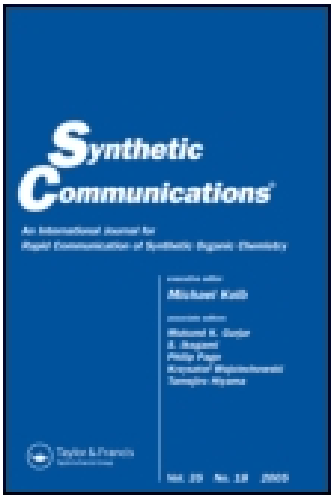

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Thermal-Induced Dimerization Cyclization of Ethyl N-(Styrylcarbamoyl)acetates: Formation of 4-Hydroxy-2(1H)-pyridone-3-carboxamide Derivatives

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THERMAL-INDUCED DIMERIZATION CYCLIZATION OF ETHYL N-(STYRYLCARBAMOYL)ACETATES: FORMATION OF 4-HYDROXY-2(1*H*)-PYRIDONE-3-CARBOXAMIDE DERIVATIVES

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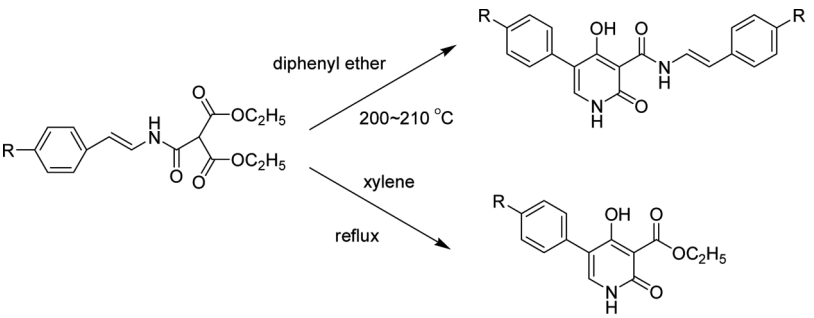
GRAPHICAL ABSTRACT



Abstract *Thermal-induced dimerization cyclization of ethyl N-(styrylcarbamoyl)acetate derivatives has been investigated, leading to 4-hydroxy-2(1H)-pyridone-3-carboxamide derivatives with good yields in diphenyl ether on 200–210 °C. Ethyl N-(styrylcarbamoyl)acetate derivatives readily provided the intermolecular cyclization products 4-hydroxy-2(1H)-pyridone-3-carboxylates on reflux in xylene. In addition, several related 3-acetyl-4-hydroxy-5-phenylpyridin-2(1H)-ones have been prepared. It provided an efficient preparation of 4-hydroxy-2(1H)-pyridone-3-carboxamide derivatives.*

Keywords Ethyl N-(styrylcarbamoyl)acetate; 4-hydroxy-2(1*H*)-pyridone-3-carboxamide; intramolecular thermal cyclization

INTRODUCTION

4-Hydroxy-2-pyridones are embedded as common structural units of many natural products. They exhibit good to excellent biological activities such as antifungal, antibacterial, and cytotoxic activities.[1] Representative examples are the pigments

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Tenellin, Ilicicolin **H**, Farunosone **A,** and the related Bassianin isolated from the insect pathogenic fungus *Beauveria bassianna*.[2] Ilicicolin **H** is an nonribosomal peptides (NRPS)-polyketide hybrid discovered in 1971 from the "imperfect fungus" *Cylindrocladium ilicicola* MFC-870 and is a potent antifungal group. It has a tetracyclic structure laced with various functional groups.[3] Recently, it was shown that Ilicicolin **H'**s antifungal activity was due to inhibiting the yeast cytochrome bc1 complex by interacting at the Qn site of the complex.[4] The class of compounds has stimulated a great deal of research interest on synthetic methodology for chemists because of their structural novelty, molecular diversity, and promising biological activities. Further optimization by chemical and biological modification to improve their biological and physiochemical profiles was developed. A series of oxime, hydroazone, pyrazole, isoxzaole, and 2,4,5-oxadiazocine Illicicolin **H** analogs were synthesized and evaluated for their antifungal activity.[5–8] However, all of the structural modifications were focused on the 4-position of 4-hydroxy-2(1*H*)-pyridone moiety in Ilicicolin **H**.

