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Iodine-Promoted Formal [3+2] Cycloaddition of Enaminone: Access to 2-Hydroxy-1,2-dihydro-pyrrol-3-ones with Quaternary Carbon Center

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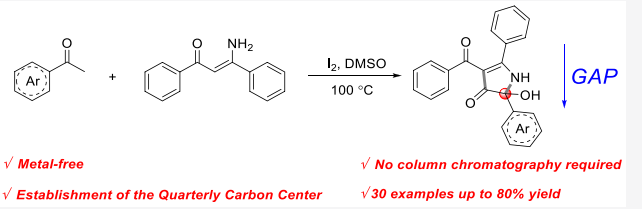
ABSTRACT: A novel iodine promoted cyclization of enaminone with aryl methyl ketones has been developed as a straightforward method for constructing 2-hydroxy-pyrrol-3(2*H*)-ones. This strategy affords structurally diverse 2-hydroxy-pyrrol-3(2*H*)-ones rings in high yields. Moreover, a quarternary alcohol has been constructed efficiently in the reaction. Product purification required only washing with CH_2Cl_2 solvent, thereby avoiding traditional chromatography and recrystallization, making this an example of group-assisted purification chemistry.



The 1*H*-pyrrol-3(2*H*)-one ring system is widely found in drug molecules and natural products (Figure 1).[1] For

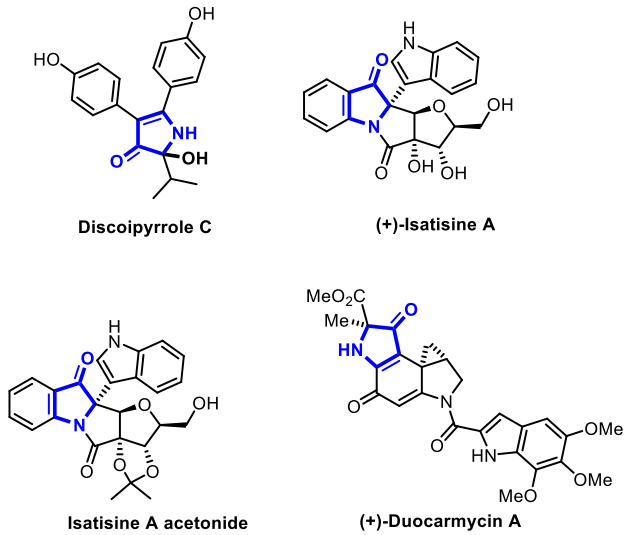


Figure 1. Selected natural products and drug molecules.

example, discoipyrrole C is one of the families of polycyclic alkaloids.[1e] Isatisine A isolated from the leaves of *Isatis indigotica* Fort is a complex bisindole natural product.[1f] Isatisine A acetonide has been shown to possess anti-HIV-1IIIB activity.[1g] Apart from this, (+)-duocarmycins A is a prominent member of the potent antitumor antibiotics isolated from *Streptomyces* species.[1h]

However, compared with the synthesis of 1*H*-pyrrol-2-ones,[2] there are only a few established methods for the construction of 1*H*-pyrrol-3(2*H*)-ones that have been reported.[3] As the carbonyl group of pyrrol-3(2*H*)-ones is prone to keto-enol equilibrium with 3-hydroxyl pyrrole, it is difficult for 1*H*-pyrrol-3(2*H*)-ones to exist stably.[4] This problem can be addressed by introducing a quaternary carbon center at the 2-position of 1*H*-pyrrol-3(2*H*)-ones so that the carbonyl group cannot undergo keto-enol equilibrium. In 2013, the Bi and Dong group reported the synthesis of pyrrol-3(2*H*)-ones with a quaternary carbon center through the copper-catalyzed reaction of a pre-prepared α-diazo-β-oxoamide with an aromatic amine, which introduced a methyl group at the 2-position (Scheme 1a).[4] In the same year, a copper-catalyzed oxidative tandem cyclization of enamino amides to construct pyrrol-3(2*H*)-ones was established by the Guan group (Scheme 1b).[5] The construction of pyrrol-3(2*H*)-ones with a quaternary carbon center was realized by introducing an alkyl group at the 2-position. The above work reports all introduced alkyl groups at the 2-position of pyrrol-3(2*H*)-ones to achieve the construction of quaternary carbon centers. We envisioned introducing more active functional groups, such as hydroxyl, at the 2-position in order to achieve pyrrol-3(2*H*)-ones diversified construction of quaternary carbon centers in view of that the tertiary alcohol scaffold is prevalent in organic molecules, ranging from biologically active compounds to natural products.[6] However, retaining the hydroxyl group under acidic conditions is difficult because it is easily

