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Synthesis of 1*H*-Pyrrol-3(2*H*)-ones *via* Three Component Reactions of 2,3-Diketo Esters, Amines, and Ketones

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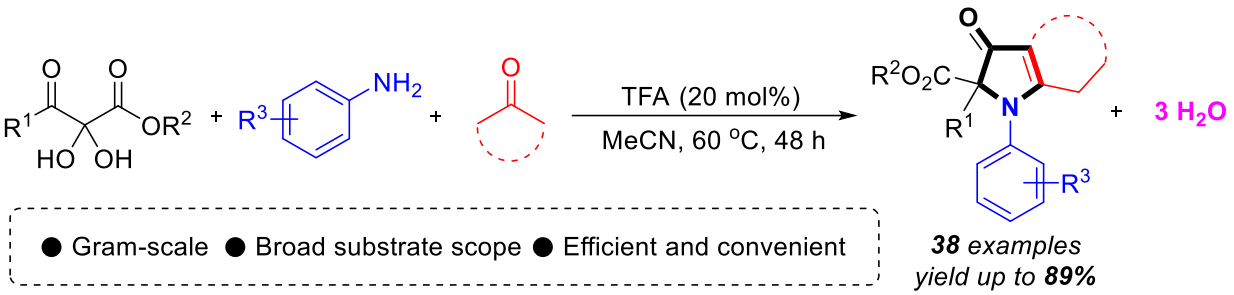


ABSTRCT: An efficient one-pot, three component reaction of 2,3-diketo esters with amines and ketones has been developed for the synthesis of 1*H*-pyrrol-3(2*H*)-ones. By using trifluoroacetic acid (TFA) as the additive and acetonitrile (MeCN) as the solvent, this convenient method provides a library of 1*H*-pyrrol-3(2*H*)-ones in moderate to good yields. The simple protocol features readily available starting materials, a straightforward process, good functional group tolerance, and broad substrate scope.

INTRODUCTION

1*H*-Pyrrol-3(2*H*)-one derivatives have received considerable attention because they widely exist in natural products and biologically active compounds.[1] Due to their importance, many efforts have been undertaken for their syntheses and modifications.[2] The main synthetic strategies occur by three routes: (1) dimerization of enamines (mediated by hypervalent iodine(III) regent,[3] TBHP/TBAI system;[4] catalyzed by *p*-TsOH,[5] $Cu(TFA)_2$[6]); (2) cyclization of corresponding open-chain precursors (catalyzed by gold,[7] platinum,[8] copper[9]; treated with I_2,[10] TEMPO,[11] thermal cyclization[12]); (3)

