Article

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

$Cd(NO_3)_2.4H_2O$ Catalyzed One-Pot Synthesis of 1,4-Dihydropyridine and Polyhydroquinoline Derivatives through the Hantzsch Multicomponent Condensation

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(Received: Mar. 21, 2012; Accepted: Jul. 31, 2012; Published Online: ??; DOI: 10.1002/jccs.201200162)

The synthesis of various 1,4-dihydropyridine and polyhydroquinoline derivatives was achieved in good to excellent yields using cadmium (II) nitrate as catalyst to promote the classical and modified Hantzsch conditions in good yields under mild conditions.

Keywords: Hantzsch reaction; 1,4-Dihydropyridines; Polyhydroquinolines; Cadmium (II) nitrate; One-pot condensation.

INTRODUCTION

Hantzsch 1,4-dihydropyridines (1,4-DHPs) and their derivatives are well known as calcium channel blockers, and have emerged for many years, as one of the most important classes of drugs for the treatment of angina pectoris, hypertension and other cardiovascular diseases.[1] Current literature reveals that these compounds possess a variety of biological activities.[2] For example, they are widely prescribed as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agents.[3] Other studies have revealed that 1,4-DHPs exhibit several other medicinal applications which include neuroprotectant[3a,4] and platelet anti-aggregratory activity,[3c] in addition to acting as a cerebral anti-ischemic agent in the treatment of Alzheimer's disease and as a chemosensitizer in tumor therapy.[3d]

Thus, the synthesis of 1,4-dihydropyridines is of continuing interest. Classical method for the synthesis of this nucleus is one-pot condensation of aldehydes with ethyl acetoacetate, and ammonia either in acetic acid or by refluxing in alcohol.[5] This method, however, involves long reaction time, harsh reaction conditions, the use of a large quantity of volatile organic solvents and generally gives low yields. Therefore, it is necessary to develop an efficient and versatile method for the preparation of 1,4-DHPs and the progress in this field is remarkable including recently the promotion of microwave,[6] TMSCl,[7] ionic liquid,[8] polymer,[9] molecular iodine,[10] silica gel/$NaHSO_4$,[11] microwave/ultrasound irradiation,[12] 2,4,6-trichloro(1,3,5)triazine,[13] ionic liquid/3,4,5-trifluorobenzeneboronic acid,[14] fermenting bakers'yeast,[15] high temperature in refluxing solvent,[16] and rare earth metal triflates such as $Yb(OTf)_3$ and $Sc(OTf)_3$.[17]

Although most of these processes offer distinct advantages, they suffer from certain drawbacks such as longer reaction times, unsatisfactory yields, high costs, harsh reaction conditions, and the use of volatile organic solvents. Thus, the possibility of performing multicomponent reactions under facile conditions with new catalysts could enhance their efficiency from an economic as well as a green point of view. Therefore, a new efficient method for the preparation of 1,4-DHPand their derivatives is desired.

RESULTS AND DISCUSSION

Previously, we have reported that phenylboronic acid[18] and triphenylphosphine,[19] could act as a beneficial catalysts in Hantzsch condensation reactions. More recently, we have disclosed the details of our study that led us to suggest the use of triethylamine as a base Lewis catalyst in the Hantzsch one pot condensation.[20]

We herein present a systematic study of a facile Hantzsch condensation by using cadmium (II) nitrate under mild conditions to produce 1,4-dihydropyridine derivatives **4** in high yields (Scheme I). In our initial experiments, we examined the effect of different solvents and others set of reaction conditions on the Hantzsch muticomponent condensation. In a first attempt, a mixture of a benzaldehyde **1a** (1 mmol), ethyl acetoacetate **2a** (2 mmol), and ammonium acetate **3** (4 mmol) in ethanol was stirred at reflux in the presence of a catalytic amount of cadmium (II) ni-

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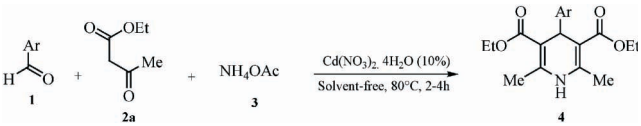
Scheme I



trate (20 mol%) for a certain period of time required to complete the reaction (TLC). Dihydropyridine **4a** was obtained as the only product but in moderate yield (Table 1, entry 2).

