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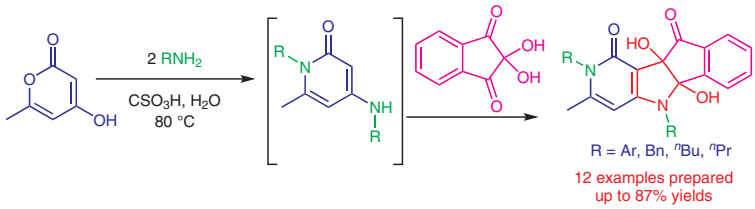
A Novel One-Pot, Two-Step Reaction for the Synthesis of Indenopyrrolo[3,2-*c*]pyridinone Derivatives with a Recyclable Catalyst

Chunmei Li
Furen Zhang*
Chenze Qi

School of Chemistry and Chemical Engineering, Zhejiang Key Laboratory of Alternative Technologies for Fine Chemicals Process, Shaoxing University, Shaoxing, Zhejiang Province 312000, P. R. of China
frzhang@usx.edu.cn



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Abstract An efficient strategy was developed for the synthesis of indenopyrrolopyridinone derivatives from 4-hydroxy-6-methyl-2*H*-pyran-2-one, an amine, and 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione by a one-pot, two-step, four-component process. The one-pot reaction gives various substituted indenopyrrolopyridinones in good yields and uses a solid acid as a recyclable catalyst in water. This procedure has the advantages of inexpensive substrates, a reusable solid-supported catalyst, and a convenient one-pot operation.

Key words multicomponent reaction, one-pot reaction, hydroxymethylpyranonone, amines, dihydroxyindenedione, indenopyrrolopyridinones

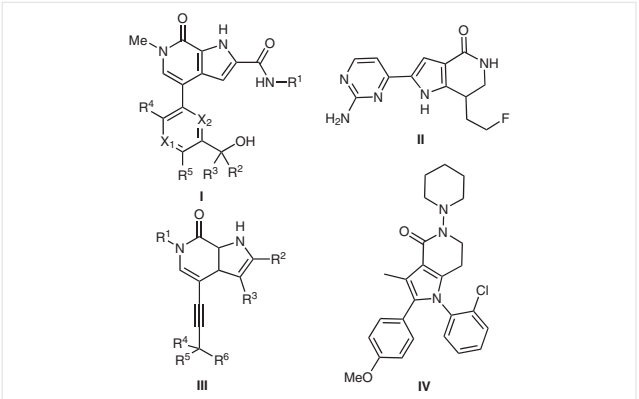


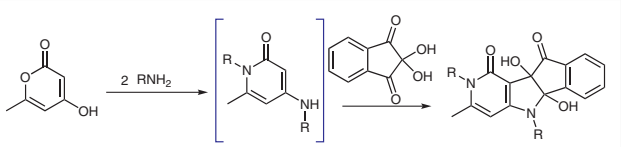
Figure 1 Biologically active pyrrolopyridinone derivatives

The simple and efficient construction of heterocyclic scaffolds that display biological and pharmaceutical activities is an active research theme in organic synthesis. Among these scaffolds, the pyrrolopyridines have distinguished themselves as heterocycles of profound chemical and biological significance.[1] For example, compounds **I** and their analogues (Figure 1) are inhibitors of BET proteins,[2] compound **II** is a potent and orally active antitumor agent,[3] compounds **III** are TAF1 inhibitors,[4] and compound **IV** and its analogues can inhibit proliferation of various tumor cells and can constrain analogues of CB-1 antagonists.[5] Other pyrrolopyridine derivatives also exhibit various biomedical and pharmacological activities.[6] Because of the unique chemical and biological characteristics of pyrrolopyridines, many methods for their synthesis have been developed.[7] However, most of these strategies involve multistep reactions and laborious operational procedures, apply to only a limited range of substrates, or require a nonreusable catalyst. Therefore, the development of more-efficient methods for the synthesis of this family of heterocyclic compounds is of great interest and is challenging.