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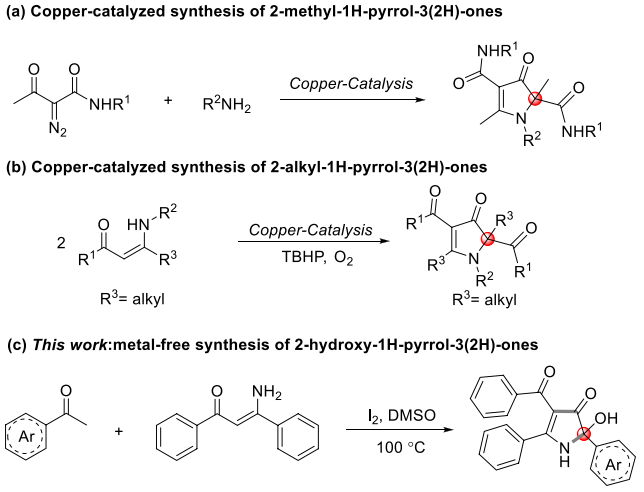
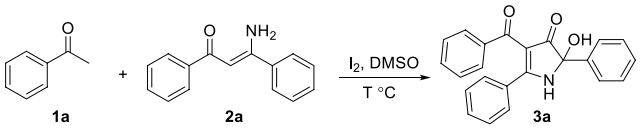
Scheme 1. Synthesis of Pyrrol-3(2*H*)-one Containing Quaternary Carbon Center



protonated and removed. Herein, we fortunately achieved the construction of 2-hydroxy-pyrrol-3(2*H*)-ones by using enaminone and aryl methyl ketones as the reaction substrates in an I_2−DMSO system, without any metal catalysts, and successfully introduced the tertiary alcohol into the 2-position of pyrrol-3(2*H*)-ones. Furthermore, in addition to introducing a hydroxyl group, we also retained *N*-H well in the reaction, providing a new method for the construction of the core skeleton of pyrrol-3-one of discoipyrrole C (Scheme 1c). Moreover, product purification required only washing with CH_2Cl_2 solvent, thereby avoiding traditional chromatography and recrystallization, making this an example of group-assisted purification (GAP) chemistry.[7]

We commenced our study with the reaction of aryl methyl ketone **1a** with enaminone **2a** as the model reaction (Table 1). To our delight, the desired product **3a** was obtained in 88% yield from the reaction with 1.6 equiv of I_2 at 100 °C (entry 1).

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	I_2 (equiv)	acid	temp (°C)	yield[b] (%)
1	1.6		100	88
2	0.5		100	trace
3	1.0		100	23
4	2.0		100	80
5	1.6	$Cu(OTf)_2$	100	50
6	1.6	HI	100	45
7	1.6	TFA	100	85
8	1.6	TfOH	100	85
9	1.6	$Fe(OTf)_2$	100	62
10	1.6	$FeCl_3$	100	56
11	1.6		80	trace
12	1.6		120	58
13	1.6		140	trace

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), I_2 (equiv), acid (2.0 equiv), 4 h, DMSO (4 mL), indicated temperature, unless otherwise noted. [b]Yield of the isolated product is given.

On this basis, we continued to screen the conditions, hoping to obtain the target compound with a higher yield. We first optimized the equivalent of iodine and finally chose 1.6 equiv as the optimal condition (entries 2−4). Next, we added acid additives to the reaction in order to further increase the yield, but it resulted in reduced yields (entries 5−10). Finally, we screened the reaction temperature again, and 100 °C was still the best reaction temperature (entries 11−13).

Under the optimized conditions, a series of aryl methyl ketones were used as substrates to investigate the compatibility of the reaction (Scheme 2). When electron-donating groups were attached to the aromatic ring of the aryl methyl ketones, such as $-CH_3$, $-C_2H_5$, $-t$-C_4H_9, −OMe, and −OEt, the target compounds can be obtained in a satisfactory yield regardless of whether it is in the *ortho*-position, *meta*-position, or *para*-position (**3b**−**3k**, 81−88%). Aryl methyl ketones with halogens on aryl rings, such as −F, −Cl, −Br, and $-OCF_3$, gave the corresponding 2-hydroxy-pyrrol-3(2*H*)-ones **3l**−**3t** in 80−87% yields. Thiomethyl-substituted aryl methyl ketone **3u** was also compatible with the reaction with a yield of 82%. Large hindered substituents, such as benzphenone, naphthophenone, and dioxane acetophenone **3v**−**3y**, all converted to the desired compounds with the yield of 80−83% under the standard conditions. Notably, electron-withdrawing groups, including $-NO_2$, −COOMe, −CN, and $-SO_2Me$, were well compatible with the reaction regardless of the *para*- or *meta*-positions (**3z**−**4d**, 80−84%).

To further investigate the mechanism of the reaction, we conducted a series of control experiments associated with this transformation (Scheme 3). The phenylglyoxal **1ab** and its hydrated species **1ac** can be obtained in quantitative yield by reacting aryl methyl ketone (**1a**) with I_2 in DMSO solvent at the temperature of 100 °C (Scheme 3a). When 2-iodoacetophenone **1aa** was used as the reaction substrate to react with **2a** under standard conditions, product **3a** can be obtained with a yield of 80% (Scheme 3b). Moreover, under the optimal conditions, when α-hydroxyacetophenone **1ad** reacted with **2a**, the same product **3a** can also be obtained in 83% yield (Scheme 3c). Finally, α-hydroxyacetophenone was replaced by phenylglyoxal **1ac** as the reaction substrate, and the desired product **3a** was formed in 85% yield under standard conditions (Scheme 3d). The above results showed that 2-iodoacetophenone **1aa**, α-hydroxyacetophenone **1ad**, and phenylglyoxal **1ac** were important intermediates in the reaction.

