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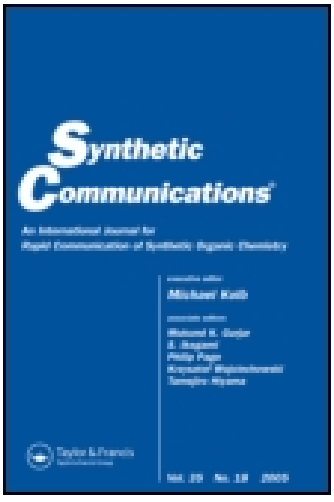

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Rapid Microwave-Assisted Liquid-Phase Synthesis of 4-Substituted-5-methoxycarbonyl-6-methyl-3,4-d on Poly(ethylene Glycol) Support

Gui-Yun Fu [a] , Xiao-Lan Zhang [a b] , Shou-Ri Sheng [a] , Mei-Hong Wei [a] & Xiao-Ling Liu [a]

[a] College of Chemistry and Chemical Engineering , Jiangxi Normal University , Nanchang, China

[b] Department of Chemistry , Shangrao Teacher's College , Shangrao, China

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Rapid Microwave-Assisted Liquid-Phase Synthesis of 4-Substituted-5-methoxycarbonyl-6-methyl-3,4-dihydropyridones on Poly(ethylene Glycol) Support

Gui-Yun Fu,[1] Xiao-Lan Zhang,[1,2] Shou-Ri Sheng,[1] Mei-Hong Wei,[1] and Xiao-Ling Liu[1]

[1]College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, China
[2]Department of Chemistry, Shangrao Teacher's College, Shangrao, China

Abstract: 4-Substituted-5-methoxycarbonyl-6-methyl-3,4-dihydropyridones have been efficiently prepared on the soluble polymer polyethylene glycol (PEG) 4000 by solvent-free microwave irradiation through a one-pot condensation of PEG-bound acetoacetate, Meldrum's acid, ammonium acetate, and the appropriate aldehyde in the presence of a catalytic amount of polyphosphoric acid. The polymer-supported synthesis provided the target compounds in excellent yield and purity with a facile workup procedure.

Keywords: Liquid-phase synthesis, microwave irradiation, PEG-bound acetoacetate, 4-substituted-5-methoxycarbonyl-6-methyl-3,4-dihydropyridones

Although already widely used as a powerful tool in the field of combinatorial chemistry, solid-phase organic synthesis (SPOS) suffers from some inherent disadvantages because of the heterogeneous reaction conditions, such as high demands on the compatibility of the individual components, relatively

Received in Japan July 28, 2007
Address correspondence to Shou-Ri Sheng, College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330027, China. E-mail: shengsr@jxnu.edu.cn

