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Ultrasound mediated synthesis of dihydropyrano-[3,2-*d*][1,3]dioxin-7-carbonitrile derivatives in H_2O/EtOH medium

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Abstract: A one-pot cyclocondensation of 1,3-dioxane-5-one (**1**) with malononitrile and aromatic aldehydes in aqueous sodium hydroxide under ultrasonic irradiation furnishes a series of pyrano[3,2-*d*][1,3]dioxin derivatives **3**. Reactions are completed after a few minutes and the precipitated products are purified by simple crystallization from ethanol. The reaction with ethyl cyanoacetate instead of malononitrile gives the respective analogous products in high yields.

Keywords: aqueous; 1,3-dioxane-5-one; multicomponent reaction; one-pot synthesis; ultrasonication.

Introduction

The pyrano[3,2-*d*][1,3]dioxin bicyclic skeleton is a key motif in many naturally occurring compounds [1] and biologically active and medicinally important carbohydrates [2–4]. Some important examples include antifungal theopederins marine sponge [5], mycalamides with antiviral and antitumor properties [6], lolitrem B as an inhibitor of human large conductance calcium-activated potassium channels [7], sialosides with bacterial sialidases activity [8] and diphenylpyrazoles as breast cancer inhibitors [9]. In addition, the pyranodioxane moieties are useful intermediates in the synthesis of natural products and other important compounds [10–15]. Examples include (+)-papulacandin D [16], substituted D-glucals [17], (−)-isatisine A [18], hydroxypyridin-4-ones as antimalarial agents [19] and hydroxyalkyl-3-hydroxypyridin-4-ones as bidentate iron(III) chelators with potential for oral administration [20].

In the framework of our studies on aldol condensation reactions [21, 22], we have reported the synthesis of bisarylmethylidene derivatives of various six-membered homocyclic and heterocyclic ketones [23, 24]. Meanwhile, substituted 2,2-dimethyl-1,3-dioxan-5-ones **2** can serve as a synthon for dihydroxyacetone derivatives [25, 26]. In addition, these specific bisarylmethylidene compounds have the potential to be converted to a vicinal 1,2,3-tricarbonyl skeleton, a motif which is found in the structure of several natural products [27]. On this track, we decided to take advantage of the functionality of products **2** by subjecting them to the reaction with malononitrile to access products **3**.

Results and discussion

A one-pot ultrasound-mediated reaction of compound **1** with two equivalents of an aromatic aldehyde generates *in situ* product **2** that undergoes a subsequent cyclocondensation with malononitrile to produce a dihydropyrano-[3,2-*d*][1,3]dioxin-7-carbonitrile **3** in high yield (Scheme 1). It should be noted that the synthesis of analogous compounds [28, 29] have been only reported using a stepwise procedure. To the best of our knowledge, the only available one-pot method in the literature is the recent work we published for the thiopyran based structures [30].

We first optimized the reaction conditions by studying the condensation of 2,2-dimethyl-1,3-dioxan-5-one (**1**) with benzaldehyde and malononitrile. Treatment of **1** with an aqueous solution of NaOH (25%) and two equivalents of benzaldehyde in EtOH resulted in complete conversion of the reactants to **2a** after 2 min of ultrasonic irradiation, as indicated by TLC analysis. When malononitrile was added to the reaction mixture and sonication was continued for another 2 min, product **3a** (94%) precipitated rapidly. To evaluate the role of ultrasonication in the process, the same treatment was repeated under silent and reflux conditions. In these two cases, much lower yields of **3a** (10% and 40%) were obtained after 24 h and 8 h, respectively.