On the basis of the previous reports and the above results, a tentative mechanism was proposed[8] (Scheme 4). First, acetophenone **1a** is converted to iodoacetophenone **1aa** through the process of iodination. Next, there are two possible ways to convert **1aa** to **1ab**. In path a, the conversion from **1aa** to **1ab** is achieved by Kornblum oxidation. In path b, **1aa** first reacts with H_2O to generate α-hydroxyacetophenone **1ad**, which is then oxidized to **1ab**. Then the aldehyde carbonyl group of **1ab** is attacked by the double bond of enaminone **2a** to afford intermediate **A**. Next, the amino group in intermediate **A** attacks the ketone carbonyl group of acetophenone to form intermediate **B**, which is further oxidized to **C**. Finally, intermediate **C** is isomerized to obtain the target compound **3a**.

CONCLUSION

In summary, we have reported a one-pot synthesis of 2-hydroxy-pyrrol-3(2*H*)-ones by using enaminone and aryl

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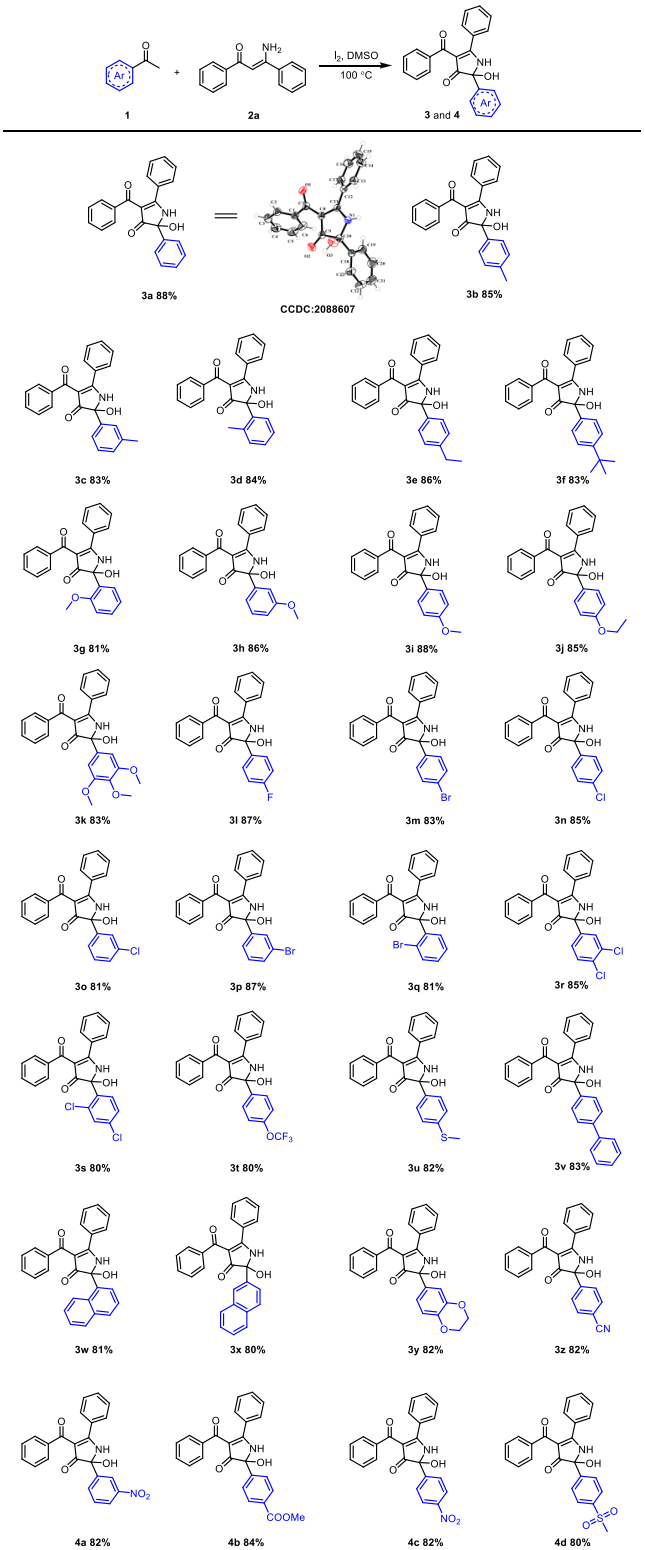
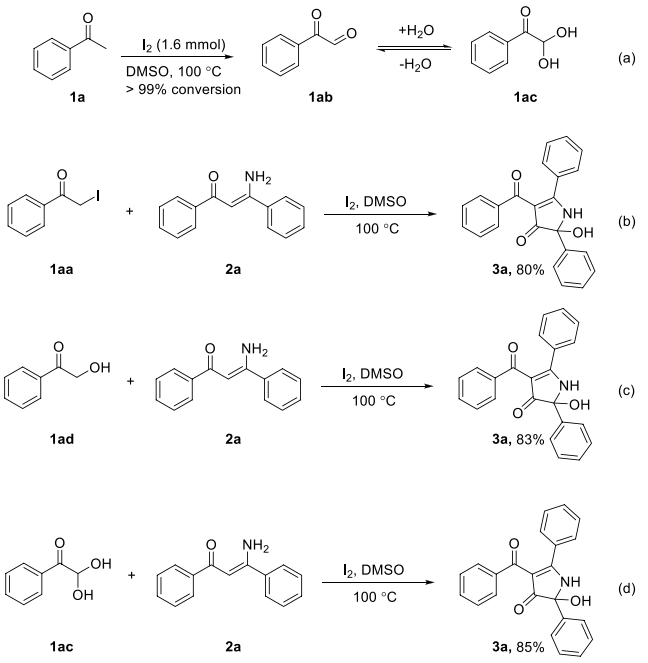
Scheme 2. Substrate Scope for the Synthesis of 3 and 4[a,b]