Ilicicolin **H** is a potent antifungal agent but lacks in vivo efficacy due to its strong plasma binding.[6] Recently, our group became interested in the synthesis and structural modification of Illicicolin **H** (Fig. 1).[1a,9] Generally, 4-hydroxy-2(1*H*)-pyridone-3-carboxylate moiety was constructed by thermal cyclization of ethyl N-(styrylcarbamoyl)acetate derivatives.[10] Subsequently, a few natural alkaloids with 3-acetyl-4-hydroxy-2(1*H*)-pyridone moieties were synthesized following this protocol.[11] 3-Acylpyridin-2(1*H*)-ones were also obtained from the hydrolysis of isoxazolo[4,3-*c*]pyridin-4-one scaffold.[12] First, we tried to synthesize ethyl 4-hydroxy-2(1*H*)-pyridone-3-carboxylate derivatives and related 3-acetyl-4-hydroxy-2-pyridiones for antifungal activity evaluation. Rigby et al. developed a general and efficient preparation of functionalized 4-hydroxy-2(1*H*)-pyridones from the reaction of readily available α, β-unsaturated isocyanates with various enolates ester and thermal cyclization of the ethyl N-(styrylcarbamoyl)acetates.[10] So, our initial preparation was performed according to Rigby's procedure. However, limited substrates (only one example for the synthesis of ethyl 4-hydroxy-2(1*H*)-pyridone-3-carboxylate was given) were used in Rigby's methodology in 1986. Another careful study was not conducted until now. We found that this procedure provided an efficient synthetic strategy to prepare 3-acetyl-4-hydroxy-2(1*H*)-pyridiones. It is unsuitable to prepare ethyl 4-hydroxy-2(1*H*)-pyridone-3-carboxylate derivatives by cyclization of ethyl N-(styrylcarbamoyl)acetate in diphenyl ether at 200–210 °C. (E)-4-Hydroxy-2-oxo-5-(4-phenyl)-N-styryl-1,2-dihydropyridine-3-carboxamides was isolated and elucidated as main product. Herein, we report the results of our investigation of thermal-induced dimerization cyclization of ethyl N-(styrylcarbamoyl)acetate derivatives.

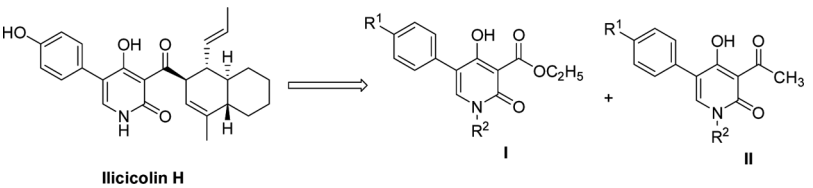
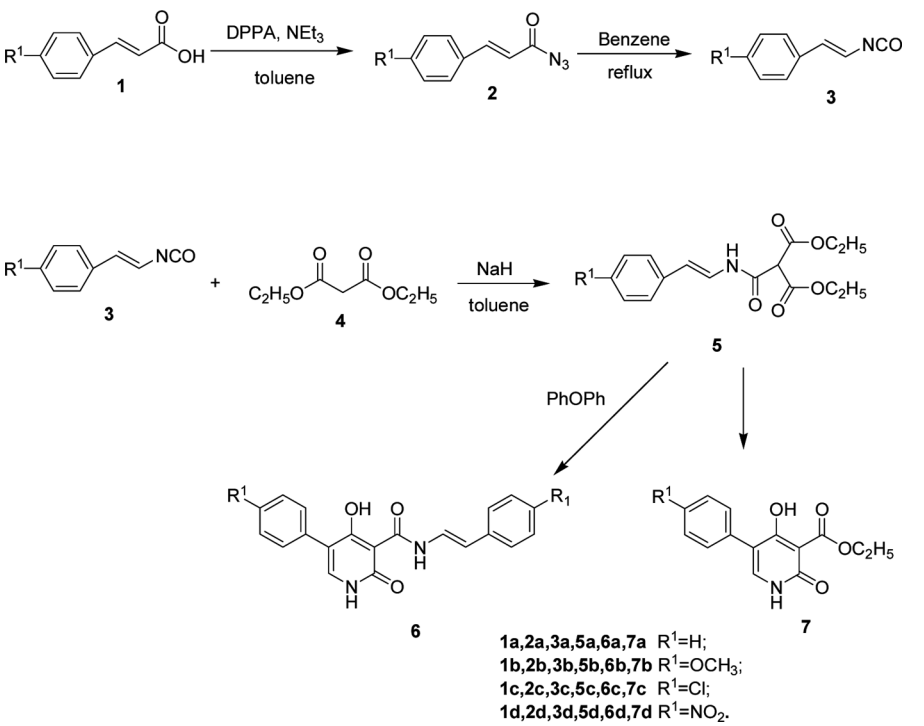