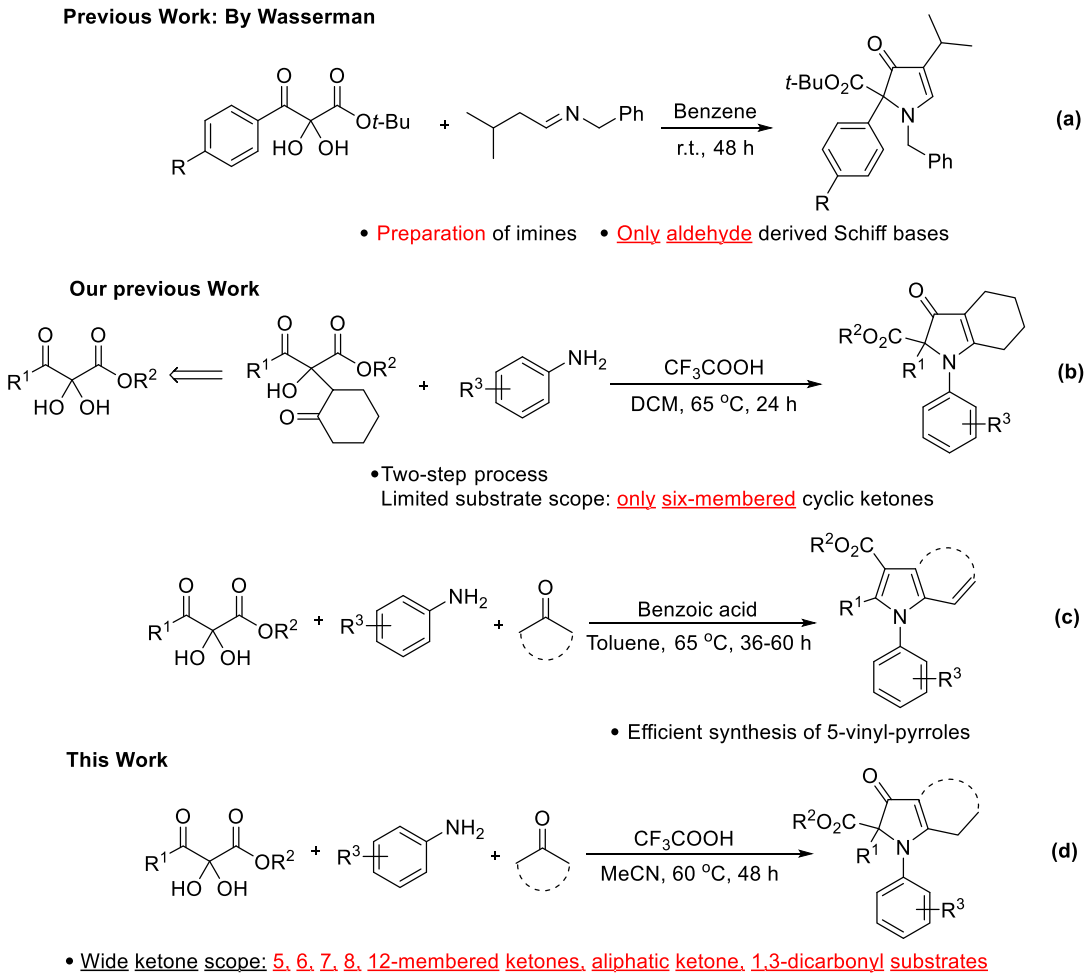
transformations based on indolin-3-ones or indoles including Michael addition reaction,[13] annulation reaction,[14] rearrangement reaction[15] and oxidation reaction[16]. Although considerable progress has been made in this field, the existing methods suffer from drawbacks such as narrow substrate scope and low availability of the starting materials. Thus developing a facile, simple and metal-free method to construct 1*H*-pyrrol-3(2*H*)-one derivatives with broad functional group tolerance starting from easily available starting materials is highly desirable.

Vicinal tricarbonyl compounds (VTCs) are important synthetic reagents because they are strongly electrophilic aggregates with several reactive sites. The pioneering work by Rubin, Wasserman and others demonstrated the wide applications of VTCs in the synthesis of natural products and synthetic intermediates especially various heterocycles.[17] Continuing investigations in recent years have developed new methods for VTC synthesis[18] and have explored their novel applications.[19]

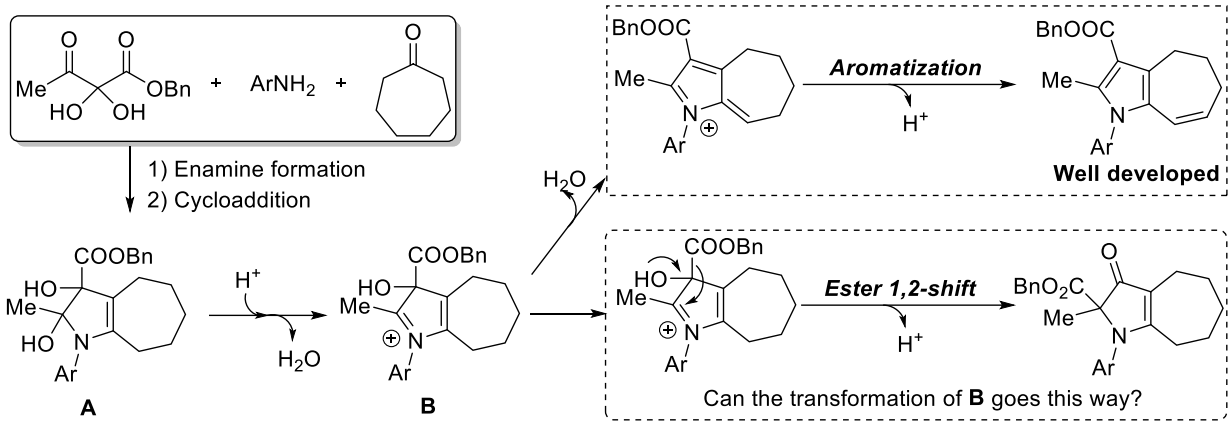
In 1991, Wasserman disclosed a novel transformation that occurs between 2,3-diketo esters with Schiff bases, affording 1*H*-pyrrol-3(2*H*)-one derivatives in moderate yields (Scheme 1, a).[20] However, only aldehyde-derived Schiff bases were involved, and the Schiff bases were prepared in advance. Despite its limitations, this strategy provides a promising way to synthesize 1*H*-pyrrol-3(2*H*)-ones. Inspired by this work, we reported a two-step reaction for asymmetric synthesis of 1*H*-pyrrol-3(2*H*)-ones from 2,3-diketo esters by combination of aldol condensation with subsequent benzilic acid rearrangement (Scheme 1, b).[19d] However, due to the narrow substrate scope determined for the aldol condensation, only six-membered cyclic ketones could be effectively used. In order to improve the universality and efficiency of this reaction, we searched for a suitable and general one-pot, one-step reaction system to synthesize 1*H*-pyrrol-3(2*H*)-ones starting from 2,3-diketo esters, amines and the general class of ketones.