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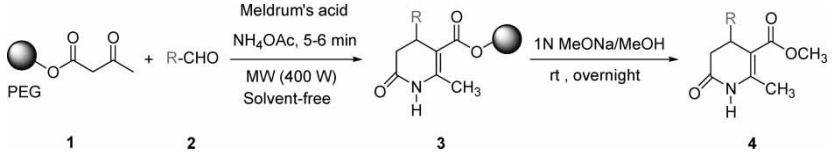
low reactivity and selectivity, harsh reactions, as well as the difficulty characterizing the insoluble polymer-supported compounds.[1] This stimulated the development of various approaches for construction of combinatorial libraries in solution, among which liquid-phase organic synthesis (LPOS) using soluble polymers provides an attractive strategy by incorporating the positive aspects of classical solution chemistry.[2] It benefits from both the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis without the cleavage-and-check procedure) and of solid-phase methods (use of excessive regents and easy isolation and purification of product). With these advantages, this strategy has recently caught the attention of the scientific community as an effective technique for the construction of combinatorial small organic molecular libraries, especially heterocyclic compounds, of which many are important structural motifs of pharmaceuticals or biologically active compounds.[3] Among the various soluble polymers, polyethylene glycol (PEG) is the most useful and promising.[4] 1,4-Dihydropyridines (1,4 DHP), as one of the most important chemicals in the treatment of cardiovascular diseases because of their calcium antagonist effects, have been widely studied and used but still generate much current interest.[5] Classical methods for the synthesis of 1,4-dihydropyridines are one-pot condensation of aldehyde with ethyl acetoacetate and ammonia acetate either in acetic acid or by refluxing in alcohols.[6] This method, however, involves long reaction time, harsh reaction conditions, and the use of a large quantity of volatile organic solvents and generally gives low yields. To the best of our knowledge, there have been no reports about liquid-phase synthesis of 1,4-dihydropyridines, despite its well-documented use in solid-phase synthetic procedure.[7] As part of an ongoing research program focused on the use PEG-supported β-keto ester in liquid-phase organic synthesis,[8] we report here on the liquid-phase synthesis of 4-substituted-5-methoxy-carbonyl-6-methyl-3,4-dihydropyridones from readily available starting materials. These 3,4-dihydro-2-oxopyridines are important key intermediates for the preparation of *o*-chloroformyl 1,4-dihydropyridine, (DHP)s by the Vilsmeier–Haack reaction, which can be further transformed in a wide variety of pyridine-fused heterocyclic systems.[9]

The LPOS of 4-substituted-5-methoxycarbonyl-6-methyl-3,4-dihydro-pyridones takes place from our previous preparation of immobilized PEG 4000–bound acetoacetate **1**[8] as shown in Scheme 1. Simple acetoacetylation



Scheme 1.

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could be performed by treatment of dihydroxyl PEG 4000 with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (toluene, 111 °C, 5 h). The quantitative conversion of PEG to **1** was observed following the presence of the C═O absorptions at 1743 and 1718 cm^{-1}, which correspond to ester and ketone carbonyl groups, respectively. In this procedure, the condensation of PEG-bound acetoacetate **1** with Meldrum's acid, aldehydes, and ammonium acetate would be the key step for the success of this protocol. As a model study, the liquid-phase combinatorial synthesis of 4-phenyl-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4a**) was first investigated using the classical solution-phase methods. When PEG-bound acetoacetate **1** was treated with benzaldehyde (**2a**), Meldrum's acid, and ammonium acetate in refluxing EtOH for 6 h[6b] or in refluxing AcOH for 14 h[6c] or even for longer times, the condensation on PEG was not complete. Microscopy fourier transform infrared (FT-IR)[10] study of the PEG-bound intermediate **3a** showed a new, moderately strong absorption at 1690 cm^{-1} corresponding to carbonyl stretch group in the dihydropyridine ring but still exhibiting a relatively intense band near 1718 cm^{-1}, which corresponds to the ketone carbonyl group of PEG-bound acetoacetate **1**. Correspondingly, the lower yields of the target compound **4a** cleaved from PEG using NaOMe were obtained using the classic methods (entries **1** and **2**). The application of microwave (MW) irradiation in organic synthesis recently has been the focus of considerable attention and is becoming an increasingly popular technology.[11] Rodríguez et al.[12] has reported that compounds **4** could be prepared from Meldrum's acid, methyl acetoacetate, and the appropriate aromatic aldehydes in the presence of ammonium acetate under MW heating. Stimulated by this, a better result was obtained in our attempts when employing the same reaction conditions.[12] Interesting, after a series of experiments, the best result was obtained when the a catalytic amount of nonvolatile, high-boiling-point, and nonoxidant polyphosphoric acid (PPA) was added under 400 W of irradiation power for 5 min at 100 °C without solvent. This reaction process, promoted by microwave, was also monitored by microscopy FT-IR and showed complete disappearance of the ketone carbonyl stretch and the appearance of a new carbonyl stretch group in the dihydropyridine ring near 1690 cm^{-1} of the PEG-bound intermediate **3a**. This was further confirmed by proton NMR spectroscopy of **3a**, because the methyl proton (CH_3) of the PEG-bound acetoacetate **1** was shifted downfield from $\delta = 2.27$ to 2.42 ppm. When the irradiation was stopped, the solids were treated with a small quantity of CH_2Cl_2; the PEG-bound intermediate **3a** was then precipitated by addition of diethyl ether and separated by filtration. The target compound **4a** was obtained in 88% yield and 95% (entry **3**) high performance liquid chromatography (HPLC) purity of crude product by cleavage from the PEG support under the treatment of the PEG-bound product **3a** with NaOMe in MeOH with stirring overnight. Apparently, the MW-assisted procedure leads to high yields, in the absence of solvent, within short reaction times, and with simplified workup, as compared to