To determine the appropriate concentration of the catalyst, we have investigated the model reaction described above under different concentrations of cadmium (II) nitrate such as 50, 10, 5, and 2 mol%. We found that the product is obtained in 47%, 88%, 76%, and 67% yields, respectively (entries 1, 3-5). This indicates that 10 mol% of $Cd(NO_3)_2.4H_2O$ produces the best results with respect to product yield. Uncatalyzed reaction run in parallel under otherwise identical conditions gave only poor yield (32%) of the corresponding product within the time required for completion of the other catalyzed transformations (entry 6).

Several solvents, such as CH_3CN, THF, H_2O were also surveyed by using $Cd(NO_3)_2.4H_2O$ as catalyst (entries 7-9). Most of the reactions worked poorly at reflux except that when the reaction was investigated at 80 °C under solvent-free conditions, the reaction was completed with high yield (90%) within 3 hours (entry 10).

When we used other Lewis acid such as $Ca(NO_3)_2.4H_2O$, $Fe(NO_3)_2.6H_2O$, and $Ni(NO_3)_2.4H_2O$, the condensations smoothly proceeded whereas longer reaction times were required (entries 11-13). It was found that the reaction in the presence of 10 mol % of $Cd(NO_3)_2$ need shorter reaction time and excellent yield of the desired product than that with other catalysts.

Using the optimized conditions, we continued to study the reaction using various aldehydes. The results summarized in Table 2 indicate that both aromatic and heterocyclic aldehydes underwent smooth reactions with ethyl acetoacetate and ammonium acetate to give well to high yields of the corresponding DHPs. Also, both the electron rich and electron-deficient aldehydes worked well leading to high yields of products. Clearly, the effect of the nature of the substituents on the aromatic ring showed no obvious effect on this conversion.

For benzaldehyde (entry 1), and 4-methylbenzaldehyde (entry 4), the resulting yields of the corresponding DHPs were higher than those for the reactions with 4-methoxybenzaldehyde (entry 2) and 3-methylbenzaldehyde (entry 5). The reaction with 2-methoxybenzaldehyde (entry 3) is longer but the yield is comparable with other reactions. Similar results were obtained with electron-withdrawing aldehydes (entries 6-9). When heterocyclic aldehydes were used (entries 11 and 12), the conversions were lower even if the high yields are achieved.

The reactions are fairly general, clean and efficient.

Table 1. Optimization of the reaction using different conditions[a]

Entry	Solvent	Catalyst	Amount of catalyst (%)	Time (h)	Yield[b] (%)
1	EtOH[c]	$Cd(NO_3)_2.4H_2O$	50	8	47
2	EtOH[c]	$Cd(NO_3)_2.4H_2O$	20	8	72
3	EtOH[c]	$Cd(NO_3)_2.4H_2O$	10	8	88
4	EtOH[c]	$Cd(NO_3)_2.4H_2O$	5	8	76
5	EtOH[c]	$Cd(NO_3)_2.4H_2O$	2	8	67
6	EtOH[c]	-	-	8	32
7	CH_3CN[c]	$Cd(NO_3)_2.4H_2O$	10	8	65
8	THF[c]	$Cd(NO_3)_2.4H_2O$	10	10	35
9	H_2O[c]	$Cd(NO_3)_2.4H_2O$	10	8	51
10	None[d]	$Cd(NO_3)_2.4H_2O$	10	3	90
11	None[d]	$Ca(NO_3)_2.4H_2O$	10	6	81
12	None[d]	$Fe(NO_3)_2.6H_2O$	10	8	68
13	None[d]	$Ni(NO_3)_2.4H_2O$	10	8	76

[a] The reactions were conducted by condensation of benzaldehyde **1a** (1 equiv.), ethyl acetoacetate **2a** (2 equiv.), and ammonium acetate **3** (4 equiv.).
[b] Isolated yields.
[c] At reflux.
[d] At 80 °C.