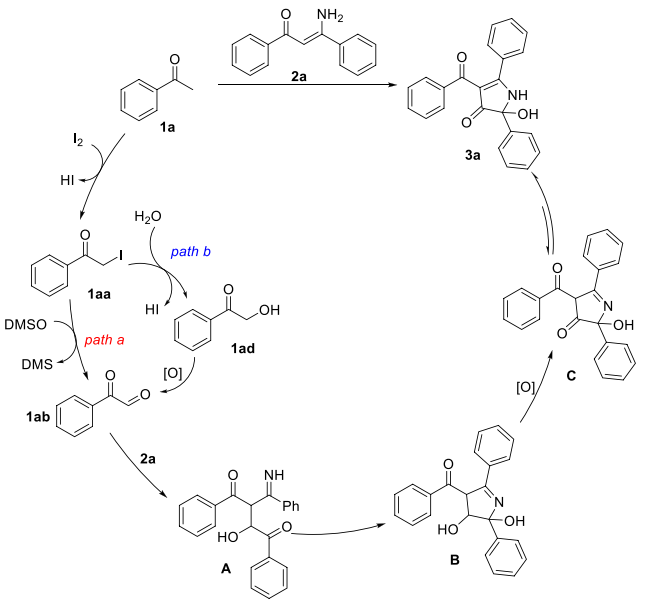
[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), I_2 (1.6 mmol) heated at 100 °C in 4 mL of DMSO. [b]Yield of the isolated product is given.

methyl ketones as the reaction substrates in a I_2−DMSO system under metal-free conditions, and we successfully introduced a quaternary alcohol at the 2-position, which can be combined with GAP chemistry. The reaction was highly

Scheme 3. Control Experiments



Scheme 4. Proposed Mechanism



efficient and showed good functional group compatibility, while the operating conditions were mild and simple.

EXPERIMENTAL SECTION

General Methods. All other substrates and reagents were commercially available and used without further purification. TLC analysis was performed using precoated glass plates. ^{1}H NMR, ^{13}C{^{1}H} NMR, and ^{19}F NMR spectra were recorded in DMSO-d_6 on 400 MHz NMR spectrometers, and chemical shifts of ^{1}H NMR are reported in ppm, relative to the internal standard of DMSO-d_6 (DMSO-d_6, δ = 2.50 ppm). Chemical shifts of ^{13}C{^{1}H} NMR were reported in ppm with the solvent as the internal standard (DMSO-d_6, δ = 39.5 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and integration. ^{13}C{^{1}H} NMR spectra were

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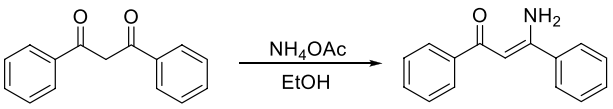
recorded in DMSO-d_6 on 100 MHz NMR spectrometers, and resonances (δ) are given in ppm. ^{19}F spectra were recorded in DMSO-d_6 on 376 MHz NMR spectrometers, and resonances (δ) are given in ppm. HRMS data were obtained on a Bruker 7-tesla FT-ICR MS equipped with an electrospray source. The X-ray crystal structure determinations of **3a** were obtained on a Bruker SMART APEX CCD system. Melting points were determined using an XT-4 apparatus and not corrected.

Synthesis of Enaminone.



2a

Prepared according to a literature procedure.[9] To an oven-dried round-bottom flask were added 1.0 equiv of dibenzoylmethane, 5.0 equiv of NH_4OAc, and EtOH (0.5 M). The reaction mixture was heated to reflux for overnight. After cooling to room temperature, EtOH was removed. H_2O was added, and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (5:1 hexanes:EtOAc) to afford the title compound as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.14 (s, 1H), 8.01 (d, J = 7.6 Hz, 2H), 7.85−7.81 (m, 2H), 7.55−7.46 (m, 6H), 6.22 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 187.8, 163.3, 140.2, 136.4, 130.8, 130.7, 128.7, 128.3, 127.0, 126.8, 89.7.

General Procedures for the Synthesis of Products 3 and 4 (3a as an Example). A mixture of acetophenone (colorless liquid, commercially available) **1a** (1.0 mmol) and iodine (1.6 mmol) in DMSO (4 mL) was stirred at 100 °C; after 1 h later, enaminone (yellow solid) **2a** (1.0 mmol) was added in the reaction, until almost completion of the conversion of the substrates by TLC analysis. The mixture was quenched with saturated $Na_2S_2O_3$ solution (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by CH_2Cl_2 solvent to afford the product **3a** (white solid).