Figure 1. Structural modification of Ilicicolin H.

RESULTS AND DISCUSSION

Cinnamic acid derivatives were used as starting materials. The target compounds were synthesized according to the route shown in Scheme 1. A series of synthetic procedures were developed for the synthesis of acyl azides **2** from aromatic acids using triphosgene[13] or chloroformate ester and sodium azide.[14] A facile synthesis was used in the preparation of the title compounds. Cinnamoyl azides **2** were easily obtained by treating cinnamic acids with diphenyl phosphorazidate (DPPA) in toluene in the presence of triethylamine (80% yields). Then, they are subjected to thermally induced Curtius rearrangement to provide isocyanates **3**.[8] Without further purification, isocyanates **3** were treated with enolates of diethyl malonate to give diethyl N-(styrylcarbamoyl)malonates **5** as white solids. With compounds **5** in hand, we hoped the desired ethyl 4-hydroxy-2(1*H*)-pyridone-3-carboxylates **7** could be obtained by thermal cyclization of compounds **5** in diphenyl ether. However, this reaction failed. For example, after the completion of thermally induced cyclization of compounds **5a**, a white solid was precipitated, isolated, and carried out spectral detection. ^{1}H NMR spectrum data showed that no hydrogen signals were exhibited in the range of 2–6 ppm. The data suggested the ethyl group did not exist in this obtained compound. ^{13}C NMR data suggested that this compound should contain 20 carbons. Our desired product contained 14 carbon atoms a difference of 6 carbons.



Scheme 1. Synthetic route for 4-hydroxy-2(1*H*)-pyridone-3-carboxamides and ethyl 4-hydroxy-2(1-*H*)-pyridione-3-carboxylates.

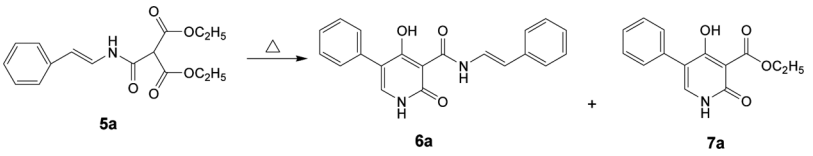
On the other hand, we supposed the intermolecular cyclization of ethyl N-(styrylcarbamoyl) acetate happened in diphenyl ether on 200–210 °C. Furthermore, the electron impact (EI) mass spectrum of this compound showed a molecular ion at 332(M^+). High-resolution mass spectrography suggested the formula was $C_{20}H_{16}N_2O_3$. On the basis of spectral data, its structure was assigned to (E)-4-hydroxy-5-(4-cholorophenyl)-N-styryl-2-oxo-1,2-dihydropyridine-3-carboxamide **6a**. To get more information about this cyclization reaction, a series of substrates was used. The cyclization productions **6a–6d** were obtained with 50–60% yield after being heated in phenyl ether at 200–210 °C.