Table 2. $Cd(NO_3)_2.4H_2O$-Mediated Hantzsch synthesis of 1,4-dihydropyridine **4a-l**[a]

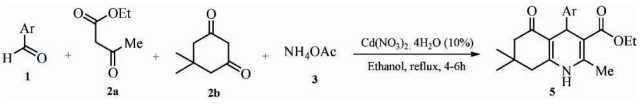
Entry	DHP	Ar	Time (h)	Yield[b] (%)	M.p (°C)	
					Measured	Reported
1	**4a**	C_6H_5	3	90	157-159	158-160 [21]
2	**4b**	4-(MeO)-C_6H_4	2	77	162-164	161-163 [21]
3	**4c**	2-(MeO)-C_6H_4	4	84	141-143	140-142[22]
4	**4d**	4-(Me)-C_6H_4	2	81	136-138	135-137[23]
5	**4e**	3-(Me)-C_6H_4	3	72	122-124	122-124[18]
6	**4f**	4-(NO_2)-C_6H_4	2	80	128-130	129-131[21]
7	**4g**	3-(NO_2)-C_6H_4	3	92	163-165	162-164[21]
8	**4h**	3,5-(Cl_2)-C_6H_3	3	89	130-132	128-130[18]
9	**4i**	3-(Cl)-C_6H_4	3	82	140-142	141-143[12b]
10	**4j**	Styryl	4	87	145-147	148-150[22]
11	**4k**	2-thienyl	4	90	172-174	171-173[21]
12	**4l**	2-furyl	4	79	160-162	160-161[21]

[a] All reactions were performed using aldehyde (1 equiv.), ethyl acetoacetate (2 equiv.), and ammonium acetate (4 equiv.) under solvent-free conditions at 80 °C.
[b] Isolated yields.

The experimental procedures are very simples. The high yields transformation did not form any significant amount of undesirable side-products.

After successfully synthesizing a series of Hantzsch 1,4-dihydropyridines in excellent yields, we turned our attention towards the synthesis of polyhydroquinoline derivatives (PHQs) via unsymmetrical Hantzsch reaction under similar conditions. We carried out the four component condensation reaction of benzaldehyde **1a**, ethyl acetoacetate **2a**, dimedone **2b**, and ammonium acetate **3** in the presence of 10 mol% of $Cd(NO_3)_2.4H_2O$ at 80 °C under solvent free conditions. The corresponding polyhydroquinoline **5a** was obtained in good yield (72%) after 8 hours; however very better result was achieved when the reaction was investigated in ethanol at reflux (yield = 92%). So the best conditions were that the reaction was catalyzed by 10 mol% of $Cd(NO_3)_2.4H_2O$ under refluxing ethanol (Scheme II).

Scheme II



As shown in Table 3, it was found that this procedure works also with a wide variety of substrates. Aromatic, heterocyclic and conjugated aldehydes afforded the desired products in high yields under the same reaction conditions.

The proposed mechanism for the formation of 1,4-dihydropyridines or polyhydroquinolines is shown in Scheme III. There is evidence that $Cd(NO_3)_2.4H_2O$ can catalyze aldol related reactions such as Knovenagel condensation as well as Michael additions. In this Hantzsch reaction, cadmium (II) nitrate is supposed to facilitate the condensation between aldehyde **1** and ethyl acetoacetate **2a** for the formation of the corresponding Knovenagel product **6a**, and the Michael addition between this intermediate and enamines **7a-b** obtained from the reaction of ethyl acetoacetate **2a** (or dimedone **2b**) and ammonium acetate **3**, for the formation of an open chain intermediates **8a-b** which