Indenopyrrole and its analogues are also common structural motifs in many biologically active molecules and pharmaceutical substances.[8] Some of them have been reported to act as powerful lipid peroxidation inhibitors,[9] potassium-channel openers,[10] DNS intercalators, or topoisomerase II inhibitors.[11] Consequently, many modern methods have been developed for the formation of these compounds.[12] However, most of these methods involve expensive substrates, laborious steps, or nonreusable catalysts. Therefore, the exploration of a versatile strategy for the formation of these scaffolds is still highly desirable.

In recent decades, solid acids as heterogeneous catalysts for organic synthesis have gained much attention due to their recyclability, mildness, and environmentally friendly nature.[13] More importantly, because they are insoluble in almost all solvents, it is easy to separate the catalyst from reaction mixtures. Thus, a series of organic reactions catalyzed by various solid acids have been developed.[14] Recently, our group has developed a series of multicomponent reactions for the synthesis of heterocycles of chemical and

pharmaceutical interest.[15] As a result of our continuing efforts on these one-pot processes, we wish to report a solid-acid-promoted multicomponent reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one, various amines, and 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione in water to give polysubstituted indenopyrrolo[3,2-*c*]pyridinone derivatives; the reaction involves a one-pot, two-step strategy (Scheme 1). To the best of our knowledge, the use of a multicomponent reaction to construct an indenopyrrolo[3,2-*c*]pyridinone scaffold has not been previously reported.



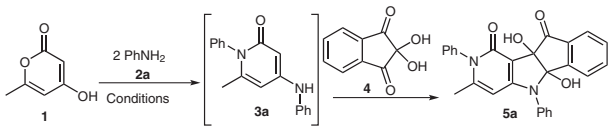
Scheme 1 The synthesis of indenopyrrolopyridinone derivatives

To screen the reaction conditions, we chose 4-hydroxy-6-methyl-2*H*-pyran-2-one, aniline, and 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione as model substrates in our one-pot, two-step strategy. Representative results are summarized in Table 1. The product **5a** was not obtained when the model reaction was carried out in the absence of a catalyst (Table 1, entry 1). Initially, **5a** was obtained in yields of only 30–55% when various Brønsted acids (HOAc, TsOH, and H_2SO_4) or Lewis acids [$Y(OTf)_3$ or $Sc(OTf)_3$] were used to homogeneous catalysts for the model reaction (entries 2–6). Heterogeneous catalysts, such as Amberlyst-15 or zeolite HY exhibited even worse activities, giving **5a** in yields of only 18 and 32%, respectively (entries 7 and 8). However, sulfonated amorphous carbon (CSO_3H) as a solid-acid catalyst exhibited a high reactivity and gave product **5a** in 81% yield (entry 9). Subsequent screening of the catalyst loading indicated that CSO_3H (10 mg) was enough to drive the reaction forward successfully.

Subsequently, the reaction was performed by using CSO_3H (10 mg) as the catalyst in various solvents (MeOH, EtOH, $CHCl_3$, THF, DMF, and MeCN); however, water proved to be the best solvent (Table 1, entries 9 and 12–17). The reaction in water was then repeated several times at various temperature in a sealed tube, and the best yield of product **5a** (81%) was obtained when the temperature was 80 °C (entries 9 and 18–20). A further increase in the reaction temperature did not enhance the yield of **5a** (entry 21).