Analytical Data for Products 3a−4d. *4-Benzoyl-2-hydroxy-2,5-diphenyl-1,2-dihydro-3H-pyrrol-3-one (**3a**).* Yield 88%; 312.7 mg; white solid; mp 212−214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 7.65−7.61 (m, 4H), 7.56 (d, J = 7.2 Hz, 3H), 7.50−7.42 (m, 6H), 7.39−7.34 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.3, 189.2, 179.0, 139.2, 138.1, 131.9, 131.8, 130.3, 129.1, 128.6, 128.4, 128.3, 127.8, 125.5, 105.0, 88.5. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{23}H_{18}NO_3^+$: 356.1281; found: 356.1282.

*4-Benzoyl-2-hydroxy-5-phenyl-2-(p-tolyl)-1,2-dihydro-3H-pyrrol-3-one (**3b**).* Yield 85%; 314.0 mg; white solid; mp 232−234 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 7.66−7.61 (m, 4H), 7.56 (d, J = 7.2 Hz, 1H), 7.50−7.43 (m, 6H), 7.38−7.35 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.4, 189.2, 178.8, 139.3, 137.6, 135.2, 131.84, 131.77, 130.4, 129.1, 128.9, 128.6, 128.3, 127.7, 125.4, 105.0, 88.5, 20.8. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{24}H_{20}NO_3^+$: 370.1438; found: 370.1437.

*4-Benzoyl-2-hydroxy-5-phenyl-2-(m-tolyl)-1,2-dihydro-3H-pyrrol-3-one (**3c**).* Yield 83%; 306.6 mg; white solid; mp 194−196 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 7.70−7.65 (m, 5H), 7.50 (s, 5H), 7.38 (s, 4H), 7.22 (s, 1H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.3, 189.3, 178.9, 139.3, 138.1, 137.5, 131.9, 131.8, 130.4, 129.2, 129.0, 128.7, 128.4, 127.8, 126.1, 122.6, 105.1, 88.5, 55.0, 21.3. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{24}H_{20}NO_3^+$: 370.1438; found: 370.1444.

*4-Benzoyl-2-hydroxy-5-phenyl-2-(o-tolyl)-1,2-dihydro-3H-pyrrol-3-one (**3d**).* Yield 84%; 310.3 mg; white solid; mp 195−197 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 7.81 (d, J = 40.0 Hz, 3H), 7.58−7.42 (m, 10H), 7.28 (d, J = 28.4 Hz, 3H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.7, 189.2, 178.4, 139.4, 136.4, 135.9, 131.8, 131.5, 130.5, 129.2, 128.5, 128.4, 127.8, 127.6, 125.5, 106.7, 87.8, 19.8. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{24}H_{20}NO_3^+$: 370.1438; found: 370.1434.

*4-Benzoyl-2-(4-ethylphenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3e**).* Yield 86%; 329.8 mg; white solid; mp 184−186 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 7.63−7.54 (m, 5H), 7.49−7.41 (m, 6H), 7.37−7.34 (m, 2H), 7.26 (d, J = 8.0 Hz, 2H), 2.61 (d, J = 7.2 Hz, 2H), 1.19−1.16 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.3, 189.2, 178.8, 144.0, 139.2, 135.4, 131.85, 131.77, 130.4, 129.1, 128.6, 128.4, 127.8, 125.5, 105.0, 88.5, 27.9, 15.8. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{25}H_{22}NO_3^+$: 384.1594; found: 384.1603.

*4-Benzoyl-2-(4-(tert-butyl)phenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3f**).* Yield 83%; 341.5 mg; white solid; mp 265−267 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 7.59−7.52 (m, 5H), 7.45−7.41 (m, 7H), 7.35−7.30 (m, 3H), 1.25 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.3, 189.1, 178.8, 150.8, 139.2, 135.2, 131.8, 131.7, 130.4, 129.1, 128.5, 128.3, 127.7, 125.2, 125.1, 105.0, 88.4, 34.3, 31.1. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{27}H_{26}NO_3^+$: 412.1907; found: 412.1918.

*4-Benzoyl-2-hydroxy-2-(2-methoxyphenyl)-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3g**).* Yield 81%; 312.2 mg; white solid; mp 94−96 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 7.84−7.74 (m, 3H), 7.53−7.36 (m, 9H), 7.30 (s, 1H), 7.04 (s, 2H), 3.76 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 196.2, 189.0, 178.2, 156.5, 139.6, 131.6, 131.3, 131.2, 129.8, 129.2, 128.5, 128.3, 128.2, 127.6, 126.8, 120.0, 111.2, 106.9, 85.7, 55.6. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{24}H_{20}NO_4^+$: 386.1387; found: 386.1390.

*4-Benzoyl-2-hydroxy-2-(3-methoxyphenyl)-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3h**).* Yield 86%; 331.5 mg; white solid; mp 160−162 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H), 7.62−7.57 (m, 5H), 7.51−7.47 (m, 5H), 7.35 (d, J = 4.0 Hz, 2H), 7.11−7.05 (m, 2H), 6.95 (d, J = 8.0 Hz, 1H), 3.76 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.1, 189.2, 179.0, 159.3, 139.6, 139.2, 131.9, 131.8, 130.3, 129.6, 129.1, 128.6, 128.4, 127.8, 117.4, 113.5, 111.6, 105.0, 88.3, 55.1. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{24}H_{20}NO_4^+$: 386.1387; found: 386.1391.