We have also reported a metal-free aldol/cyclization/aromatization cascade reaction of 2,3-diketo esters with anilines and cyclic ketones from which a variety of 5-vinyl-pyrrole and 4-hydroxy-indole

derivatives could be easily accessed (Scheme 1, c).[21] In the mechanism for this reaction (Scheme 2) acid promoted loss of water and aromatization produces the pyrrole products. We speculated that the key intermediate **B** has the potential to circumvent dehydration and undergo the benzylic rearrangement that was not realized in the reactions promoted by benzoic acid in toluene. Herein we report a simple and general method to synthesize 1*H*-pyrrol-3(2*H*)-ones from 2,3-diketo esters, ketones and anilines in one pot.



Scheme 1. General routes toward 1*H*-pyrrol-3(2*H*)-ones or 5-vinyl-pyrroles from 2,3-diketo esters.



Scheme 2. Mechanism of the 5-vinyl-pyrrole formation and our assumption.

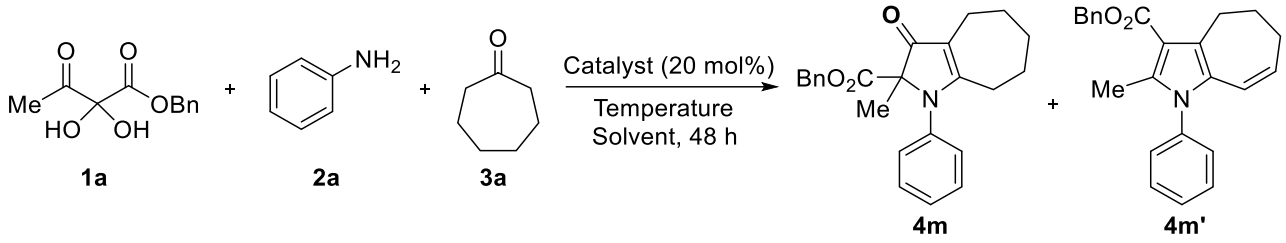
RESULTS AND DISCUSSION

At the outset, we chose benzyl 2,2-dihydroxy-3-oxobutanoate (**1a**),[22] aniline (**2a**), and cycloheptanone (**3a**) as the model substrates to explore reaction conditions favourable to 1*H*-pyrrol-3(2*H*)-one formation. Reaction occurs smoothly at 60 ºC without catalyst by using toluene as the solvent, but 1*H*-pyrrol-3(2*H*)-one **4m** was obtained in 33% yield along with pyrrole **4m'** in 30% yield (Table 1, entry 1). To improve the yield of **4m**, the reaction was performed in a spectrum of solvents of different polarity, including THF, MeOH, DCE, $CHCl_3$, MeCN and DCM (Table 1, entries 2-7). The results reveal that polar solvents increase the relative yield of **4m** and that MeCN privides the highest yield, giving **4m** and **4m'** in 76% and 14% yield, respectively (Table 1, entry 6). Two additives were then tested of which TFA at 20 mol% produced **4m** with near exclusivity (Table 1, entries 8-9) in 89% yield (Table 1, entry 9). The reaction also occurred with TFA catalysis at a lower temperature or under solvent-free conditions, but the yield of **4m** decreased dramatically (Table 1, entries 10-11).