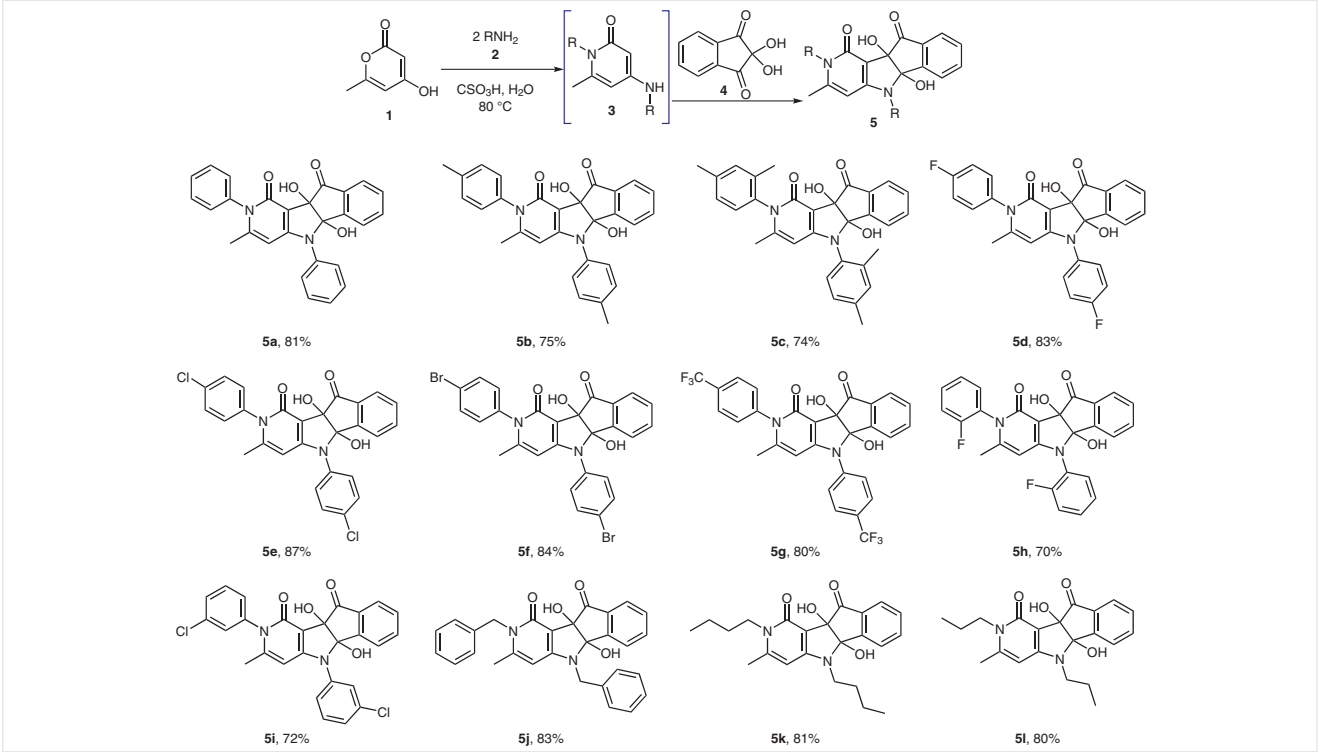
With the above optimized conditions in hand, we then proceeded to probe the substrate diversity of this one-pot, two-step reaction by using easily available starting materials. The reactions of various amines **2** with 4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**) in water were performed for two hours at 80 °C; this was followed by the addition of 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione (**4**) to the mixture under the conditions described above. The results are summarized in Scheme 2. Amines with either electron-deficient or electron-rich substituents were suitable reactants. We also noted that aromatic amines **2d–g** with an electron-withdrawing substituent (fluoro, chloro, bromo, or trifluoromethyl) in the *para*-position of the benzene ring exhibited better reactivities and gave higher yields of the desired products than did **2b** or **2c**, bearing electron-donating methyl and methoxy substituents, respectively. In addition, amines with *ortho*- or *meta*-substituents **2h** and **2i** exhibited lower activities and gave the desired products **5h** and **5i** in 70 and 72% yield, respectively, as a result of steric effects. To further expand the scope of the reaction, the aliphatic amines benzylamine, butylamine, and propylamine were chosen to react with 4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**) and 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione (**4**). To our

Table 1 Optimization of the Synthesis of Compound **5a**[a]