*4-Benzoyl-2-hydroxy-2-(4-methoxyphenyl)-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3i**).* Yield 88%; 339.2 mg; white solid; mp 260−262 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 7.66−7.61 (m, 5H), 7.50−7.47 (m, 5H), 7.43 (s, 1H), 7.39−7.35 (m, 2H), 7.00 (d, J = 8.4 Hz, 2H), 3.76 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.5, 189.3, 178.8, 159.4, 139.3, 131.9, 131.8, 130.4, 130.1, 129.2, 128.7, 128.4, 127.8, 126.9, 113.8, 105.0, 88.4, 55.2. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{24}H_{20}NO_4^+$: 386.1387; found: 386.1386.

*4-Benzoyl-2-(4-ethoxyphenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3j**).* Yield 85%; 339.5 mg; white solid; mp 122−124 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 7.77−7.70 (m, 4H), 7.58−7.52 (m, 7H), 7.41 (s, 2H), 7.06 (d, J = 6.8 Hz, 2H), 4.07 (s, 2H), 1.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.7, 189.4, 178.9, 158.8, 139.4, 132.0, 131.9, 130.6, 130.1, 129.4, 128.8, 128.5, 127.9, 127.1, 114.3, 105.1, 88.6, 63.3, 14.8. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{25}H_{22}NO_4^+$: 400.1543; found: 400.1546.

*4-Benzoyl-2-hydroxy-5-phenyl-2-(3,4,5-trimethoxyphenyl)-1,2-dihydro-3H-pyrrol-3-one (**3k**).* Yield 83%; 369.7 mg; white solid; mp 235−237 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 7.71 (d, J = 7.2 Hz, 2H), 7.66 (d, J = 7.2 Hz, 2H), 7.57 (d, J = 6.0 Hz, 2H), 7.52−7.48 (m, 3H), 7.42−7.38 (m, 2H), 6.91 (s, 2H), 3.83 (s, 6H), 3.72 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.6, 189.7, 179.3, 153.3, 139.7, 138.2, 134.2, 132.3, 130.9, 129.6, 129.0, 128.9, 128.2, 105.7, 103.4, 88.7, 60.5, 56.4, 40.5, 40.3. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{26}H_{24}NO_6^+$: 446.1598; found: 446.1587.

*4-Benzoyl-2-(4-fluorophenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3l**).* Yield 87%; 324.8 mg; white solid; mp 215−217 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H), 7.63−7.53 (m, 8H), 7.49−7.45 (m, 3H), 7.37−7.34 (m, 2H), 7.27−7.23 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.0, 189.2, 178.9, 162.1 (d, J = 243.0 Hz, $^1J_{CF}$), 151.1, 139.1, 134.3, 131.8 (d, J = 8.0 Hz, $^3J_{CF}$), 130.3, 129.1, 128.6, 128.3, 127.7, 115.2 (d, J = 22.0 Hz, $^2J_{CF}$), 112.0,

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104.9, 88.0, 51.1, 36.7, 33.0, 31.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ −114.04. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{23}H_{17}FNO_3^+$: 374.1187; found: 374.1192.

*4-Benzoyl-2-(4-bromophenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3m**).* Yield 83%; 360.5 mg; white solid; mp 232−234 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.74−7.68 (m, 7H), 7.60−7.56 (m, 3H), 7.52−7.48 (m, 3H), 7.41−7.38 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.0, 189.3, 179.2, 139.2, 137.6, 132.0, 131.9, 131.4, 130.3, 129.2, 128.7, 128.4, 127.9, 127.8, 121.8, 105.1, 88.1. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{23}H_{17}BrNO_3^+$: 434.0386; found: 434.0383.

*4-Benzoyl-2-(4-chlorophenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3n**).* Yield 85%; 331.4 mg; white solid; mp 243−245 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 7.67−7.62 (m, 5H), 7.60−7.56 (m, 3H), 7.52−7.47 (m, 5H), 7.39−7.35 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.9, 189.2, 179.1, 139.1, 137.1, 133.1, 132.0, 131.9, 130.3, 129.2, 128.7, 128.45, 128.41, 127.8, 127.5, 105.0, 88.0. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{23}H_{17}ClNO_3^+$: 390.0891; found: 390.0897.

*4-Benzoyl-2-(3-chlorophenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3o**).* Yield 81%; 315.8 mg; white solid; mp 189−191 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 7.72−7.62 (m, 6H), 7.57 (d, J = 6.8 Hz, 1H), 7.51−7.48 (m, 6H), 7.40−7.36 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.8, 189.2, 179.3, 140.6, 139.1, 133.2, 132.1, 131.9, 130.4, 130.2, 129.2, 128.7, 128.4, 127.8, 125.7, 124.1, 112.1, 105.1, 87.8. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{23}H_{17}ClNO_3^+$: 390.0891; found: 390.0895.

*4-Benzoyl-2-(3-bromophenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3p**).* Yield 87%; 377.8 mg; white solid; mp 117−119 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 7.68 (s, 1H), 7.65 (s, 1H), 7.61−7.52 (m, 6H), 7.46−7.43 (m, 4H), 7.38−7.31 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.7, 189.2, 179.2, 140.7, 139.0, 132.1, 131.9, 131.3, 130.7, 130.2, 129.1, 128.6, 128.5, 128.4, 127.8, 124.5, 121.7, 105.0, 87.7. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{23}H_{17}BrNO_3^+$: 434.0386; found: 434.0376.