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Table 1. Synthesis of 4-substituted-5-methoxycarbonyl-6-methyl-3,4-dihydropyridones **4a–k**

Entry	R (Aldehydes **2**)	Product	Yield (%)[a]	Purity (%)[b]
1	C_6H_5 (**2a**)	**4a**	30	—[c]
2	C_6H_5 (**2a**)	**4a**	60	—[c]
3	C_6H_5 (**2a**)	**4a**	88	95
4	2-$NO_2C_6H_4$ (**2b**)	**4b**	85	94
5	3-$NO_2C_6H_4$ (**2c**)	**4c**	84	93
6	4-$NO_2C_6H_4$ (**2d**)	**4d**	86	94
7	2,4-$(NO_2)_2C_6H_3$ (**2e**)	**4e**	90	96
8	4-$MeOC_6H_4$ (**2f**)	**4f**	91	96
9	2-ClC_6H_4 (**2g**)	**4g**	92	97
10	4-ClC_6H_4 (**2h**)	**4h**	91	96
11	4-CNC_6H_4 (**2i**)	**4i**	89	95
12	4-$CH_3OCOC_6H_4$ (**2j**)	**4j**	86	93
13	*n*-C_3H_7 (**2k**)	**4k**	85	93

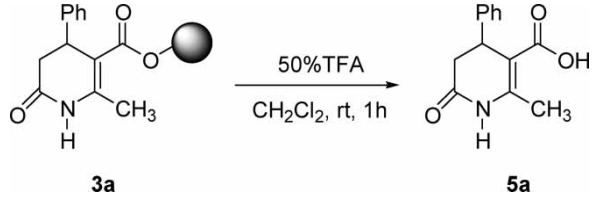
[a]Isolated yield based on loading of original HO-PEG-OH; The known products were characterized from their spectra (^{1}H NMR and IR) and comparison with authentic samples.

[b]Determined on HPLC analysis of crude products before purification.

[c]Not determined.

conventional heating methods. Following the synthesis of **4a** on PEG, a set of related compounds (**4b–k**) was prepared using an analogous synthetic protocol. As shown in Table 1, the yields (84–92%) are excellent and the purities are satisfactory (≥93%). Additionally, it appeared that the present method was effective for both aromatic (either with electron-withdrawing or electron-donating groups) (entries 1–12) and aliphatic aldehydes (entry 13). In some cases, a trace amount of the PEG residue might contaminate the final products **4**, which could be easily further purified by recrystallization from hot ethanol or by passing the crude product through a silica-gel column (10–15% ethyl acetate in hexane as the eluent).

On the other hand, the resin-bound intermediate **4** cleaved via another process was further investigated as shown in Scheme 2. For example, treatment of **3a** with 50% trifluoroacetic acid (TFA) in CH_2Cl_2 at room



3a **5a**

Scheme 2.

temperature for 1 h yielded 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridine-5-carboxylic acid **5a** in 90% yield and 95% HPLC purity.