In the next step, we turn our attention to investigate the influence of reaction temperature on the yield of product **6a** and product **7a**. A series of solvents with low boiling points were chosen for this cyclization reaction, such as toluene, xylene, diethyleneglycoldiethyl ether, diethyleneglycoldimethyl ether, and so on (Table 1). Our results suggested the yield of compounds **7a** increased with the decrease of the reaction temperature. Isolated yield of compounds **7a** is around 12–61%. For instance, xylene was chose as solvent. Product **6a** and product **7a** were obtained in 15% and 61% yields, respectively.

Thermal-induced dimerization cyclization of ethyl N-(styrylcarbamoyl)acetate derivatives were carried out in diphenyl ether at 200–210 °C. The effect of substitute group on the reaction yield was discussed in Table 2. Electron-rich group in phenyl ring can favor the reaction. For example, compound **5b** with methoxyl group provided the compound **6b** in 70% yield. Compound **6d** was obtained with 50% yield when the nitro group was introduced in the compound **5d**.

Based on these experimental results, a plausible mechanism is shown in Scheme 2. Initially, compound **5a** was subjected to intramolecular electrophilic addition to give the intermediate **8** under the xylene reflux condition. The compound **8** eliminates the ethoxyl group to form a 4-hydroxy-2(1*H*)-pyridinone ring **7a** in the heating condition. However, intermolecular cyclization happened in the diphenyl ether at greater reaction temperature. The compounds **5a** contain active hydrogen atom between two ethoxycarbonyl groups. First, the carbon attacked the carbonyl

Table 1. Influence of reaction temperature on cyclization of ethyl N-(styrylcarbamoyl)acetates

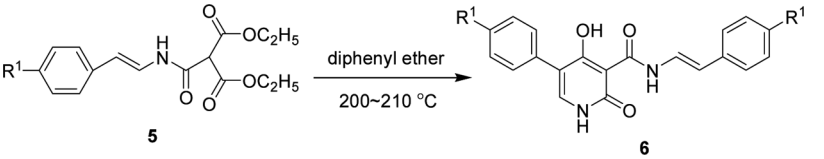


5a 6a 7a

Entry[a]	Solvent	Reaction time	Product **6a** yield (%)[b]	Product **7a** yield (%)[b]
1	Diphenyl ether (200–210 °C)	5 min	65	12
2	Diethyleneglycoldiethyl ether (reflux)	30 min	55	25
3	Diethyleneglycoldimethyl ether (reflux)	2 h	45	30
4	Xylene (reflux)	12 h	15	61

[a]Reaction conditions: compounds **5a** (2.0 mmol) was stirred in solvent for the time indicated in Table 1.
[b]Isolated yield with column chromatography.