Entry	Catalyst (mg)	Solvent	Temp (°C)	Yield[b] (%)
1[c]	–	H_2O	80	–
2	HOAc (10)[d]	H_2O	80	55
3	TsOH (10)[d]	H_2O	80	42
4	H_2SO_4 (10)[d]	H_2O	80	30
5	$Y(OTf)_3$ (10)[d]	H_2O	80	46
6	$Sc(OTf)_3$ (10)[d]	H_2O	80	49
7	Amberlyst-15 (10)	H_2O	80	18
8	zeolite HY (10)	H_2O	80	32
9	CSO_3H (10)	H_2O	80	81
10	CSO_3H (5)	H_2O	80	36
11	CSO_3H (15)	H_2O	80	83
12	CSO_3H (10)	MeOH	reflux	57
13	CSO_3H (10)	EtOH	80	71
14	CSO_3H (10)	$CHCl_3$	reflux	19
15	CSO_3H (10)	THF	reflux	16
16	CSO_3H (10)	DMF	80	42
17	CSO_3H (10)	MeCN	80	46
18[c]	CSO_3H (10)	H_2O	r.t.	–
19	CSO_3H (10)	H_2O	40	17
20	CSO_3H (10)	H_2O	60	32
21	CSO_3H (10)	H_2O	100	81

[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), catalyst, solvent (3.0 mL), sealed tube, 2 h; then, **4** (0.5 mmol), 4 h.
[b] Isolated yield.
[c] Reaction time 24 h.
[d] 10 mol%.

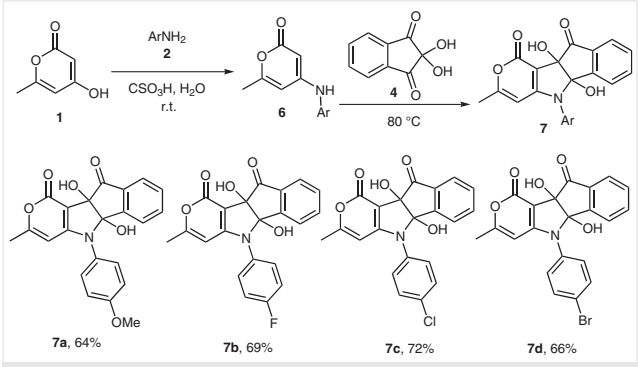


Scheme 2 The synthesis of compounds **5a–l**. *Reaction conditions*: **1** (0.5 mmol), **2** (1.0 mmol), CSO_3H (10 mg), H_2O (3.0 mL), sealed tube, 2 h, 80 °; then, **4** (0.5 mmol), 80 °C, 4 h. Isolated yields are reported.

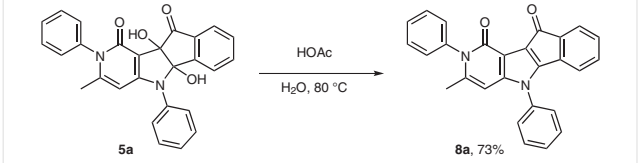
delight, the corresponding products **5j–l** were obtained in yields of 80–83%, probably due to the high reactivities of these amines.

Having explored the diversity of the fused indanone scaffolds, we then turned our attention to investigating the three-component reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**), aryl amines **2**, and 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione (**3**).[16] Initially, none of the desired product **7** was obtained when the three-component two-step reaction was carried out under the above conditions. However, various substituted 5-aryl-5a,10a-dihydroxy-3-methyl-5a,10a-dihydro-1*H*-indeno[1,2-*b*]pyrano[3,4-*d*]pyrrole-1,10(5*H*)-diones **7** were obtained after a series of optimizations of the reaction conditions (Scheme 3). The reactions of substituted amines bearing electron-withdrawing groups, such as fluoro, chloro, or bromo, or electron-donating groups, such as methoxy, all worked well to give the corresponding products **7a–d** in yields of 64–72%. We also noted that aromatic amines bearing electron-withdrawing groups exhibited slightly higher reactivities than those bearing electron-donating groups.

