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ONE-POT SYNTHESIS OF DIHYDROPYRIMIDIONES VIA ENVIRONMENTALLY FRIENDLY ENZYME-CATALYZED BIGINELLI REACTION

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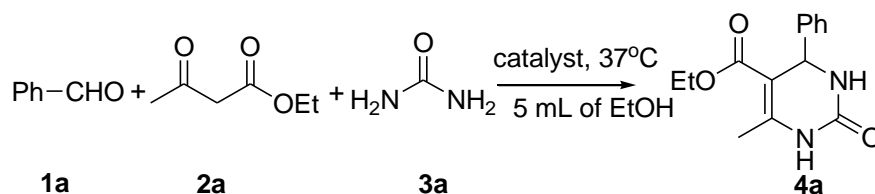
Abstract – A novel enzyme-catalyzed Biginelli reaction of acetoacetate, aromatic aldehyde and urea (thiourea) was described. Great acceleration of the one-pot multicomponent reaction was observed by the aid of enzymes. Various dihydropyrimidiones were prepared in good yields under the conditions using trypsin from *porcine pancreas* as the catalyst.

INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in the fields of organic and medicinal chemistry, for their high atom economy, extensive applications in combinatorial chemistry, and diversity-oriented synthesis.¹⁻⁶ As one of the most useful multicomponent reactions, the Biginelli reaction, originally described by Biginelli in 1893, offers an efficient route to obtain multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) and related heterocyclic compounds.⁷ These heterocycles exhibit a wide spectrum of biological effects such as antibacterial,⁸ antiviral,⁹ anticancer,¹⁰ anti-inflammatory,¹¹ and antihypertensive effects.¹² The first one-pot cyclocondensation reaction of ethylacetoacetate, benzaldehyde and urea was carried out by simply heating the three components mixture dissolved in ethanol with a catalytic amount of HCl at reflux temperature. However, the product yields are quite low (20–50%). Biginelli reactions with higher yields up to 95% have been achieved by replacing the HCl catalyst to ZnCl₂,¹³ FeCl₃,¹⁴ BF₃,¹⁵ ZrCl₄,¹⁶ InBr₃,¹⁷ In(OTf)₃,¹⁸ Ln(OTf)₃,¹⁹ Cu(OTf)₂,²⁰ Sr(OTf)₂,²¹ MgBr₂,²² [bmim]BF₄-immobilized Cu(II) acetylacetonate,²³ [bmim] [FeCl₄],²⁴ etc. However, all the above methods displayed some drawbacks, such as environmental pollution, strongly acidic reaction conditions, unsatisfactory yields, toxic catalysts, and complicated operations.

high yield of 75% if α -amylase from hog pancreas was used as catalyst (Entry 11). Excitingly, pepsin from hog stomach and trypsin from porcine pancreas show significant catalytic activities, and the final yields of the desired product 3,4-dihydropyrimidin-2(1*H*)-ones **4a** were 85% and 88% respectively, after 72 h reaction in our tests (Entries 12 and 13). If trypsin from porcine pancreas was denatured or deactivated, only trace amount of the desired product **4a** was detected. Bovine serum albumin, as a non-catalytic protein, either shew none catalysis in this reaction.

Table 1. Specific catalytic effect of enzymes^a



Entry	Catalyst	Amount (mg)	Time (h)	Yield (%)
1	none	-	72	0
2	PPL	30	96	10
3	lipase AY30	30	96	< 5
4	lipase CAL-B	30	96	< 5
5	lipase A from <i>Aspergillus niger</i>	30	96	0
6	lipase AK from <i>Pseudomonas fluorescens</i>	30	96	0
7	lipase M from <i>Mucor javanicus</i>	30	72	65
8	α -amylase from <i>Bacillus subtilis</i>	30	96	0
9	α -amylase from <i>Aspergillus oryzae</i>	30	96	0
10	β aAmylase from soybean	30	96	0
11	α -amylase from hog pancreas	30	72	75
12	pepsin from hog stomach	20	72	85
13	trypsin from porcine pancreas	20	72	88
14	trypsin from porcine pancreas ^b	20	72	trace
15	bovine serum albumin	30	72	0

^a 2 mmol of **1a**, 2.1 mmol of **2a** and 2.1 mmol of **3a** in 5 mL of anhydrous EtOH.

^b Trypsin from porcine pancreas was denatured or deactivated at 100 °C.