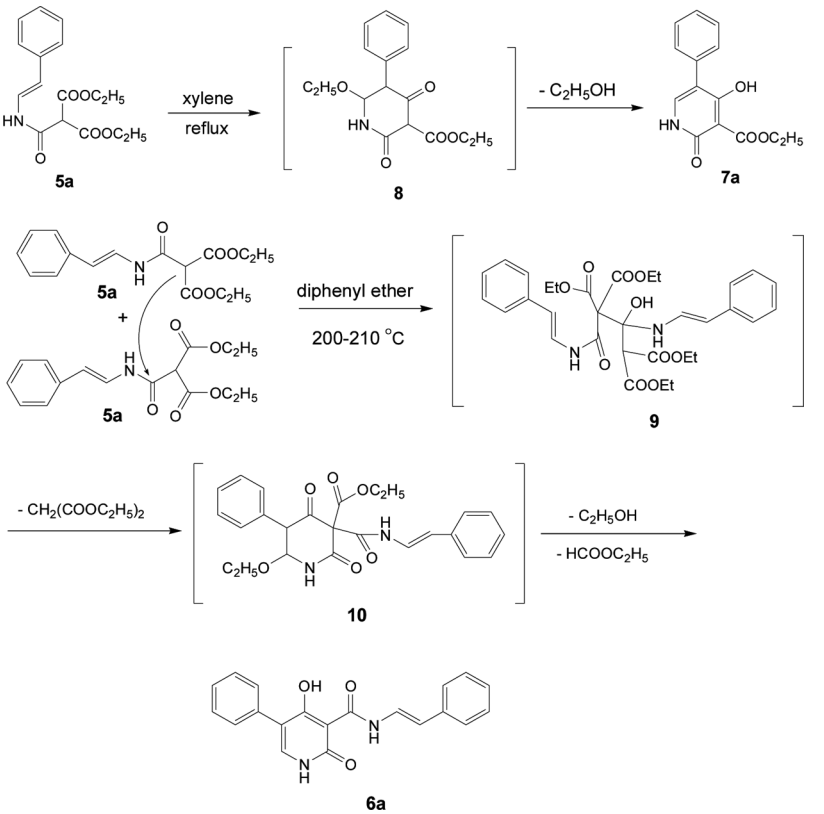
Table 2. Thermally induced dimerization cyclization of ethyl N-(styrylcarbamoyl)acetates



Entry[a]	R_1	Reaction time (min)	Yield (%)[b]
6a	H	5	60
6b	OCH_3	5	70
6c	Cl	5	55
6d	NO_2	10	51

[a]Reaction conditions: compounds **5** (2.0 mmol) was stirred in diphenyl ether at 200–210 °C for the time indicated in Table 2.

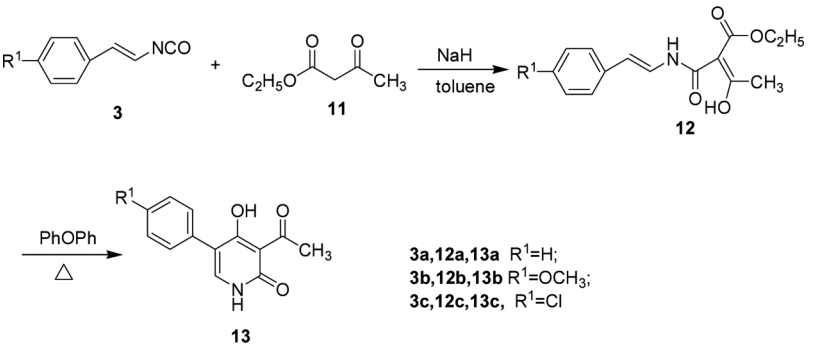
[b]Isolated yield with column chromatography.



Scheme 2. Plausible mechanism of the formation of compounds **7a** and **6a**.

group in another molecule to form intermediate **9** by nucleophile addition reaction. Second, compound **9** was subjected to intramolecular cyclization to give compound **10**. Herein, ethanol and diethyl malonate was released from the compunds **10** to complete this reaction. The structure of compound **6a** was confirmed by spectral analysis.

To elucidate the reaction mechanism of thermally induced dimerization of ethyl N-(styrylcarbamoyl)acetate derivatives to form 4-hydroxy-2(1*H*)-pyridone-3-carboxamide derivatives, compounds **12**, prepared from isocynates **3** with 72–85% yield and acetoacetate ethyl esters **11**, were heated in diphenyl ether in 200–210 °C to give 3-acetyl-4-hydroxy-5-(4-methoxyphenyl)-2(1*H*)-pyridinones **13** with 65–79% yield in Scheme 3. No dimerization product was obtained. An enolate and carbonyl group tautomerization existed in compound **12**.[15] We suggested that enol form, not keto form, existed in this molecule. The crystal structure of compound **12b** provided strong evidence to help understand this reaction mechanism. The crystal of compound **12b** was obtained by slow evaporation of a 1:1 ethyl acetate–petroleum ether solution to clarify this mechanism. The x-ray structural analysis of this compound reported here confirmed the assignment of its structure determined from spectroscopic data. The stereochemistry of this molecule is stabilized by intramolecular N—H…O and O—H…O hydrogen bonds (Figure 2). In



Scheme 3. Synthetic route for 3-acetyl-4-hydroxy-2(1*H*)-pyridiones.