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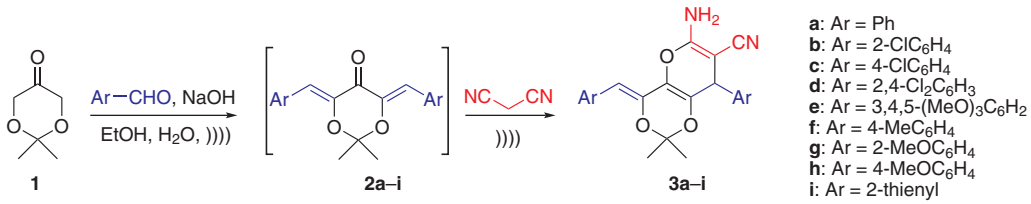
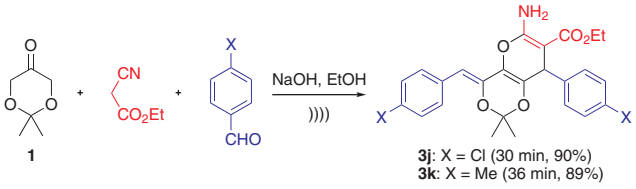


Scheme 1

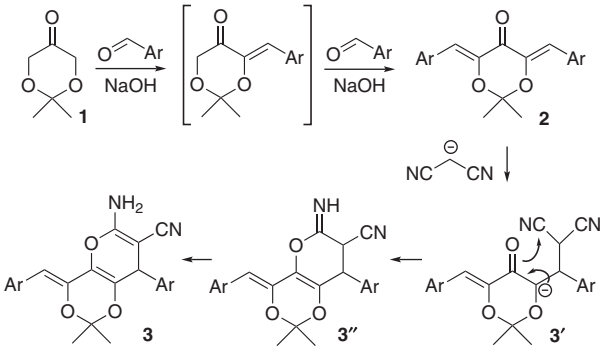
The use of other inorganic bases including $Ca(OH)_2$, LiOH, KOH and K_2CO_3 resulted in a decreased efficiency of the reaction. Similarly, replacement of NaOH with organic bases such as Et_2NH, Et_3N, morpholine and pyrrolidine lowered the yield of **3a**. Further optimization experiments showed that ethanol is the optimum medium and other solvents including MeCN, EtOAc and water are not as efficient as ethanol, giving 21%–65% of the desired product. Variation of the quantity of the base showed that the optimum concentration of NaOH is 25%.

The optimized conditions were used to evaluate the generality of the process. In addition to benzaldehyde, the use of other aromatic aldehydes bearing electron withdrawing or electron releasing substituents gave the respective products **3a**–**h** in high yields in a short reaction time between 3 min and 9 min. Similarly, thiophene-2-carbaldehyde reacted within 4 min to produce **3i** in 90% (Scheme 1). In all cases, the product precipitated from the reaction mixture spontaneously and was purified by simple crystallization from EtOH. To further explore the procedure, malononitrile was replaced with ethyl cyanoacetate. The use of two different aldehydes showed that the reactions were successful but the final products were obtained in relatively longer time periods (Scheme 2). The structure of all products **3a**–**3k** was elucidated based on spectral analysis.

The proposed mechanism is shown in Scheme 3. To support the intermediary of **2**, four different derivatives **2a** (Ar = C_6H_5), **2c** (Ar = 4-ClC_6H_4), **2f** (Ar = 4-MeC_6H_4), and **2i** (Ar = 2-thienyl) were synthesized independently and subjected to the treatment with malononitrile. As expected, the respective products **3a**, **c**, **f**, **i** were obtained efficiently in high yields and after short reaction times [80% (6 min), 83% (5 min), 75% (10 min) and 85% (5 min), respectively].



Scheme 2



Scheme 3

Conclusion

An efficient procedure for the synthesis of a series of dihydropyrano[3,2-*d*][1,3]dioxin heterocycles was developed. The one-pot procedure is suitable for the preparation of various derivatives under sonochemical conditions within a few minutes. The product precipitates spontaneously.

Experimental

Melting points are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded using KBr disks on a Bruker Vector-22 spectrometer. NMR spectra were obtained on a Bruker Ultra Shield™ spectrometer at 500 MHz for ^1H and 125 MHz for ^{13}C in $CDCl_3$ or DMSO-d_6. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. Mass spectra were obtained on a Finnigan Mat 8430 instrument at ionization potential of 70 eV. TLC experiments were carried out on pre-coated silica gel plates using petroleum ether/EtOAc (4:1) as eluent. Ketone **1** was prepared as previously reported [31]. Aldehydes were distilled or crystallized immediately before use.