*4-Benzoyl-2-(2-bromophenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3q**).* Yield 81%; 351.8 mg; white solid; mp 248−250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (d, J = 10.0 Hz, 1H), 8.11−8.07 (m, 1H), 7.80−7.71 (m, 3H), 7.64 (d, J = 7.6 Hz, 1H), 7.55−7.43 (m, 7H), 7.40−7.32 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.8, 188.9, 179.6, 139.4, 137.4, 133.7, 131.7, 131.6, 130.9, 130.6, 130.5, 129.3, 128.4, 128.3, 127.6, 127.3, 120.4, 108.1, 86.5. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{23}H_{17}BrNO_3^+$: 434.0386; found: 434.0385.

*4-Benzoyl-2-(3,4-dichlorophenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3r**).* Yield 85%; 360.6 mg; white solid; mp 94−96 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 7.78 (s, 1H), 7.74−7.69 (m, 2H), 7.65−7.61(m, 4H), 7.57 (d, J = 7.2 Hz, 1H), 7.50−7.47 (m, 4H), 7.38−7.35 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.4, 189.2, 179.4, 139.1, 139.0, 132.1, 132.0, 131.2, 130.8, 130.1, 129.1, 128.7, 128.4, 127.8, 125.9, 105.1, 87.4. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{23}H_{16}Cl_2NO_3^+$: 424.0502; found: 424.0509.

*4-Benzoyl-2-(2,4-dichlorophenyl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3s**).* Yield 80%; 339.4 mg; white solid; mp 150−152 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (d, J = 4.8 Hz, 1H), 8.41−8.38 (m, 1H), 8.05−7.97 (m, 2H), 7.80−7.73 (m, 2H), 7.64−7.47 (m, 7H), 7.40−7.36 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 196.0, 189.3, 178.5, 139.3, 133.9, 133.8, 131.9, 130.5, 129.7, 129.2, 128.8, 128.6, 128.4, 127.8, 126.1, 125.7, 125.0, 105.8, 88.4. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{23}H_{16}Cl_2NO_3^+$: 424.0502; found: 424.0503.

*4-Benzoyl-2-hydroxy-5-phenyl-2-(4-(trifluoromethoxy)phenyl)-1,2-dihydro-3H-pyrrol-3-one (**3t**).* Yield 80%; 351.5 mg; white solid; mp 97−99 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 7.80−7.75 (m, 5H), 7.71 (d, J = 7.2 Hz, 2H), 7.58 (d, J = 7.2 Hz, 1H), 7.53−7.49 (m, 5H), 7.42−7.38 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.1, 189.4, 179.3, 148.6, 139.3, 137.7, 132.1, 132.0, 130.4, 129.3, 128.8, 128.5, 127.9, 121.1, 120.3 (q, J = 255.0 Hz, $^1J_{CF}$), 105.3, 88.1. ^{19}F NMR (376 MHz, DMSO-d_6) δ −56.80. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{24}H_{17}F_3NO_4^+$: 440.1104; found: 440.1102.

*4-Benzoyl-2-hydroxy-2-(4-(methylthio)phenyl)-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3u**).* Yield 82%; 329.2 mg; yellow solid; mp 195−197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 7.62−7.54 (m, 6H), 7.49−7.45 (m, 3H), 7.37−7.30 (m, 1H), 2.48 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.2, 189.2, 178.9, 139.2, 138.4, 134.6, 131.9, 131.8, 130.3, 129.1, 128.6, 128.3, 127.7, 126.1, 125.7, 105.0, 88.2, 14.7. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{24}H_{20}NO_3S^+$: 402.1158; found: 402.1164.

*2-([1,1′-Biphenyl]-4-yl)-4-benzoyl-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3v**).* Yield 83%; 358.1 mg; white solid; mp 227−229 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.71−7.64 (m, 8H), 7.60−7.56 (m, 2H), 7.52−7.47 (m, 5H), 7.39−7.36 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.2, 189.2, 179.0, 140.2, 139.7, 139.2, 137.3, 131.9, 131.8, 130.4, 129.1, 129.0, 128.8, 128.6, 128.4, 127.8, 127.6, 126.7, 126.2, 105.1, 88.4. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{29}H_{22}NO_3^+$: 432.1594; found: 432.1598.

*4-Benzoyl-2-hydroxy-2-(naphthalen-1-yl)-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3w**).* Yield 81%; 328.4 mg; white soild; mp 224−226 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.05 (s, 1H), 7.98 (s, 1H), 7.76 (d, J = 7.6 Hz, 2H), 7.55−7.47 (m, 10H), 7.42−7.38 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.4, 189.0, 179.5, 139.3, 138.1, 132.0, 131.9, 131.8, 130.6, 130.1, 129.80, 129.75, 129.2, 128.4, 127.8, 107.7, 85.4. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{27}H_{20}NO_3^+$: 406.1438; found: 406.1438.