When TFA was used as the additive, the ratio (**4m** and **4m'**) and the yield of **4m** increased dramatically. This suggested further investigations to evaluate additives with different acidities. Acids with a range of acidities were used (pKa order: Phenol > Benzoic acid > TFA > CH_3SO_3H > HCl (conc.) > CF_3SO_3H), and the results are shown in Table 2. After the analysis of Table 1 and Table 2, we can conclude that the highest yields of 1*H*-pyrrol-3(2*H*)-one are obtained in polar media

at moderate temperature using relatively strong acids as catalysts.

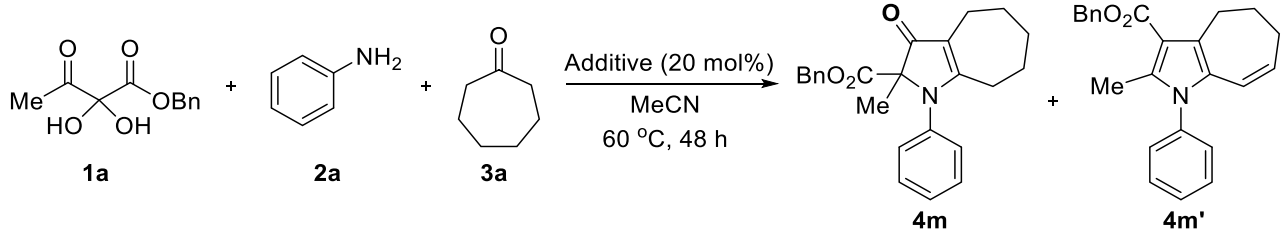
Table 1. Optimization of the reaction conditions. [a]



Entry	Solvent	Additive	Temperature	Yield (%)[b]	
				4m	**4m'**
1	Toluene	---	60 °C	33	30
2	THF	---	60 °C	24	22
3	MeOH	---	60 °C	54	6
4	DCE	---	60 °C	66	20
5	$CHCl_3$	---	60 °C	50	31
6	MeCN	---	60 °C	76	14
7	DCM	---	60 °C	23	35
8	MeCN	$Zn(OTf)_2$	60 °C	75	<5
9	**MeCN**	**TFA[c]**	**60 °C**	**89**	**trace**
10	MeCN	TFA[d]	25 °C	51	18
11	---	TFA	60 °C	57	30

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.22 mmol), **3a** (0.40 mmol), additive (0.040 mmol), solvent (2.0 mL), at indicated temperature for 48 h. [b] Isolated yield. [c] TFA refers to trifluoroacetic acid. [e] 72 h.

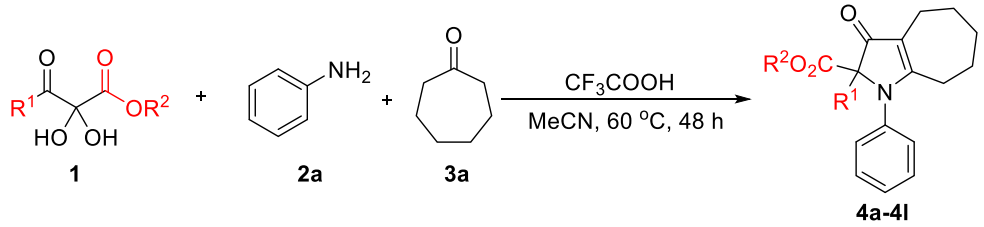
Table 2. Evaluation of acid additives.[a]