General procedure

To a solution of the aldehyde ArCHO (2.0 mmol) and **1** (130 mg, 1.0 mmol) in EtOH (2.0 mL) was added an aqueous solution of NaOH

(25%, 33 μL, 0.21 mmol). The resulting mixture was irradiated in a Sartorius Ultrasonic-homogenizer LABSONIC®P 230V/50 Hz instrument with a frequency of 24 KHz and nominal power of 460 W/cm^2 for 2 min until a yellowish precipitate of the intermediate **2** was observed. At this point, malononitrile (100 mg, 1.5 mmol) or ethyl cyanoacetate (170 mg, 1.5 mmol) was added and the mixture was irradiated for another 2 min. TLC showed that the starting materials and the intermediate **2** were completely consumed. The product that precipitated spontaneously from the reaction mixture was separated by filtration and crystallized from EtOH.

(*Z*)-6-Amino-4-benzylidene-2,2-dimethyl-8-phenyl-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carbonitrile (3a) Yield 94%; mp 198–200°C; ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 3H, Me), 1.65 (s, 3H, Me), 4.27 (s, 1H, CHAr), 4.66 (s, 2H, NH_2), 5.86 (s, 1H, =CH), 7.23 (t, 1H, *J* = 7.5 Hz, Ar), 7.30–7.36 (m, 5H, Ar), 7.38–7.41 (m, 2H, Ar), 7.62 (d, 2H, *J* = 7.5 Hz, Ar); ^{13}C NMR ($CDCl_3$): δ 23.9, 25.7, 41.2, 60.9, 102.7, 103.6, 119.6, 126.3, 127.0, 128.2, 128.4, 128.8, 129.1, 129.2, 134.2, 135.3, 138.6, 140.6, 159.1; MS: *m/z* 372 (M^+), 270, 142, 114; IR: 3435, 3344, 2191, 1641 cm^{-1}. Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41. Found: C, 73.95; H, 5.01.

(*Z*)-6-Amino-4-(2-chlorobenzylidene)-8-(2-chlorophenyl)-2,2-dimethyl-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carbonitrile (3b) Yield 90%; mp 200–202°C; ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 3H, Me), 1.62 (s, 3H, Me), 4.73 (s, 2H, NH_2), 4.93 (s, 1H, CHAr), 6.26 (s, 1H, =CH), 7.14 (ddd, 1H, *J* = 1.5, 7.5, 7.5 Hz, Ar), 7.25–7.27 (m, 2H, Ar), 7.31 (dd, 1H, *J* = 1.5, 7.5 Hz, Ar), 7.33 (dd, 1H, *J* = 1.5, 7.5 Hz, Ar), 7.40 (dd, 1H, *J* = 1.5, 8.0 Hz, Ar), 7.41 (dd, 1H, *J* = 1.5, 8.0 Hz, Ar), 8.00 (dd, 1H, *J* = 1.5, 8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$): δ 23.4, 25.3, 37.6, 59.5, 98.7, 102.6, 118.8, 126.4, 126.6, 127.3, 127.5, 129.0, 129.4, 130.1, 130.2, 132.5, 133.0, 134.0, 134.1, 137.3, 139.3, 159.0; MS: *m/z* 441 (M^+), 382, 347, 271, 240; IR: 3462, 3359, 2194, 1638 cm^{-1}. Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_3$: C, 62.60; H, 4.11. Found: C, 62.51; H, 4.15.