*4-Benzoyl-2-hydroxy-2-(naphthalen-2-yl)-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3x**).* Yield 80%; 324.4 mg; pink soild; mp 220−222 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.17 (s, 1H), 8.04−7.93 (m, 3H), 7.68 (d, J = 3.2 Hz, 6H), 7.61−7.46 (m, 6H), 7.38−7.35 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.3, 189.3, 179.1, 139.2, 135.6, 132.8, 132.7, 131.9, 131.8, 130.4, 129.2, 128.7, 128.4, 128.3, 128.1, 127.8, 127.5, 126.4, 124.6, 123.4, 105.2, 88.6. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{27}H_{20}NO_3^+$: 406.1438; found: 406.1440.

*4-Benzoyl-2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-hydroxy-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**3y**).* Yield 82%; 339.0 mg; white soild; mp 108−110 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 7.61−7.54 (m, 5H), 7.48−7.45 (m, 3H), 7.38−7.34 (m, 3H), 6.99−6.94 (m, 2H), 6.88 (d, J = 8.8 Hz, 1H), 4.24 (s, 4H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 195.2, 189.2, 178.7, 143.5, 143.1, 139.2, 131.9, 131.8, 131.1, 130.3, 129.1, 128.6, 128.4, 127.7, 118.2, 116.9, 114.6, 104.9, 88.1, 64.1, 55.0. HRMS (ESI-TOF): m/z [M + Na]$^+$ calcd for $C_{25}H_{19}NO_5Na^+$: 436.1155; found: 436.1157.

*4-(4-Benzoyl-2-hydroxy-3-oxo-5-phenyl-2,3-dihydro-1H-pyrrol-2-yl)benzonitrile (**3z**).* Yield 82%; 311.9 mg; yellow soild; mp 252−254 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.79 (s, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.64−7.56 (m, 5H), 7.50−7.46 (m, 3H), 7.38−7.34 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.5, 189.2, 179.5, 143.3, 139.0, 132.5, 132.1, 132.0, 130.1, 129.1, 128.7, 128.4, 127.8, 126.6, 118.7, 111.2, 105.0, 88.0. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{24}H_{17}N_2O_3^+$: 381.1234; found: 381.1240.

*4-Benzoyl-2-hydroxy-2-(3-nitrophenyl)-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**4a**).* Yield 82%; 328.3 mg; white solid; mp 186−188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.40 (d, J = 1.6 Hz, 1H), 8.28−8.26 (m, 1H), 7.97−7.91 (m, 2H), 7.78−7.73 (m, 1H), 7.67−7.57 (m, 5H), 7.53−7.47 (m, 3H), 7.39−7.35 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.5, 189.2, 179.5, 147.9, 140.3, 139.0, 132.2, 132.0, 130.3, 130.1, 129.1, 128.7, 128.5, 127.8, 123.4, 120.6, 105.2, 87.6. HRMS (ESI-TOF): m/z [M + H]$^+$ calcd for $C_{23}H_{17}N_2O_5^+$: 401.1132; found: 401.1130.

*Methyl-4-(4-benzoyl-2-hydroxy-3-oxo-5-phenyl-2,3-dihydro-1H-pyrrol-2-yl)benzoate (**4b**).* Yield 84%; 347.3 mg; white solid; mp 114−116 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 6.8 Hz, 3H), 7.66−7.63 (m, 4H), 7.58 (s, 1H), 7.51−7.48 (m, 3H), 7.38−7.35 (m, 2H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.8, 189.2, 179.3, 166.0, 143.2, 139.1, 132.1, 131.9, 130.2, 129.6, 129.4, 129.2, 128.7, 128.4,

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127.8, 126.0, 105.0, 88.3, 52.3. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{25}H_{20}NO_5^+$: 414.1336; found: 414.1341.

*4-Benzoyl-2-hydroxy-2-(4-nitrophenyl)-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**4c**).* Yield 82%; 328.3 mg; yellow solid; mp 132−134 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 8.30 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.8 Hz, 3H), 7.63−7.56 (m, 5H), 7.50 (d, J = 6.4 Hz, 3H), 7.37 (d, J = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.4, 189.1, 179.4, 147.5, 145.2, 138.9, 132.1, 131.9, 130.1, 129.1, 128.6, 128.4, 127.8, 127.0, 123.7, 105.1, 88.0. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{23}H_{17}N_2O_5^+$: 401.1132; found: 401.1139.

*4-Benzoyl-2-hydroxy-2-(4-(methylsulfonyl)phenyl)-5-phenyl-1,2-dihydro-3H-pyrrol-3-one (**4d**).* Yield 80%; 346.8 mg; white solid; mp 130−132 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.80−7.76 (m, 3H), 7.64−7.56 (m, 5H), 7.50−7.47 (m, 3H), 7.38−7.34 (m, 2H), 3.22 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 194.5, 189.1, 179.3, 143.6, 140.7, 139.0, 132.0, 131.9, 130.1, 129.1, 128.6, 128.4, 127.8, 127.2, 126.6, 105.1, 88.0, 43.5. HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{24}H_{20}NO_5S^+$: 434.1057; found: 434.1053.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01476.

Crystallographic data and copies of the ^{1}H, ^{13}C{^{1}H}, and ^{19}F NMR spectra are involved (PDF)

Accession Codes

CCDC 2088607 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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