Solvent effect was also carefully investigated in the case of using trypsin from porcine pancreas as catalyst due to its highest catalytic activity. It is found that the Biginelli multicomponent reaction could proceed in most common polar solvents, such as MeOH, EtOH, DMSO, MeCN and DMF (Table 2, Entries 1, 2, 3, 4, 9). Among them, the dihydropyrimidione **4a** was obtained with much higher yield when MeOH or EtOH is used as solvent (Table 2, Entries 2, 3). In other solvents including THF, CH₂Cl₂, chloroform, and cyclohexane, only small amount of product was detected (Table 2, Entries 5–8). It is also found that water could greatly influence the reaction rate. None of desired product was obtained if the reaction was carried out using H₂O as solvent (Table 2, Entry 11). When 1 mL of H₂O was added into EtOH solvent, the yield decreased from 88 to 10% (Table 2, Entries 3 and 10).

Table 2. Effects of different solvents on MCR of benzaldehyde **1a** and ethyl acetoacetate **2a** with urea **3a**^a

Entry	Solvent	Temperature (°C)	Yield (%)
1	DMSO	37	80
2	MeOH	37	85
3	EtOH	37	88
4	MeCN	37	86
5	THF	37	21
6	CH ₂ Cl ₂	37	33
7	CHCl ₃	37	35
8	cyclohexane	37	trace
9	DMF	37	65
10	EtOH + H ₂ O(1 mL)	37	10
11	H ₂ O	37	-
12	EtOH	37	95 ^b
13	EtOH	25	8 ^c

^a Condition: 2 mmol of **1a**, 2.1 mmol of **2a** and 2.1 mmol of **3**, 20 mg of trypsin from porcine pancreas, 5 mL of solvent, 72 h.

^b 3A molecular sieve was used. ^c The reaction was carried out at 25 °C for 72 h.

When 0.2 g of 3A molecular sieve was added into the reaction mixture to further remove the water byproduct formed during the reaction, the yield of **4a** product can be increased up to 95% in 72 h (Table 2, Entry 12).

The influence of reaction temperature on the enzymatic Biginelli reaction was also considered. It is found that the yield decreased with the decrease of temperature. The yield was only 8% at 25 °C (Table 2, Entry

13). This is quite reasonable result because most of the enzymes give highest activities at about 35 - 40 °C, which close to the body temperature of most mammals.

With the optimal conditions in hand, we applied this protocol to other substrates and the obtained results are shown in Table 3. In the presence of 20 mg of trypsin from porcine pancreas at 37 °C, most three components condensation reactions reached the equilibrium after 72 h in anhydrous ethanol and could provide expected products in good yields.

Table 3. Preparation of different dihydropyrimidiones *via* enzyme-catalyzed Biginelli reaction^a

Entry	R'	X	Time (h)	R	Yield (%)
1	Et	O	72	Ph(4a)	95 (93, 92, 92, 89) ^b
2	Et	O	72	3,4-(OCH ₂ O)-C ₆ H ₃ (4b)	94
3	Et	O	72	4-MeO- C ₆ H ₄ (4c)	96
4	Et	O	72	4-Cl-C ₆ H ₄ (4d)	95
5	Me	O	72	4-Cl-C ₆ H ₄ (4e)	93
6	Me	O	72	4-NO ₂ -C ₆ H ₄ (4f)	89
7	Et	O	72	4-HO-C ₆ H ₄ (4g)	90
8	Et	O	72	4-(NMe ₂)-C ₆ H ₄ (4h)	93
9	Et	O	72	3-Cl-C ₆ H ₄ (4i)	93
10	Me	O	72	3-HO-C ₆ H ₄ (4j)	92
11	Et	O	72	3-Br-C ₆ H ₄ (4k)	89
12	Et	O	72	3-MeO-4-HO-C ₆ H ₃ (4l)	92
13	Et	O	96	2-Cl-C ₆ H ₄ (4m)	82
14	Et	O	72	2-furyl (4n)	87
15	Et	O	72	2-pyridyl (4o)	85
16	Et	S	72	4-Me-C ₆ H ₄ (4p)	91
17	Me	S	72	4-CN-C ₆ H ₄ (4q)	90
18	Et	S	72	4-CN-Ph (4r)	93

^a 2 mmol of **1**, 2.1 mmol of **2** and 2.1 mmol of **3**, 20 mg of trypsin from porcine pancreas, 5 mL of anhydrous EtOH, 37 °C, 72 h, 0.4 g 3A molecular sieve.