Scheme III

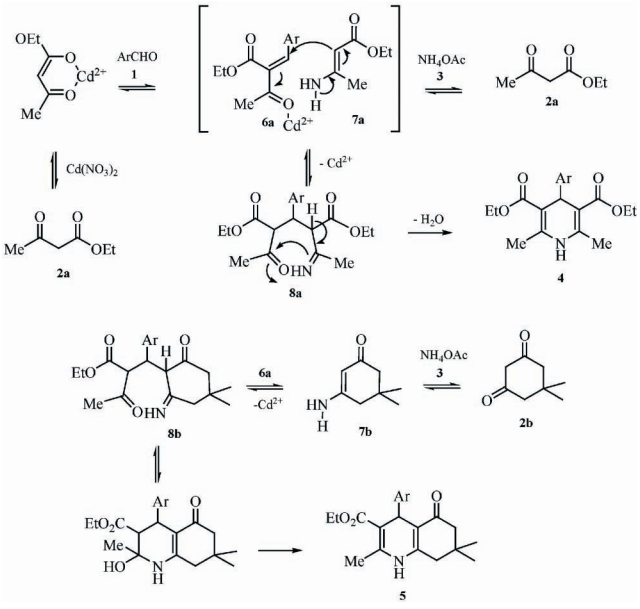


Table 3. Cadmium(II)nitrate-Catalyzed Hantzsch synthesis of polyhydroquinolines **5a-l** under optimized conditions[a]

Entry	PHQ	Ar	Time (h)	Yield[b] (%)	M.p (°C)	
					Measured	Reported
1	**5a**	C_6H_5	6	92	202-204	204-205[17a]
2	**5b**	4-(OMe)-C_6H_4	5	86	252-254	258-259[17a]
3	**5c**	2-(OMe)-C_6H_4	4.5	89	198-200	193-195[24]
4	**5d**	4-(Me)-C_6H_4	4	83	258-260	261-262[17a]
5	**5e**	3-(Me)-C_6H_4	6	82	256-258	-
6	**5f**	4-(OH)-C_6H_4	5	90	234-236	237-238[17a]
7	**5g**	3-(NO_2)-C_6H_4	4.5	84	180-182	182-184[25]
8	**5h**	2.4-(Cl_2)-C_6H_3	5	69	242-244	240-242[25]
9	**5i**	3-(Cl)-C_6H_4	6	87	236-238	234-235[26]
10	**5j**	Styryl	5	90	204-206	206-207[17a]
11	**5k**	2-Thienyl	6	96	238-240	241-242[17a]
12	**5l**	2-furyl	6	92	246-248	248-249[17a]

[a] All reactions were carried out using aldehyde (1 equiv.), dimedone (1 equiv.), ethyl acetoacetate (1 equiv.), and ammonium acetate (4 equiv) under refluxing ethanol.
[b] Isolated yields.

undergo cyclohydration to furnish the desired DHPs **4** or PHQs **5** products.

CONCLUSION

In conclusion, we have demonstrated an easy, efficient and versatile method for the synthesis of dihydropyridine and polyhydroquinoline derivatives from the reaction of aromatic or heterocyclic aldehydes, β-ketoesters or 1,3-dicarbonyl compounds, and ammonium acetate catalyzed by cadmium (II) nitrate under mild conditions. The process does not require the use of harmful metal catalyst and thus, is a simple, environmentally friendly, and high yielding reaction for the synthesis of 1,4-dihydropyridines or polyhydroquinolines via one-pot multicomponent Hantzsch reaction. Furthermore, all aromatic aldehydes that carry either electron-donating or electron-withdrawing substituents reacted under this protocol, allowing the production of 1,4-DHPs or PHQs in high yields.