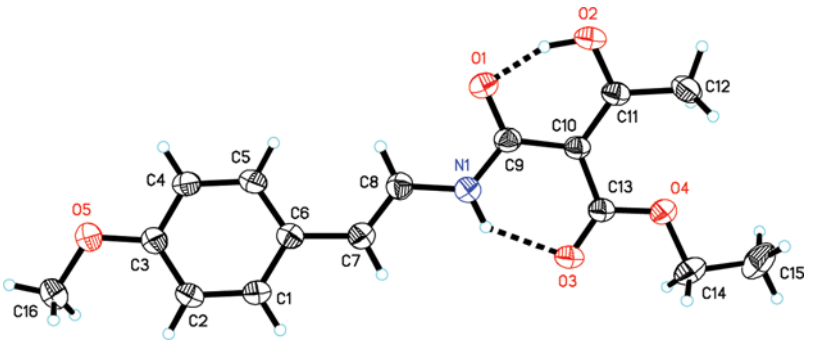


Figure 2. Molecular structure of **12b**.

the crystal, molecules are linked by weak intermolecular C—H···O hydrogen bonds. The layers are further connected into a three-dimensional network by weak π–π stacking interactions involving neighboring benzene rings. No carbon atom containing active hydrogen atom exists in this compounds **12**. Hence, carbon atom with acetate ester moiety was unable to attack the carbonyl group in another molecular to form the dimerization products because of enol form. No thermally induced intermolecular dimerization product was observed. So, we supposed the nucleophilic addition is the key step for intermolecular dimerization cyclization. Further biological evaluation and structural optimizing of Illicicolin **H** are currently under way in our laboratories.

CONCLUSIONS

We have demonstrated thermally induced intermolecular dimerization cyclization of ethyl (E)-3-oxo-2-(styrylcarbamoyl)butanoate derivatives to give (E)-4-hydroxy-5-phenyl-N-styryl-2-oxo-1,2-dihydropyridine-3-carboxamides as main products in diphenyl ether on 200–210 °C. A number of 4-hydroxy-2(1*H*)-pyridone-3-carboxylates were synthesized via an intramolecular cyclization of ethyl N-(styrylcarbamoyl)acetates in xylene at reflux. 3-Acetyl-4-hydroxy-2(1*H*)-pyridones were prepared by intramolecular cyclization in diphenyl ether on 200–210 °C. The preparation procedures of 4-hydroxy-2(1*H*)-pyridone-3-carboxylates and 3-acetyl-4-hydroxy-2(1*H*)-pyridones were simple and gave a satisfactory yield. Their structures were confirmed by spectra analysis.

EXPERIMENTAL

(E)-Diethyl 2-(Styrylcarbamoyl)malonate 5a

Typical procedure. Triethylamine (10.3 mL, 74.7 mmol) and diphenyl phosphorazidate (DPPA, 18.6 g, 67.6 mmol) were added to an ice-cooled solution of cinnamic acid (10.0 g, 67.6 mmol) in 100 mL toluene. The reactant solution was stirred at room temperature for 3 h. The acyl azide product was isolated by dilution with cold water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo to provide the crude product. The acyl azide was dissolved in 20 mL of benene and heated at reflux until azide decomposition was complete as monitored by thin-layer chromatography (TLC). The reaction mixture was then cooled to 0 °C, and diethylsodiomalonate (prepared from diethyl malonate (10.3 g, 67.6 mmol) and sodium hydride (2.23 g, 80% dispersion in oil, 74.3 mmol) in toluene (100 mL) at 0 °C) were added. The reaction mixture was allowed to warm to room temperature over 2 h, quenched with a saturated aqueous ammonium chloride solution, extracted with ether (3 × 100 mL), rinsed with brine (3 × 100 mL), and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give the compound **5a** as white crystals.