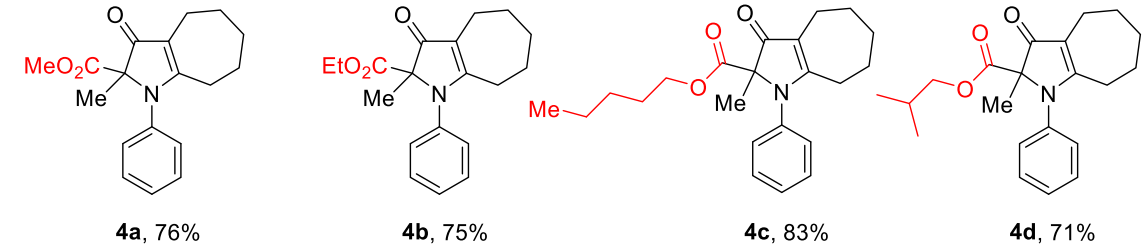
Entry	Additive	Ratio (**4m**:**4m'**)[b]	Yield of **4m**[c]
1	Phenol	16:1	72%
2	Benzoic acid	9:1	75%
3	TFA	>50:1	89%
4	CH_3SO_3H	49:1	85%
5	HCl (conc.)	>50:1	86%
6	CF_3SO_3H	>50:1	87%

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.22 mmol), **3a** (0.40 mmol), additive (0.040 mmol), MeCN (2.0 mL), at 60 °C for 48 h; [b] The ratio was determined by ^{1}H NMR; [c] Yields refer to isolated yields.

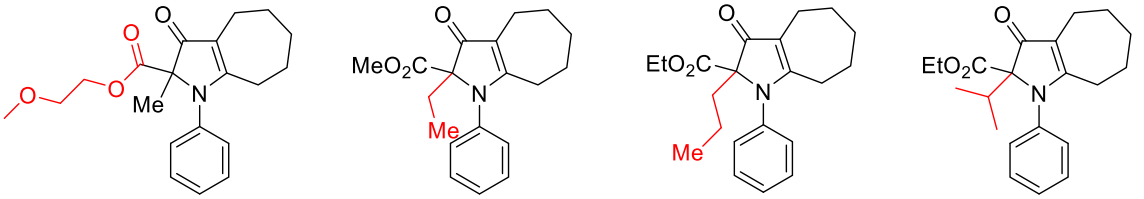
Scheme 3. Investigation of the substrate scope with 2,3-diketo esters.