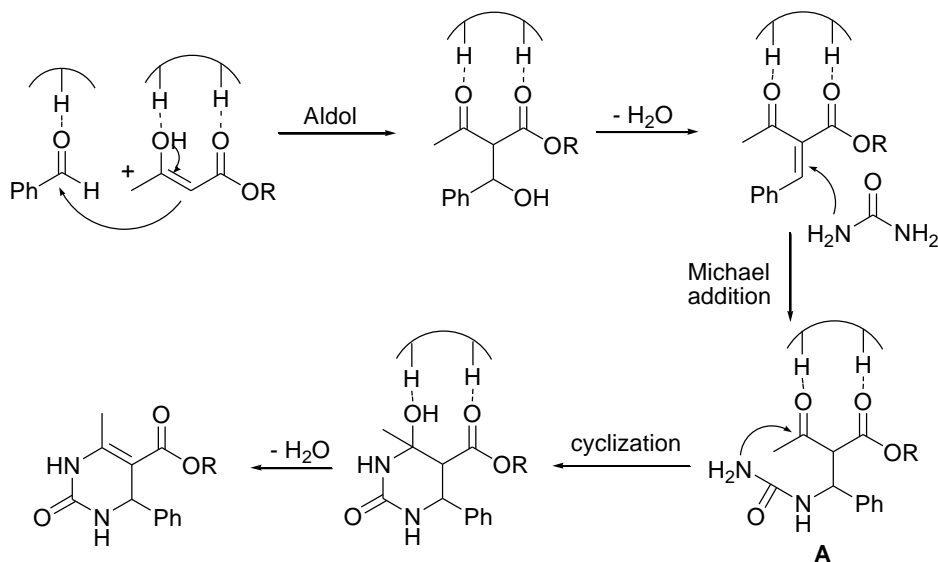
^b Enzyme was recovered and reused for four times.

The results on the reaction of the different aldehydes revealed that the substituent on the aromatic ring plays a little role in governing the reactivity. A variety of *para*-substituted aromatic aldehydes, bearing

either electron-donating or electron-withdrawing substituents, afforded high yields of the products. The similar results were obtained when using meso-substituted aromatic aldehydes. Ortho-substituted aldehydes such as 2-chlorobenzaldehyde, needed longer time and gave 82% yield (Entry 13). Heterocyclic aldehydes such as 2-pyridylaldehyde and 2-furylaldehyde worked well and afforded the desired product in 87 and 85% yield, respectively. However, the sterically hindered 2,6-dimethoxybenzaldehyde couldn't afford any desired product even after 96 h under the same conditions. In addition, thiourea **3b** was also tested, satisfactorily, corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones were obtained with 90–93% yields (Entries 16–18). Furthermore, methyl acetoacetate also afforded the desired products in high yields (Entries 5, 6, 10, and 17).

It should be pointed out that another advantage of this protocol is the easy recovering of the catalyst, and enzyme could be obtained by straight filtration due to its poor solubility in organic solvent. The enzyme was recovered and reused for four times, the recovered enzyme shows good catalytic activity under the same reaction conditions with 93%, 92%, 92%, and 89% yield respectively (Table 3, Entry 1).

According to these satisfactory results, we so proposed a tentative mechanism for this new process (Scheme 2). The proposed mechanism would start with the accommodation of the carbonyl in the active site. The intermediate **A** was formed then the final product was obtained through cyclization and dehydration.



Scheme 2. The proposed mechanism of enzyme-catalyzed Biginelli reaction

CONCLUSION

In conclusion, here we have reported a novel and environmentally friendly enzyme catalyzed multicomponent Biginelli reaction. The advantages of this method included mild reaction conditions, good yields, simple operation and environmentally friendly procedure.

EXPERIMENTAL

Lipase A from *Aspergillus niger*, AY from *Candida Antarctica*, AK from *Pseudomonas fluorescens*, and M from *Mucor javanicus* were obtained from Amano Pharmaceuticals Co., Ltd. All amylases and trypsins were obtained from Sigma-Aldrich. Analytical grade solvents and commercially available reagents were used without further purification. The Thin layer chromatography (TLC), which was used to monitor the reaction, was carried out over silica gel (GF254), purchased from Qingdao Haiyang Chemical Co., Ltd. Melting points were determined on a Büchi B-540 capillary melting point apparatus and were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at VARAIN-400 or BRUKER AC400 using $\text{DMSO-}d_6$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in relative to TMS, the coupling constants J are given in Hz.