In conclusion, an efficient liquid-phase synthetic technique for the construction of 4-substituted-5-methoxycarbonyl-6-methyl-3,4-dihydropyridones on soluble polymeric support has been developed, which utilized a one-pot condensation of PEG-bound acetoacetate, Meldrum's acid, aldehydes, and ammonium acetate in the presence of a catalytic amount of polyphosphoric acid (PPA) under solvent-free microwave promotion. Compared with the classical solution-phase reactions, the yields could be considerably improved and the reaction time could be shortened dramatically. This versatile method has potential applications in combinatorial synthesis of analogous heterocyclic compound libraries for chemical biological screening and the drug discovery process.

EXPERIMENTAL

Melting points were determined on an X_4 melting-point apparatus and are uncorrected. ^{1}H NMR (400-MHz) spectra were recorded on a Bruker Avance (400-MHz) spectrometer. FT-IR spectra were taken on a Perkin-Elmer SP One FT-IR spectrophotometer. Microanalyses were performed with a PE 2400 elemental analyzer. HPLC analysis was carried out on an Agilent 1100 automated system with a PDA detector ($\lambda_{max} = 254$ nm) using a gradient from 100% of the aqueous 0.1% TFA (eluent A) to 60% eluent A–40% of 0.5% TFA in acetonitrile (eluent B) over 35 min (0.8 mL/min) on a RP-18e column (100 × 4.6 mm). MW experiments were performed on a Galaz WP 800J-823 domestic microwave oven. Meldrum's acid, ammonium acetate, and different aldehydes were obtained from commercial sources and used without further purification.

General Procedure for the Preparation of 4-Substituted-5-methoxycarbonyl-6-methyl-3,4-dihydro-pyridones (4a–k)

At room temperature, PPA (2–3 drops) was added to the completely ground powers of PEG 4000–bound acetoacetate **1**[8] (1.0 g, 0.5 mmol), Meldrum's acid (1.0 mmol), ammonium acetate (1.2 mmol), and corresponding aldehyde **2** (1.0 mmol). The resulting mixture was added into an open vessel and stirred with a spatula for 30 s, and the vessel was placed inside a large container filled with alumina at the center of the domestic microwave oven. After irradiation at 400 W for 5–6 min at a temperature of 100 °C, the mixture was cooled to room temperature and a small volume of dichloromethane (5 mL) was added it. After filtration, diethyl ether (30 mL) was poured under stirring to precipitate the polymer **3**. For completion of the precipitation, the suspension was left at 0 °C for another 30 min. The polymer **3**

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was collected and washed several times with diethyl ether (3 × 10 mL). After drying in vacuo, the solid was added to the NaOMe (1 N)/MeOH solution (15 mL) to cleave the products at room temperature overnight (checked by thin-layer chromatography TLC). The target compounds **4** were obtained by extraction from the reaction mixture with EtOAc, dilution with H_2O (20 mL), and then removal of the solvent. The samples were further purified by recrystallization from hot ethanol or passing the crude product through a silica-gel column (10–15% ethyl acetate in hexane), if necessary.

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Data

4-Phenyl-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4a**): Mp 197–198 °C (lit.[6b] mp 197–198 °C); ^{1}H NMR: $\delta = 7.75$ (br s, 1H), 7.35–7.25 (m, 2H), 7.20–7.15 (m, 3H), 4.25 (dd, $J = 7.9$, 1.5 Hz, 1H), 3.67 (s, 3H), 2.91 (dd, $J = 16.4$, 7.9 Hz, 1H), 2.71 (dd, $J = 16.4$, 1.5 Hz, 1H), 2.43 (s, 3H); IR (KBr): 3218 (NH), 1704 (CO, ester), 1690 (C═O) and 1620 (C═C) cm^{-1}.

