Yang, J.; Tan, J.-N.; Gu, Y. *Green Chem.* **2012**, *14*, 3304.
<https://doi.org/10.1039/C2GC36083G>
14. Khaligh, N.G.; Mihankhah, T.; Johan, M.R.; Titinchi, S.J. *Green Process. Synth.* **2019**, *8*, 373.
<https://doi.org/10.1515/gps-2019-0004>
15. Buccafusco, J.J.; Shuster, L.C.; Terry Jr, A.V. *Neuroscience letters* **2007**, *413*, 68.
<https://doi.org/10.1016/j.neulet.2006.11.028>
16. Singh, P.; Dimitriou, V.; Mahajan, R.; Crossley, A. *Br. J. Anaesth.* **1993**, *71*, 685.
<https://doi.org/10.1093/bja/71.5.685>
17. Patsalos, P.N. *Epilepsia* **2005**, *46*, 140.

<https://doi.org/10.1111/j.1528-1167.2005.00326.x>

18. Shiraki, R.; Sumino, A.; Tadano, K.-i.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845.
<https://doi.org/10.1021/jo951897z>
19. Omura, S.; Fujimoto, T.; Otaguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113.
<https://doi.org/10.7164/antibiotics.44.113>
20. Ettliger, L.; Gäumann, E.; Hütter, R.; Keller-Schierlein, W.; Kradofer, F.; Neipp, L.; Prelog, V.; Zähler, H. *Helv. Chim. Acta*, **1959**, *42*, 563.
<https://doi.org/10.1002/hlca.19590420225>
21. Shiozawa, H.; Takahashi, S. *J. Antibiot.* **1994**, *47*, 851.
<https://doi.org/10.7164/antibiotics.47.851>
22. Singh, S.B.; Goetz, M.A.; Jones, E.T.; Bills, G.F.; Giacobbe, R.A.; Herranz, L.; Stevens-Miles, S.; Williams Jr, D.L. *J. Org. Chem.* **1995**, *60*, 7040.
<https://doi.org/10.1021/jo00126a071>
23. He, H.; Yang, H.Y.; Bigelis, R.; Solum, E.H.; Greenstein, M.; Carter, G.T. *Tetrahedron Lett.* **2002**, *43*, 1633.
[https://doi.org/10.1016/S0040-4039\(02\)00099-0](https://doi.org/10.1016/S0040-4039(02)00099-0)
24. Clark, A.J.; Dell, C.P.; McDonagh, J.M.; Geden, J.; Mawdsley, P. *Org. Lett.* **2003**, *5*, 2063.
<https://doi.org/10.1021/ol030045f>
25. Chen, J.; Huang, P.-Q.; Queneau, Y. *J. Org. Chem.* **2009**, *74*, 7457.
<https://doi.org/10.1021/jo901557h>
26. Asami, Y.; Takeya, H.; Onose, R.; Yoshida, A.; Matsuzaki, H.; Osada, H. *Org. Lett.* **2002**, *4*, 2845.
<https://doi.org/10.1021/ol020104+>
27. Feling, R.H.; Buchanan, G.O.; Mincer, T.J.; Kauffman, C.A.; Jensen, P.R.; Fenical, W. *Angew. Chem. Int. Ed.* **2003**, *42*, 355.
<https://doi.org/10.1002/anie.200390115>
28. Koz'minykh, V.; Igidov, N.; Zykova, S.; Kolla, V.; Shuklina, N.; Odegova, T. *Pharm. Chem. J.* **2002**, *36*, 188.
<https://doi.org/10.1023/A:1019832621371>
29. Gein, V.; Mihalev, V.; Kasimova, N.; Voronina, E.; Vakhrin, M.; Babushkina, E. *Pharm. Chem. J.* **2007**, *41*, 208.
<https://doi.org/10.1007/s11094-007-0047-9>
30. Gein, V.; Yushkov, V.; Kasimova, N.; Shuklina, N.; Vasil'eva, M.Y.; Gubanov, M. *Pharm. Chem. J.* **2005**, *39*, 484.
<https://doi.org/10.1007/s11094-006-0006-x>
31. Gein, V.; Armisheva, M.; Rassudikhina, N.; Vakhrin, M.; Voronina, E. *Pharm. Chem. J.* **2011**, *45*, 162.
<https://doi.org/10.1007/s11094-011-0584-0>
32. Zhu, Q.; Gao, L.; Chen, Z.; Zheng, S.; Shu, H.; Li, J.; Jiang, H.; Liu, S. *Eur. J. Med. Chem.* **2012**, *54*, 232.
<https://doi.org/10.1016/j.ejmech.2012.05.001>
33. Brine, G.A.; Boldt, K.G. *J. Pharm. Sci.* **1983**, *72*, 700.
<https://doi.org/10.1002/jps.2600720627>
34. Ma, K.; Wang, P.; Fu, W.; Wan, X.; Zhou, L.; Chu, Y.; Ye, D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6724.
<https://doi.org/10.1016/j.bmcl.2011.09.054>
35. Pendri, A.; Troyer, T.L.; Sofia, M.J.; Walker, M.A.; Naidu, B.N.; Banville, J.; Meanwell, N.A.; Dicker, I.; Lin, Z.; Krystal, M. *J. Comb. Chem.* **2010**, *12*, 84.
<https://doi.org/10.1021/cc9001026>

36. Khaligh, N.G.; Chong, K.F.; Mihankhah, T.; Titinchi, S.; Johan, M.R.; Ching, J.J. *Aust. J. Chem.* **2018**, *71*, 566.
<https://doi.org/10.1071/CH18246>
37. Kövilein, A.; Kubisch, C.; Cai, L.; Ochsenreither, K. *J. Chem. Technol. Biotechnol.* **2020**, *95*, 513.
<https://doi.org/10.1002/jctb.6269>
38. Sefkow, M. *J. Org. Chem.* **2001**, *66*, 2343.
<https://doi.org/10.1021/jo001547z>
39. Tufail, F.; Saquib, M.; Singh, S.; Tiwari, J.; Singh, M.; Singh, J.; Singh, J. *New J. Chem.* **2017**, *41*, 1618.
<https://doi.org/10.1039/C6NJ03907C>
40. Kumar, A.; Rai, P.; Yadav, V.B.; Sagir, H.; Siddiqui, I. *Curr. Organocatal.* **2018**, *5*, 239.
<https://doi.org/10.2174/2213337205666181008103213>
41. Ramón, D.J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.
<https://doi.org/10.1002/anie.200460548>
42. *CrysAlisCCD and CrysAlisRED in KM4-CCD software. Oxford Diffraction Ltd.: Yarnton, Oxfordshire, England 2010.*
43. *CrysAlisPro in Xcalibur software. Agilent Technologies, Yarnton, UK, 2012.*
44. Sheldrick, G.M. *Acta Crystallogr. Sect. A: Found. Crystallogr.* **2015**, *71*, 3.
<https://doi.org/10.1107/S2053273314026370>
45. Sheldrick, G.M. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 3.
<https://doi.org/10.1107/S2053229614024218>
46. Brandenburg, K., DIAMOND Version 3.2k. Crystal Impact GbR: Bonn, Germany **2014**.

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>)