General procedure for the synthesis of dihydropyrimidiones *via* enzyme-catalyzed Biginelli reaction (Using Trypsin from porcine pancreas, Table 3):

In 5 mL of anhydrous EtOH, 2 mmol of aromatic aldehyde, 2.1 mmol of ethyl acetoacetate, 2.1 mmol of urea or thiourea, 0.4g of 3A molecular sieve, 20 mg of trypsin from porcine pancreas was added successfully, and the mixture was orbitally shaken at 37 °C for the given time (see Table 3) and monitored by TLC. When the reaction completed, additional 10 mL of anhydrous EtOH was added to the mixture and heated to 37 °C. The enzyme catalyst and 3A molecular sieve were isolated by hot filtration, then the filtrate was condensed to half volume and cooled to -5 °C, finally the precipitate was collected to obtain the desired dihydropyrimidiones **4a-4r**. All products were known compounds, and were analyzed by IR, ^1H NMR and ^{13}C NMR. The spectra data were identical with authentic samples.

CHARACTERISTIC DATA

4a, Straw yellow solid,³³ Mp 201-203 °C. IR (KBr): 3440, 3210, 3102, 2936, 1710, 1655, 1579 cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ = 9.16 (s, 1 H), 7.75 (s, 1 H), 7.22–7.33 (m, 5 H), 5.13 (s, 1 H), 3.99 (q, J = 7.2 Hz, 2 H), 2.25 (s, 3 H), 1.06 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($\text{DMSO-}d_6$): δ = 165.3, 151.9, 148.3, 144.8, 128.3, 127.2, 126.2, 99.1, 59.1, 54.1, 17.9, 14.2.

4b, White solid,³³ Mp 186-188 °C. IR (KBr): 3434, 3228, 3112, 2955, 1695, 1644, 1515 cm^{-1} . ^1H NMR ($\text{DMSO-}d_6$): δ = 9.13 (s, 1 H), 7.68 (s, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 6.75 (s, 1 H), 6.64 (d, J = 8.0 Hz, 1 H), 5.98 (s, 2 H), 5.07 (d, J = 3.2 Hz, 1 H), 3.96 (q, J = 7.2 Hz, 2 H), 2.22 (s, 3 H), 1.10 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($\text{DMSO-}d_6$): δ = 165.2, 152.1, 148.2, 147.1, 146.2, 138.9, 119.2, 107.9, 106.5, 100.8, 99.2, 59.2, 53.7, 17.7, 14.0.

4c, White solid,³³ Mp 203-204 °C. IR (KBr): 3428, 3238, 3104, 2964, 1712, 1654, 1518 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 9.15 (s, 1 H), 7.67 (s, 1 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 5.07 (d, *J* = 2.8 Hz, 1 H), 3.96 (q, *J* = 7.2 Hz, 2 H), 3.73 (s, 3 H), 2.22 (s, 3 H), 1.08 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (DMSO-*d*₆): δ = 165.3, 158.3, 152.1, 148.1, 137.1, 127.5, 113.6, 99.6, 59.1, 55.0, 53.2, 17.6, 14.0.

4d, White solid,³³ Mp 213-215 °C. IR (KBr): 3423, 3241, 3121, 2970, 1705, 1655, 1477 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 9.21 (s, 1 H), 7.76 (s, 1 H), 7.37 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz, 2 H), 5.13 (d, *J* = 2.8 Hz, 1 H), 3.98 (q, *J* = 7.2 Hz, 2 H), 2.23 (s, 3 H), 1.07 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (DMSO-*d*₆): δ = 165.1, 151.9, 148.8, 143.7, 131.7, 128.3, 128.1, 98.8, 59.2, 53.4, 17.7, 14.2.

4e, White solid,³³ Mp 203-204 °C. IR (KBr): 3366, 3222, 3113, 2953, 1718, 1641, 1504 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 9.28 (s, 1 H), 7.81 (s, 1 H), 7.41 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 5.13 (d, *J* = 2.8 Hz, 1 H), 3.54 (s, 3 H), 2.26 (s, 3 H). ¹³C NMR (DMSO-*d*₆): δ = 165.5, 151.8, 148.8, 143.5, 131.7, 128.3, 128.1, 98.3, 53.1, 50.7, 17.8.