(*Z*)-6-Amino-4-(4-chlorobenzylidene)-8-(4-chlorophenyl)-2,2-dimethyl-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carbonitrile (3c) Yield 95%; mp 212–216°C; ^{1}H NMR (DMSO-d_6): δ 1.33 (s, 3H, Me), 1.57 (s, 3H, Me), 4.34 (s, 1H, CHAr), 5.88 (s, 1H, =CH), 7.02 (s, 2H, NH_2), 7.30 (d, 2H, *J* = 8.5 Hz, Ar), 7.38 (d, 2H, *J* = 8.5 Hz, Ar), 7.43 (d, 2H, *J* = 8.5 Hz, Ar), 7.55 (d, 2H, *J* = 8.5 Hz, Ar); ^{13}C NMR (DMSO-d_6): δ 23.7, 25.1, 40.2, 56.2, 101.6, 103.0, 120.1, 125.7, 129.0, 129.1, 130.2, 130.4, 131.2, 132.5, 133.8, 134.2, 139.3, 140.8, 159.7; MS: *m/z* 441 (M^+), 382, 354, 240, 205; IR: 3454, 32510, 2196, 1642 cm^{-1}. Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_3$: C, 62.60; H, 4.11. Found: C, 62.66; H, 4.18.

(*Z*)-6-Amino-4-(2,4-dichlorobenzylidene)-8-(2,4-dichlorophenyl)-2,2-dimethyl-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carbonitrile (3d) Yield 96%; mp 230–232°C; ^{1}H NMR (DMSO-d_6): δ 1.37 (s, 3H, Me), 1.57 (s, 3H, Me), 4.83 (s, 1H, CHAr), 6.20 (s, 1H, =CH), 7.17 (s, 2H, NH_2), 7.38 (dd, 1H, *J* = 2.0, 8.5 Hz, Ar), 7.46 (s, 1H, Ar), 7.47 (d, 1H, *J* = 2.0 Hz, Ar), 7.62 (d, 1H, *J* = 2.0 Hz, Ar), 7.63 (d, 1H, *J* = 2.0 Hz, Ar), 7.97 (d, 1H, *J* = 8.5 Hz, Ar); ^{13}C NMR (DMSO-d_6): δ 23.4, 25.3, 40.1, 54.9, 97.2, 103.4, 119.7, 126.2, 127.9, 128.6, 129.3, 129.6, 131.4, 131.5, 131.7, 133.0, 133.4, 134.1, 134.2, 137.6, 140.6, 160.0; MS: *m/z* 510 (M^+), 415, 210, 147; IR: 3438, 3315, 2204, 1655 cm^{-1}. Anal. Calcd for $C_{23}H_{16}Cl_4N_2O_3$: C, 54.15; H, 3.16. Found: 54.23; H, 3.22.

(*Z*)-6-Amino-2,2-dimethyl-4-(3,4,5-trimethoxybenzylidene)-8-(3,4,5-trimethoxyphenyl)-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carbonitrile (3e) Yield 90%; mp 160–164°C; ^{1}H NMR (DMSO-d_6): δ 1.42 (s, 3H, Me), 1.60 (s, 3H, Me), 3.66 (s, 3H, Me), 3.67 (s, 3H, Me), 3.76 (s, 6H, Me), 3.77 (s, 6H, Me), 4.25 (s, 1H, CHAr), 5.84 (s, 1H, =CH), 6.53 (s, 2H, NH_2), 6.87 (s, 2H, Ar), 6.91 (s, 2H, Ar); ^{13}C NMR (DMSO-d_6): δ 23.5, 25.5, 40.1, 56.0, 56.4, 56.7, 60.4, 60.5, 102.6, 103.0, 105.5, 106.0, 120.2, 125.8, 130.5, 133.7, 136.8, 137.2, 137.5, 138.3, 153.1, 153.4, 159.7; MS: *m/z* 552 (M^+), 486, 274, 232, 181; IR: 3315, 2963, 2197, 1645 cm^{-1}. Anal. Calcd for $C_{29}H_{32}N_2O_9$: C, 63.03; H, 5.84. Found: C, 62.91; H, 5.95.