Spectral data. Yield 83%. White solid, mp 78–80 °C. IR (KBr, $\nu\,cm^{-1}$): 3267, 1745, 1652, 1310, 1176, 1036, 924, 693. ^1H NMR (400 MHz, $CDCl_3$) $\delta = 1.30$ (t, $J = 7.1$ Hz, 3H), 1.32 (t, $J = 7.1$ Hz, 3H), 4.29 (t, $J = 10.7$ Hz, 4H), 4.41 (s, 1H), 6.24 (d, $J = 14.7$ Hz, 1H), 7.18–7.21 (m, 1H), 7.30–7.45(m, 4H), 7.49–7.52 (m, 1H),

9.22 (d, $J = 10.3$ Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 13.9$, 58.7, 63.0, 115.1, 121.7, 125.7, 126.9, 128.6, 135.7, 159.4, 165.4. HRMS-EI: $[M]^+$ calc. for $C_{16}H_{19}NO_5$ 305.1263; found 305.1262.

(E)-4-Hydroxy-2-oxo-5-phenyl-N-styryl-1,2-dihydropyridine-3-carboxamide 6a

Typical procedure. Compounds **5a** (0.4 g, 1.3 mol) were stirred in diphenyl ether (5 mL) at 200–210 °C for 5 min. The reaction mixture was cooled to room temperature. The precipitate was collected and washed with ethyl acetate and n-hexane (1:2) to give the compound **6a** as colorless solid.

Spectral data. Yield 62%. Colorless solid, mp 258–260 °C. IR (KBr, ν cm^{-1}): 3331, 3030, 2850, 1665, 1587, 1287, 752, 692. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 6.50$ (d, $J = 10.8$ Hz, 1H), 7.19 (s, 1H), 7.52–7.21 (m, 9H), 7.57 (t, $J = 10.8$ Hz, 1H), 7.67 (s, 1H), 12.27(s, 1H), 12.35 (d, 1H), 15.90 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 97.7$, 114.2, 116.0, 121.3, 126.1, 127.3, 127.8, 128.7, 129.1, 129.7, 133.2, 136.3, 139.2, 163.1, 168.5, 173.4. MS (EI, 70 eV): $m/z = 333$ (M + 1), 332 (M^+), 214, 120, 119, 118, 117, 91. HRMS (EI): calc. for $C_{20}H_{16}N_2O_3[M]^+$ 332.1161; found 332.1162.

Ethyl 4-Hydroxy-2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxylate 7a

Typical procedure. Compounds **5a** (0.4 g, 1.3 mol) were refluxed in xylene (20 mL) for 12 h. The solvent was removed in vacuo to give an oil. The residue was purified by column chromatography (ethyl acetate / hexane = 1:6) to give the compound **7a** as white solid.

Spectral data. Yield 60%. White solid, mp 187–190 °C. IR (KBr, ν cm^{-1}): 3125: 2981, 2358, 1660, 1548, 1200, 813, 763, 697. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.30$ (t, 3H), 4.53 (q, 2H), 7.32–7.34 (m, 1H), 7.38–7.41 (m, 2H), 7.44–7.46 (m, 2H), 7.59 (s, 1H), 11.71 (s, 1H), 13.67 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 14.5$, 61.7, 98.8, 111.9, 127.6, 128.6, 129.4, 133.6, 140.0, 159.7, 172.3, 172.6. MS (EI, 70 eV): $m/z = 259$ (M^+), 214, 213, 145, 144, 119, 112, 89. HRMS: calc. for $C_{14}H_{13}NO_4$ $[M]^+$ 259.0845, found 259.0847. This compound was reported in literature.[16]

FUNDING

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SUPPORTING INFORMATION

Full experimental details and ^{1}H NMR and ^{13}C NMR spectra data for all of the compounds can be accessed on the publisher's website.

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