4f, White solid,³³ Mp 235-237 °C. IR (KBr): 3361, 3225, 3111, 2959, 1719, 1638, 1510 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 9.40 (s, 1 H), 8.21 (d, *J* = 8.4 Hz, 2 H), 7.94 (s, 1 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 5.26 (d, *J* = 2.8 Hz, 1 H), 3.53 (s, 3 H), 2.28 (s, 3 H). ¹³C NMR (DMSO-*d*₆): δ = 165.5, 151.6, 149.4, 146.6, 127.4, 123.7, 109.1, 97.8, 53.3, 50.8, 17.9.

4g, Straw yellow solid,³³ Mp 226-227 °C. IR (KBr): 3412, 3249, 3125, 2974, 1695, 1659, 1508 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 9.33 (s, 1 H), 9.11 (s, 1 H), 7.62 (s, 1 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.67 (d, *J* = 8.4 Hz, 2 H), 5.03 (d, *J* = 3.2 Hz, 1 H), 3.98 (q, *J* = 7.2 Hz, 2 H), 2.22 (s, 3 H), 1.07 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (DMSO-*d*₆): δ = 165.3, 156.5, 152.3, 147.8, 135.4, 127.4, 115.0, 99.7, 59.1, 53.5, 17.8, 14.1.

4h, Straw yellow solid,³³ Mp 255-257 °C. IR (KBr): 3417, 3241, 3115, 2986, 1713, 1637, 1520 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 9.06 (s, 1 H), 7.56 (s, 1 H), 7.02 (d, *J* = 8.4 Hz, 2 H), 6.65 (d, *J* = 8.4 Hz, 2 H), 5.03 (d, *J* = 3.2 Hz, 1 H), 3.97 (q, *J* = 7.2 Hz, 2 H), 2.84 (s, 6 H), 2.22 (s, 3 H), 1.10 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (DMSO-*d*₆): δ = 165.6, 152.3, 149.8, 147.6, 132.7, 126.9, 112.2, 100.0, 59.2, 53.4, 17.6, 14.2.

4i, Straw yellow solid,³³ Mp 189-190 °C. IR (KBr): 3431, 3231, 3102, 2978, 2931, 1709, 1653, 1598 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 8.32 (s, 1 H), 7.25–7.36 (m, 4 H), 6.94 (s, 1 H), 5.37 (d, *J* = 3.2 Hz, 1 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 2.38 (s, 3 H), 1.14 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (DMSO-*d*₆): δ = 166.0, 152.5, 149.0, 148.2, 134.5, 131.0, 128.2, 127.4, 125.8, 100.8, 60.2, 55.5, 18.4, 14.4.

4j, White solid,³⁴ Mp 220-221 °C. IR (KBr): 3323, 3180, 1678, 1579, 1474, 1283, 1190, 1112 cm⁻¹. ¹H NMR (DMSO-*d*₆) δ = 10.30 (s, 1H), 9.61 (br, 1H), 9.46 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 3H), 5.08 (d, *J* = 3.6 Hz, 1H), 3.57 (s, 3H), 2.28 (s, 3H). ¹³C NMR (DMSO-*d*₆) δ = 174.6, 166.3, 158.1, 145.5, 145.2, 130.0, 117.3, 115.2, 113.6, 101.1, 54.3, 51.5, 17.7.

4k, Straw yellow solid,³³ Mp 185-186 °C. IR (KBr): 3419, 3230, 3111, 2966, 2931, 1708, 1649, 1615, 1587cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 9.27 (s, 1 H), 7.77 (s, 1 H), 7.22–7.45 (m, 4 H), 5.13 (d, *J* = 3.2 Hz, 1 H), 3.95 (q, *J* = 7.2 Hz, 2 H), 2.26 (s, 3 H), 1.10 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (DMSO-*d*₆): δ = 165.1, 151.9, 148.8, 147.6, 130.8, 130.1, 129.2, 125.2, 121.5, 98.7, 59.3, 53.7, 17.9, 14.2.

4l, Straw yellow solid,³³ Mp 232-234 °C. IR (KBr): 3530, 3233, 3109, 2978, 2930, 1705, 1651, 1519 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 9.16 (s, 1 H), 8.96 (s, 1 H), 7.66 (s, 1 H), 6.80 (s, 1 H), 6.76 (d, *J* = 8.4 Hz, 2 H), 6.61 (d, *J* = 8.4 Hz, 1 H), 5.03 (d, *J* = 2.8 Hz, 1 H), 3.96 (q, *J* = 7.2 Hz, 2 H), 3.75 (s, 3 H), 2.21 (s, 3 H), 1.12 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (DMSO-*d*₆): δ = 165.3, 152.2, 147.7, 145.6, 135.8, 118.0, 115.2, 110.7, 99.4, 59.1, 55.4, 53.3, 17.6, 14.1.