(*Z*)-6-Amino-2,2-dimethyl-4-(4-methylbenzylidene)-8-(p-tolyl)-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carbonitrile (3f) Yield 87%; mp 193–196°C; ^{1}H NMR (DMSO-d_6): δ 1.34 (s, 3H, Me), 1.58 (s, 3H, Me), 2.31 (s, 3H, Me), 2.32 (s, 3H, Me), 4.22 (s, 1H, CHAr), 5.88 (s, 1H, =CH), 6.93 (s, 2H, NH_2), 7.16 (d, 2H, *J* = 8.0 Hz, Ar), 7.17 (d, 2H, *J* = 8.0 Hz, Ar), 7.19 (d, 2H, *J* = 8.0 Hz, Ar), 7.46 (d, 2H, *J* = 8.0 Hz, Ar); ^{13}C NMR (DMSO-d_6): δ 21.5, 21.7, 24.2, 25.5, 40.1, 57.3, 102.9, 103.1, 126.1, 128.6, 129.1, 130.0, 130.1, 131.5, 132.6, 134.5, 136.7, 137.4, 138.6, 139.4, 160.0; MS: *m/z* 400 (M^+), 334, 296, 156, 115; IR: 3426, 3315, 2203, 1637 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04. Found: C, 75.05; H, 6.11.

(*Z*)-6-Amino-4-(2-methoxybenzylidene)-8-(2-methoxyphenyl)-2,2-dimethyl-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carbonitrile (3g) Yield 85%; mp 187–190°C; ^{1}H NMR (DMSO-d_6): δ 1.32 (s, 3H, Me), 1.53 (s, 1H, Me), 3.78 (s, 3H, OMe), 3.83 (s, 3H, OMe), 4.67 (s, 1H, CHAr), 6.24 (s, 1H, =CH), 6.87 (s, 2H, NH_2), 6.91 (dd, 1H, *J* = 7.5, 7.5 Hz, Ar), 6.95–7.00 (m, 3H, Ar), 7.15 (d, 1H, *J* = 7.5 Hz, Ar), 7.17 (d, 1H, *J* = 7.5 Hz, Ar), 7.24 (dd, 1H, *J* = 7.5, 8.0 Hz, Ar), 7.85 (d, 1H, *J* = 8.0 Hz, Ar); ^{13}C NMR (DMSO-d_6): δ 23.4, 25.4, 34.8, 55.9, 56.2, 56.3, 96.2, 102.3, 111.2, 112.0, 120.4, 120.8, 121.2, 123.5, 126.5, 128.1, 129.1, 129.4, 129.6, 129.7, 134.1, 138.6, 156.4, 157.6, 160.2; MS: *m/z* 432 (M^+), 343, 229, 172, 150; IR: 3436, 3314, 2195, 1643 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59. Found: C, 69.59; H, 5.66.

(*Z*)-6-Amino-4-(4-methoxybenzylidene)-8-(4-methoxyphenyl)-2,2-dimethyl-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carbonitrile (3h) Yield 89%; mp 212–216°C; ^{1}H NMR (DMSO-d_6): δ 1.27 (s, 3H, Me), 1.55 (s, 3H, Me), 3.75 (s, 6H, OMe), 4.26 (s, 1H, CHAr), 5.83 (s, 1H, =CH), 6.77 (s, 2H, NH_2), 6.91 (d, 2H, *J* = 8.0 Hz, Ar), 6.92 (d, 2H, *J* = 8.0 Hz, Ar),7.16 (d, 2H, *J* = 8.0 Hz, Ar), 7.49 (d, 2H, *J* = 8.0 Hz, Ar); ^{13}C NMR (DMSO-d_6): δ 23.8, 25.2, 40.1, 55.5, 57.0, 102.4, 102.4, 114.4, 114.5, 120.4, 125.6, 127.7, 129.3, 130.1, 133.7, 134.0, 137.1, 158.3, 159.0, 159.6; MS: *m/z* 432 (M^+), 374, 330, 239, 187; IR: 3395, 3309, 2194, 1642 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59. Found: C, 69.67; H, 5.68.