4-(2-Nitrophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4b**): Mp 205–206 °C (lit.[6b] mp 205–207 °C); ^{1}H NMR: $\delta = 7.98$ (br s, 1H), 7.84 (d, $J = 8.2$ Hz, 1H), 7.52–7.49 (m, 1H), 7.36–7.31 (m, 1H), 7.27 (d, $J = 7.8$ Hz, 1H), 4.75 (dd, $J = 7.9$, 1.5 Hz, 1H), 3.53 (s, 3H), 3.05 (dd, $J = 16.3$, 7.9 Hz, 1H), 2.82 (dd, $J = 16.3$, 1.5 Hz, 1H), 2.45 (s, 3H); IR (KBr): 3231 (NH), 1708 (CO, ester), 1688 (C═O), 1624 (C═C), 1351 and 1525 (NO_2) cm^{-1}.

4-(3-Nitrophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4c**): Mp 206–207 °C (lit.[6b] mp 206–207 °C); ^{1}H NMR: $\delta = 8.21$ (br s, 1H), 8.01–7.89 (m, 1H), 7.52–7.49 (m, 3H), 4.38 (dd, $J = 8.0$, 1.5 Hz, 1H), 3.58 (s, 3H), 3.03 (dd, $J = 16.4$, 8.0 Hz, 1H), 2.70 (dd, $J = 16.4$, 1.5 Hz, 1H), 2.45 (s, 3H); IR (KBr): 3230 (NH), 1703 (CO, ester), 1687 (C═O), 1633 (C═C), 1352 and 1526 (NO_2) cm^{-1}.

4-(4-Nitrophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4d**): Mp 224–225 °C (lit.[6b] mp 223–225 °C); ^{1}H NMR: $\delta = 8.14$ (d, $J = 8.8$ Hz, 2H), 7.60 (br s, 1H), 7.18 (d, $J = 8.8$ Hz, 2H), 4.30 (dd, $J = 8.0$, 1.8 Hz, 1H), 3.62 (s, 3H), 3.01 (dd, $J = 16.5$, 8.0 Hz, 1H), 2.50 (dd, $J = 16.5$, 1.8 Hz, 1H), 2.46 (s, 3H); IR (KBr): 3230 (NH), 1705 (CO, ester), 1685 (C═O), 1637 (C═C), 1350 and 1518 (NO_2) cm^{-1}.

4-(2,4-Dinitrophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4e**): Mp 212–213 °C (lit.[12] mp 212–213 °C); ^{1}H NMR: $\delta = 8.08$ (s, 1H), 7.75 (br s, 1H), 7.25 ~ 7.15 (m, 2H), 4.38 (dd, $J = 8.2$, 1.9 Hz, 1H), 3.65 (s, 3H), 3.11 (dd, $J = 16.5$, 8.2 Hz, 1H), 2.75 (dd, $J = 16.5$, 1.9 Hz, 1H), 2.52

(s, 3H); IR (KBr): 3235 (NH), 1710 (CO, ester), 1698 (C═O), 1641 (C═C), 1350 and 1525 (NO_2) cm^{-1}.

4-(4-Methoxyphenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4f**): Mp 187–188 °C (lit.[6b] mp 188–190 °C); ^1H NMR: $\delta = 8.78$ (br s, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 6.80 (d, $J = 8.4$ Hz, 2H), 4.20 (dd, $J = 7.9$, 1.5 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 2.94 (dd, $J = 16.5$, 7.9 Hz, 1H), 2.62 (dd, $J = 16.5$, 1.5 Hz, 1H), 2.39 (s, 3H); IR (KBr): 3220 (NH), 1702 (CO, ester), 1690 (C═O) and 1618 (C═C) cm^{-1}.

4-(2-Chlorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4g**): Mp 198–199 °C (lit.[9a] mp 198–200 °C); ^1H NMR: $\delta = 8.80$ (br s, 1H), 7.40–7.04 (m, 4H), 4.67 (dd, $J = 8.2$, 1.8 Hz, 1H), 3.60 (s, 3H), 2.91 (dd, $J = 16.4$, 8.2 Hz, 1H), 2.71 (dd, $J = 16.4$, 1.8 Hz, 1H), 2.45 (s, 3H); IR (KBr): 3216 (NH), 1706 (CO, ester), 1686 (C═O) and 1620 (C═C) cm^{-1}.