In all cases, the reactions occurred rapidly. Water was almost the only byproduct, which made the workup green and convenient. Furthermore, increasing the reaction times did not lead to the elimination of the OH groups. However, the addition of homogeneous acids, such as acetic acid, led to the dehydration products (e.g., Scheme 4). The structures of the products were determined by means of ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry.[17,18]



Scheme 3 Synthesis of compounds **7** by the three-component reaction



Scheme 4 The elimination reaction of compound **5a**

Subsequently, we examined the recyclability of the solid-acid catalyst by using the model substrates 4-hydroxy-6-methyl-2*H*-pyran-2-one (**1**), aniline, and 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione (**4**). After the completion of the model reaction, the catalyst was recovered by filtration and washed with 95% EtOH and water. The solid-acid catalyst could be reused easily after drying in a vacuum oven at 120 °C for four hours. The recovered catalyst was used repetitively ten times, and the results are shown in Figure 2. The slight decline in catalytic activity after each run might be due to minor losses in the recovery process. Therefore, the solid-acid catalyst has good reusability.

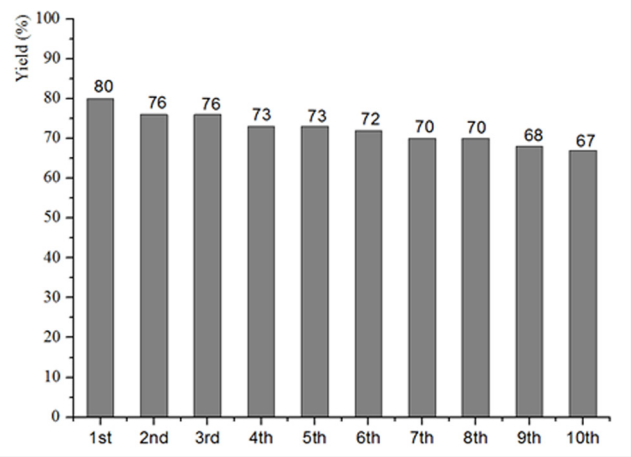
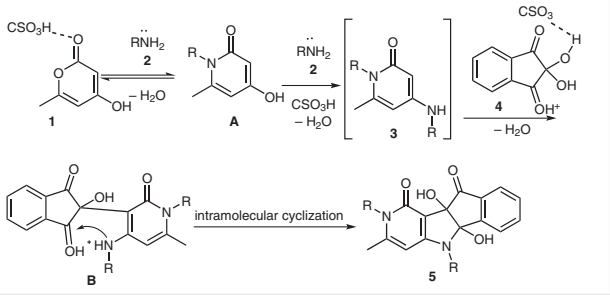


Figure 2 Study on the recyclability of the solid acid in the synthesis of **5a**

The plausible mechanism for the one-pot reaction was proposed and is shown in Scheme 5. The initial nucleophilic addition of **2** to activated **1** gives intermediate **A**, which can be separated from the mixture. Compound **3** is then formed by nucleophilic substitution of **2** with intermediate **A** in the presence of the solid acid. Finally, the target product **5** is obtained after nucleophilic substitution of substrate **3** with protonated 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione **4**, and the subsequent intramolecular cyclization.



Scheme 5 Probable mechanism for the formation of the indenopyrrolo[3,2-*c*]pyridinones

In conclusion, we have established a new four-component, one-pot, two-step reaction that provides an efficient synthesis of 5a,10a-dihydroxy-3-methyl-2,5,5a,10a-tetrahydroindeno[2′,1′:4,5]pyrrolo[3,2-*c*]pyridine-1,10-diones, and a three-component one-pot, two-step reaction that gives 5a,10a-dihydroxy-3-methyl-5a,10a-dihydro-1*H*-indeno[1,2-*b*]pyrano[3,4-*d*]pyrrole-1,10(5*H*)-diones in good yields. Both reaction processes employ readily available 4-hydroxy-6-methyl-2*H*-pyran-2-one, an amine, and 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione as starting materials. The one-pot operational simplicity, the environmentally friendly reaction media, and the recyclable solid-supported catalyst make this synthetic strategy highly attractive for accessing compounds of potential biological and pharmacological interest.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609655.