(*Z*)-6-Amino-2,2-dimethyl-8-(thiophen-2-yl)-4-(thiophen-2-ylmethylene)-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carbonitrile (3i) Yield 90%; mp 200–203°C; ^{1}H NMR (DMSO-d_6): δ 1.37 (s, 3H, Me), 1.61 (s, 3H, Me), 4.65 (s, 1H, CHAr), 6.23 (s, 1H, =CH), 6.98–7.03 (m, 3H, Ar), 7.04 (s, 2H, NH_2), 7.09 (d, 1H, *J* = 3.0, 1H, Ar), 7.45 (d, 1H, *J* = 5.0 Hz, Ar), 7.46 (d, 1H, *J* = 5.0 Hz, Ar); ^{13}C NMR (DMSO-d_6): δ 23.5, 25.3, 36.0, 56.9, 98.4, 103.2, 120.1, 125.0, 126.2, 126.9, 127.0, 127.4, 133.6, 136.6, 137.2, 146.2, 159.7; MS: *m/z* 384 (M^+), 326, 282, 254, 203, 177; IR: 3452, 3339, 2188, 1686 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_2O_3S_2$: C, 59.35; H, 4.19; S, 16.68. Found: 59.51; H, 4.27, S, 16.74.

Ethyl (*Z*)-6-amino-4-(4-chlorobenzylidene)-8-(4-chlorophenyl)-2,2-dimethyl-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carboxylate (3j) Yield 90%; mp 170–172°C; ^{1}H NMR ($CDCl_3$): δ 1.13 (t, 3H, *J* = 7.0 Hz, Me), 1.28 (s, 3H, Me), 1.61 (s, 3H, Me), 4.01–4.05 (m, 2H, CH_2), 4.40 (s, 1H, CHAr), 5.78 (s, 1H, =CH), 6.39 (br s, 2H, NH_2), 7.21 (d, 2H, *J* = 7.5 Hz, Ar), 7.25 (d, 2H, *J* = 7.5 Hz, Ar) 7.27 (d, 2H, *J* = 7.5 Hz, Ar), 7.52 (d, 2H, *J* = 7.5 Hz, Ar); ^{13}C NMR ($CDCl_3$): δ 14.2, 23.2, 25.5, 39.7,

59.6, 76.8, 101.3, 102.2, 125.1, 128.1, 128.5, 129.4, 129.8, 131.7, 132.3, 133.6, 136.5, 139.1, 142.1, 159.3, 169.0; MS: *m/z* 487 (M^+), 429, 376, 272, 176; IR: 3387, 3292, 1660, 1594 cm^{-1}. Anal. Calcd for $C_{25}H_{23}Cl_2NO_5$: C, 61.49; H, 4.75. Found: C, 61.59; H, 4.82.

Ethyl (*Z*)-6-amino-2,2-dimethyl-4-(4-methylbenzylidene)-8-(p-tolyl)-4,8-dihydropyrano[3,2-*d*][1,3]dioxin-7-carboxylate (3k) Yield 89%; mp 182–184°C; ^{1}H NMR ($CDCl_3$): δ 1.13 (t, *J* = 7.0 Hz, 3H, Me), 1.29 (s, 3H, Me), 1.62 (s, 3H, Me), 2.33 (s, 3H, Me), 2.35 (s, 3H, Me), 3.98–4.09 (m, 2H, CH_2), 4.37 (s, 1H, CHAr), 5.80 (s, 1H, =CH), 6.32 (br s, 2H, NH_2), 7.08 (d, 2H, *J* = 8.0 Hz, Ar), 7.13 (d, 2H, *J* = 8.0 Hz, Ar) 7.16 (d, 2H, *J* = 8.0 Hz, Ar), 7.51 (d, 2H, *J* = 8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$): δ 14.2, 21.1, 21.2, 23.3, 25.5, 39.7, 59.4, 76.8, 101.9, 102.1, 125.2, 128.0, 128.5, 128.6, 129.1, 132.5, 135.9, 136.7, 138.3, 140.6, 159.4, 169.3; MS: *m/z* 447 (M^+), 389, 356, 232,156; IR: 3400, 3294, 1659, 1592 cm^{-1}. Anal. Calcd for $C_{27}H_{29}NO_5$, C, 72.46; H, 6.63. Found: C, 72.31; H, 6.80.

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