EXPERIMENTAL

Typical experimental procedure for the synthesis of dihydropyridines 4a-j

A mixture of aldehyde (1 mmol), ammonium acetate (4 mmol), ethyl acetoacetate (2 mmol) and cadmium (II) nitrate (10 mol%), was magnetically stirred at 80 °C under solvent free conditions. After complete conversion as indicated by TLC, the reaction mixture was cooled then poured onto crushed ice and the separated solid was filtered. The crude product was purified by recrystallization from ethanol.

Spectroscopic data for selected compounds:

Ethyl 4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4a)

M.p = 157-159 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.23 (t, *J* = 7.1 Hz, 6H), 2.35 (s, 6H), 4.09 (q, *J* = 7.1 Hz, 4H), 5.10 (s, 1H), 6.07 (s, 1H), 7.48-7.12 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 14.2, 19.5, 39.3, 59.1, 103.1, 126.2, 128.3, 131.7, 137.7, 144.9, 167.2. FT-IR (KBr) ν_{max}: 3349, 1701, 1649, 1488, 1217 cm^{-1}.

Ethyl 4-(4-methylphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4d)

M.p = 136-138 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.23 (t, *J* = 7.1 Hz, 6H), 2.30 (s, 3H), 2.35 (s, 6H), 4.09 (q, *J* = 7.1 Hz, 4H), 5.10 (s, 1H), 6.07 (s, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 8.07 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 14.2, 19.5, 21.6, 40.1, 59.9, 103.0, 123.8, 128.9, 143.1, 144.8, 146.2, 167.5. FT-IR (KBr) ν_{max}: 3319, 1701, 1647, 1487, 1215 cm^{-1}.

Ethyl 4-(3,5-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h)

M.p = 130-132 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.30 (t, *J* = 7.1 Hz, 6H), 2.33 (s, 6H), 4.10 (q, *J* = 7.1 Hz, 4H), 5.34 (s, 1H), 6.15 (s, 1H), 7.32-7.12 (m, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 14.1, 19.4, 39.7, 59.9, 102.9, 127.1, 127.8, 134.6, 144.9, 151.1, 167.2. FT-IR (KBr) ν_{max}: 3332, 1701, 1649, 1487, 1211 cm^{-1}.

Ethyl 4-styryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4j)

M.p = 145-147 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 1.31 (t, *J* = 7.1 Hz, 6H), 2.33 (s, 6H), 4.20 (q, *J* = 7.1 Hz, 4H), 5.37 (d, *J* =

5.9 Hz, 1H), 6.17 (s, 1H), 6.21 (dd, J = 15.8, 5.9 Hz, 1H), 6.29 (d, J = 15.8 Hz, 1H), 7.43-7.31 (m, 5H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ: 14.4, 19.5, 39.4, 59.7, 102.4, 121.4, 126.8, 128.0, 128.3, 130.5, 131.7, 137.7, 144.9, 167.2. FT-IR (KBr) ν_{max}: 3336, 1691, 1645, 1488, 1218 cm^{-1}.

Typical experimental procedure for the synthesis of polyhydroquinolines 5a-q

A mixture of aldehyde (1mmol), ammonium acetate (4 mmol), dimedone (1 mmol) ethyl acetoacetate (1 mmol), and cadmium (II) nitrate (10 mol%), was refluxed in ethanol for the appropriate time indicated in Table 3. After complete conversion as indicated by TLC, the reaction mixture was cooled then poured onto crushed ice, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. The crude product was purified by recrystallization from ethanol.

Spectroscopic data for selected compounds:

Ethyl 4-phenyl-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5a)

M.p = 202-204 °C. ^{1}H NMR (250 MHz, $CDCl_3$, DMSO-d_6) δ: 0.94 (s, 3H), 1.08 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H), 2.14-2.33 (m, 4H), 2.38 (s, 3H), 4.05 (q, J = 7.1 Hz, 2H), 5.05 (s, 1H), 5.78 (s, 1H), 7.08-7.31 (m, 5H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DMSO-d_6) δ: 14.4, 19.4, 26.5, 31.2, 40.4, 46.8, 50.5, 59.5, 101.3, 111.2, 124.7, 128.6, 129.5, 137.6, 145.1, 149.5, 157.4, 162.7, 195.9. FT-IR (KBr) ν_{max}: 3290, 1698, 1612 cm^{-1}.