4-(4-Chlorophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4h**): Mp 202–203 °C (lit.[12] mp 202–203 °C); ^1H NMR: $\delta = 8.80$ (br s, 1H), 8.47 (d, $J = 1.7$ Hz, 1H), 7.75 (d, $J = 8.7$ Hz, 2H), 4.65 (dd, $J = 8.3$, 1.9 Hz, 1H), 3.64 (s, 3H), 2.92 (dd, $J = 16.5$, 8.3 Hz, 1H), 2.72 (dd, $J = 16.5$, 1.9 Hz, 1H), 2.47 (s, 3H); IR (KBr): 3218 (NH), 1708 (CO, ester), 1685 (C═O), 1623 (C═C) cm^{-1}.

4-(4-Cyanophenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4i**): Mp 258–259 °C (lit.[9a] mp 259–260 °C); ^1H NMR: $\delta = 8.40$ (br s, 1H), 7.64 (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 4.32 (dd, $J = 8.1$, 1.0 Hz, 1H), 3.68 (s, 3H), 3.02 (dd, $J = 16.6$, 8.1 Hz, 1H), 2.70 (dd, $J = 16.6$, 1.0 Hz, 1H), 2.46 (s, 3H); IR (KBr): 3224 (NH), 2222 (CN), 1700 (CO, ester), 1655 (C═O) and 1613 (C═C) cm^{-1}.

4-(4-Methoxycarbonylphenyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4j**): Mp 186–187 °C (lit.[9a] mp 186–188 °C); ^1H NMR: $\delta = 8.90$ (br s, 1H), 96 (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 8.3$ Hz, 2H), 4.32 (dd, $J = 8.2$, 1.1 Hz, 1H), 3.90 (s, 3H), 3.67 (s, 3H), 2.99 (dd, $J = 16.5$, 8.2 Hz, 1H), 2.70 (dd, $J = 16.5$, 1.1 Hz, 1H), 2.45 (s, 3H); IR (KBr): 3225 (NH), 1725 (CO, ester), 1650 (C═O) and 1612 (C═C) cm^{-1}.

4-(n-Propyl)-5-methoxycarbonyl-6-methyl-3,4-dihydropyridone (**4k**): Mp 125–126 °C; ^1H NMR: $\delta = 7.85$ (br s, 1H), 4.17 (m, 1H), 3.65 (s, 3H), 2.90 (dd, $J = 16.2$, 7.5 Hz, 1H), 2.86 (dd, $J = 16.2$, 1.5 Hz, 1H), 2.42 (s, 3H), 1.10–1.37 (m, 4H), 0.78 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ =170.4, 166.2, 149.3, 105.6, 51.6, 36.8, 34.1, 29.6, 24.5, 18.8, 13.8; IR (KBr): 3220 (NH), 1721 (CO, ester), 1658 (C═O) and 1625 (C═C) cm^{-1}. Anal. calcd. for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.58; H, 8.17; N, 6.68.

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Data for Compound 5a

^{1}H NMR (DMSO-d_6): $\delta = 9.97$ (br s, 1H), 7.48–7.45 (m, 2H), 7.03–7.07 (m, 3H), 4.01 (dd, $J = 7.5$, 1.0 Hz, 1H), 2.90 (dd, $J = 16.4$, 7.5 Hz, 1H), 2.41 (dd, $J = 16.4$, 1.0 Hz, 1H), 1.93 (s, 3H); ^{13}C NMR (DMSO-d_6): $\delta = 171.5$, 170.1, 145.3, 141.1, 128.3, 126.2, 123.5, 109.5, 40.1, 38.4, 18.8; IR (neat): 3220 (NH), 1700 (CO, acid), 1692 (C═O) and 1624 (C═C) cm^{-1}.

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