4m, Straw yellow solid,³³ Mp 211-213 °C. IR (KBr): 3368, 3255, 3107, 1698, 1657 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 1.05 (t, *J* = 7.6 Hz, 3H), 2.46 (s, 3H), 3.99 (q, *J* = 7.6 Hz, 2H), 5.63 (s, 1H), 5.87 (d, *J* = 2.4 Hz, 1H), 7.20–7.25 (m, 3H), 7.37–7.39 (m, 1H), 7.86 (s, 1H). ¹³C NMR (DMSO-*d*₆): δ = 165.9, 156.4, 152.4, 147.2, 140.1, 136.5, 129.4, 128.2, 127.2, 103.1, 58.0, 53.2, 17.9, 15.0.

4n, White solid,³³ Mp 203-204 °C. IR (KBr): 3428, 3302, 3109, 2988, 1712, 1654, 1463 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 9.23 (s, 1 H), 7.74 (s, 1 H), 7.54 (s, 1 H), 6.34 (d, *J* = 2.8 Hz, 1 H), 6.06 (d, *J* = 2.8 Hz, 1 H), 5.22 (d, *J* = 3.6 Hz, 1 H), 3.98 (q, *J* = 7.2 Hz, 2 H), 2.21 (s, 3 H), 1.11 (t, *J* = 7.2 Hz, 3 H). ¹³C NMR (DMSO-*d*₆): δ = 165.1, 156.0, 152.3, 149.2, 142.2, 110.3, 105.2, 96.7, 59.2, 47.6, 17.8, 14.0.

4o, White solid,³⁵ Mp 196-198 °C. IR (KBr): 3420, 3228, 2932, 2863, 1659, 1566, 1487, cm⁻¹. ¹H NMR (DMSO-*d*₆) δ = 9.21 (s, 1H), 8.51 (s, 1H), 7.72-7.74 (m, 2H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.22-7.24 (m, 1H), 5.33 (s, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (DMSO-*d*₆): δ = 167.8, 154.8, 150.4, 147.8, 147.2, 138.1, 125.1, 121.1, 106.8, 62.1, 50.1, 17.2, 14.1.

4p, Straw yellow solid,³⁴ Mp 212-213 °C. IR (KBr): 3323, 3190, 3116, 2983, 1676, 1613, 1572, 1513 cm⁻¹. ¹H NMR (DMSO-*d*₆): δ = 10.18 (s, 1H), 9.60 (s, 1H), 7.14 (d, 2H, *J* = 8.0 Hz), 6.92 (d, 2H, *J* = 8.0 Hz), 5.11 (s, 1H), 3.99 (q, 2H, *J* = 6.8 Hz), 3.73 (s, 3H), 2.30 (s, 3H), 1.11 (t, 3H, *J* = 6.8 Hz). ¹³C NMR

(DMSO-*d*₆): δ = 174.1, 165.1, 158.6, 144.7, 135.6, 127.5, 113.9, 100.7, 59.3, 55.0, 53.5, 17.1, 14.2.

4q, White solid,³⁴ Mp 157-168 °C. IR (KBr): 3335, 3158, 2931, 2225, 1692, 1536, and 1174 cm⁻¹. ¹H NMR (DMSO-*d*₆) δ = 10.43 (s, 1H), 9.71 (d, *J* = 2.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.21 (d, *s* = 3.2 Hz, 1H), 3.50 (s, 3H), 2.23 (s, 3H). ¹³C NMR (DMSO-*d*₆) δ = 175.1, 165.2, 147.1, 143.5, 132.7, 127.6, 118.2, 112.3, 102.1, 55.5, 51.6, 18.3.

4r, White solid,³⁴ Mp 240-242 °C. IR (KBr): 3327, 3155, 2225, 1536, 1420, 1178, 776 cm⁻¹. ¹H NMR (DMSO-*d*₆) δ = 8.68 (s, 1H), 7.96 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 5.46 (d, *J* = 3.2 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (DMSO-*d*₆) δ = 174.6, 164.7, 146.9, 143.4, 132.9, 127.3, 118.1, 112.0, 101.9, 60.7, 55.4, 18.2, 14.0.

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