Ethyl 4-(4-methylphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5d)

M.p = 258-260 °C. ^{1}H NMR (500 MHz, $CDCl_3$, DMSO-d_6) δ: 0.95 (s, 3H), 1.07 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H), 2.12–2.22 (m, 4H), 2.25 (s, 3H), 2.36 (s, 3H), 4.09 (q, J = 7.1 Hz, 2H), 5.01 (s, 1H), 5.73 (s, 1H), 7.00 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DMSO-d_6) δ: 14.1, 18.2, 20.9, 26.4, 32.1, 43.5, 50.2, 51.5, 58.9, 103.2, 110.1, 128.2, 128.3, 135.4, 139.8, 144.6, 149.1, 150.2, 166.9, 194.2. FT-IR (KBr): ν_{max} 3275, 1702, 1647 cm^{-1}.

Ethyl 4-(3-methylphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5e)

M.p = 256-258 °C. ^{1}H NMR (250 MHz, $CDCl_3$, DMSO-d_6) δ: 0.97 (s, 3H, CH_3), 1.05 (s, 3H), 1.23 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H), 2.10-2.20 (m, 4H), 2.50 (s, 3H), 4.08 (q, J = 7.1 Hz, 2H), 4.98 (s, 1H), 5.65 (s, 1H), 6.95-7.15 (m, 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DMSO-d_6) δ: 14.2, 19.1, 21.5, 27.2, 28.9, 32.2, 35.9, 40.2, 50.4, 58.7, 103.8, 113.2, 120.1, 124.7, 137.6, 145.1, 157.4, 161.2, 162.7, 195.9. FT-IR (KBr) ν_{max}: 2962, 2191, 1654, 1365 cm^{-1}. HRMS (ESI): *m/z* calcd for $C_{22}H_{27}NO_3Na$: 376.18886 $[M+Na]^+$, found: 376.189.

Ethyl-5-(3-nitrophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5g)

M.p = 180-182 °C· ^{1}H NMR (250 MHz, $CDCl_3$, DMSO-d_6) δ: 0.97 (s, 3H, CH_3), 1.13 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H), 2.17-2.30 (m, 4H), 2.51 (s, 3H), 4.10 (q, J = 7.1 Hz, 2H), 4.87 (s, 1H), 5.87 (s, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.69 (dt, J = 1.4, 7.9 Hz, 1H), 8.06-8.11, (m, 2H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DMSO-d_6) δ: 14.1, 19.3, 27.6, 32.2, 40.6, 43.5, 50.5, 59.9, 103.2, 112.8, 118.3, 122.3, 129.5, 134.4, 145.4, 148.5, 149.5, 157.9, 162.4, 195.9. FT-IR (KBr) ν_{max}: 3618, 2318, 1689, 1523 cm^{-1}.

Ethyl-5-(3-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (5i)

M.p = 236-238 °C. ^{1}H NMR (200 MHz, $CDCl_3$, DMSO-d_6) δ: 0.95 (s, 3H), 1.05 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H), 2.01-2.21 (m, 4H), 2.40 (s, 3H), 4.05 (q, J = 7.2 Hz, 2H), 4.60 (s, 1H), 5.60 (s, 1H), 7.10-7.30 (m 4H). ^{13}C NMR (62.9 MHz, $CDCl_3$, DMSO-d_6) δ: 14.4, 19.4, 26.6, 31.2, 40.4, 46.8, 52.9, 60.2, 103.3, 111.2, 125.9, 127.1, 128.7, 131.1, 132.3, 141.0, 149.5, 150.7, 167.5, 195.7. FT-IR (KBr) ν_{max}: 3063, 2956, 1721, 1640 cm^{-1}.

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