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(17) **2,5-Disubstituted 5a,10a-Dihydroxy-3-methyl-2,5,5a,10a-tetrahydroindeno[2′,1′:4,5]pyrrolo[3,2-*c*]pyridine-1,10-diones 5a–l; General Method**

A mixture of pyranone **1** (0.5 mmol), the appropriate amine **2** (1.0 mmol), and solid acid (10 mg) in H_2O (3.0 mL) in sealed tube was heated at 80 °C until starting material was completely converted (~2 h; TLC). Indenedione **4** (0.5 mmol) was then added and the mixture was heated at 80 °C for another 4 h. The mixture was cooled to r.t. and the solid product was collected by filtration and washed with H_2O. The crude product and solid acid were treated with hot 95% EtOH. The catalyst was removed by filtration, and the pure product **5** was obtained from the mother liquor.

5a,10a-Dihydroxy-3-methyl-2,5-diphenyl-2,5,5a,10a-tetrahydroindeno[2′,1′:4,5]pyrrolo[3,2-*c*]pyridine-1,10-dione (5a)

Yellow crystals; yield: 177.0 mg (81%); mp 238–240 °C. IR (KBr): 3403, 1721, 1638, 1487, 1454, 1357, 1197, 1021, 943, 870, 772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.86 (m, 1 H, ArH), 7.39–7.52 (m, 10 H, ArH), 7.20–7.23 (m, 1 H, ArH), 7.11–7.14 (m, 1 H, ArH), 6.78 (dd, *J* = 5.6, 2.8 Hz, 1 H, ArH), 6.41 (br s, 1 H, OH), 5.63 (s, 1 H, CH), 5.36 (s, 1 H, OH), 1.83 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 161.2, 155.9, 150.7, 147.7, 138.3 (2 C), 136.9, 135.2 (2 C), 135.0, 129.9, 129.4, 128.8, 128.7, 128.5, 128.4, 127.8 (2 C), 124.9, 124.5, 100.2, 96.2, 93.4, 82.7, 77.3, 22.5. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2O_4^+$: 437.1496; found: 437.1495..

(18) **5-Aryl-5a,10a-dihydroxy-3-methyl-5a,10a-dihydro-1*H*-indeno[1,2-*b*] pyrano[3,4-*d*]pyrrole-1,10(5*H*)-diones 7a–d; General Procedure**

A mixture of pyranone **1** (0.5 mmol), the appropriate amine **2** (0.5 mmol), and solid acid (10 mg) in water (3.0 mL) in a sealed tube was stirred at r.t. until the starting material was completely converted (~12 h; TLC). Indenedione **4** (0.5 mmol) was then added and the mixture was heated at 80 °C for another 4 h. The mixture was cooled to r.t. and the solid product was collected by filtration and washed with H_2O. The crude product and the solid acid were treated with hot 95% EtOH and water. The catalyst was removed by filtration, and the pure product **7** was obtained from the mother liquor.

5a,10a-Dihydroxy-5-(4-methoxyphenyl)-3-methyl-5a,10a-dihydro-1*H*-indeno[1,2-*b*]pyrano[3,4-*d*]pyrrole-1,10(5*H*)-dione (7a)

Gray solid; yield: 147.2 mg (75%); mp 286–288 °C. IR (KBr): 3401, 1720, 1637, 1488, 1451, 1356, 1149, 1028, 875, 758 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.60 (d, *J* = 7.2 Hz, 1 H, ArH), 7.53–7.63 (m, 2 H, ArH), 7.38 (s, 1 H, OH), 7.20 (d, *J* = 8.0 Hz, 2 H, ArH), 7.07 (d, *J* = 8.8 Hz, 2 H, ArH), 6.73 (d, *J* = 7.6 Hz, 1 H, ArH), 6.36 (s, 1 H, OH), 5.59 (s, 1 H, CH), 3.83 (s, 3 H, OMe), 2.06 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 197.4, 167.4, 159.4, 158.5, 158.2, 147.7, 135.7 (2 C), 135.0, 130.8, 128.4 (2 C), 125.6 (2 C), 123.8, 114.9, 97.1, 93.1, 91.4, 83.1, 55.8, 20.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{18}NO_6^+$: 392.1129; found: 392.1131.