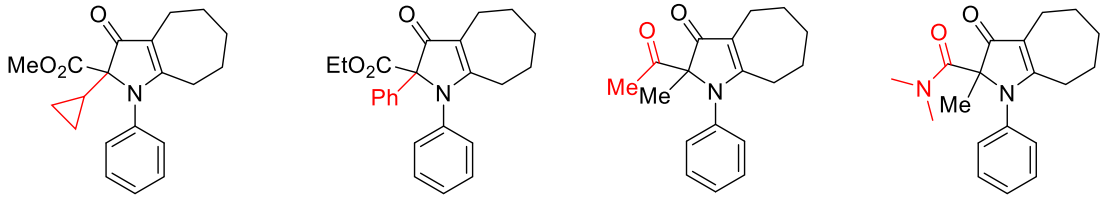
1 **2a** **3a** **4a-4l**



4a, 76% **4b**, 75% **4c**, 83% **4d**, 71%



4e, 60% **4f**, 85% **4g**, 83% **4h**, 67%



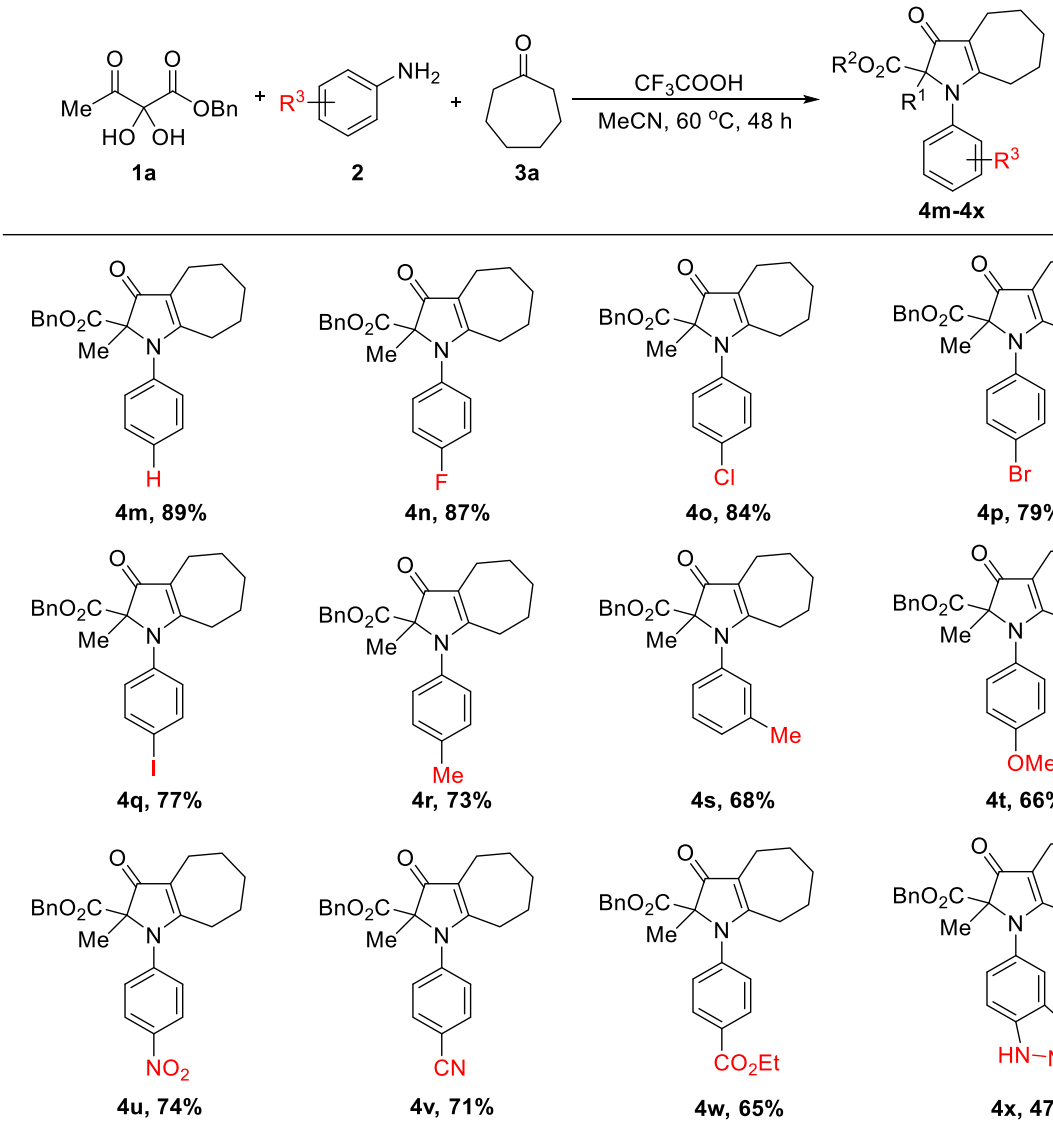
4i, 70% **4j**, 77% **4k**, 0% **4l**, 0%

[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.22 mmol), **3a** (0.40 mmol), TFA (0.040 mmol), at 60 ºC for 48 h; yields refer to isolated yields.

With the optimized reaction conditions in hand, we then investigated the scope of 2,3-diketo esters, amines and ketones for this process. 2,3-Diketo esters with different ester groups were examined first (Scheme 3, **4a**-**4e**) which gave the desired products in good yields ranging from 60% to 83%. Then various 2,3-diketo esters with different alkyl ketone chains were tested. As expected, those with ethyl or *n*-propyl groups gave **4f** and **4g** in good yields, while those with isopropyl, cyclopropyl, and phenyl substituents gave the products **4h**, **4i**, **4j** in somewhat lower yields, which can probably be ascribed to steric effects. The scope of vicinal tricarbonyl compounds was limited to 2,3-diketo esters; when pentane-2,3,4-trione and *N*,*N*-dimethyl-2,3-dioxobutanamide were used, no desired product was detected (**4k**, **4l**). This means the ketone group or amide group cannot undergo the rearrangement process similar as can the ester group.

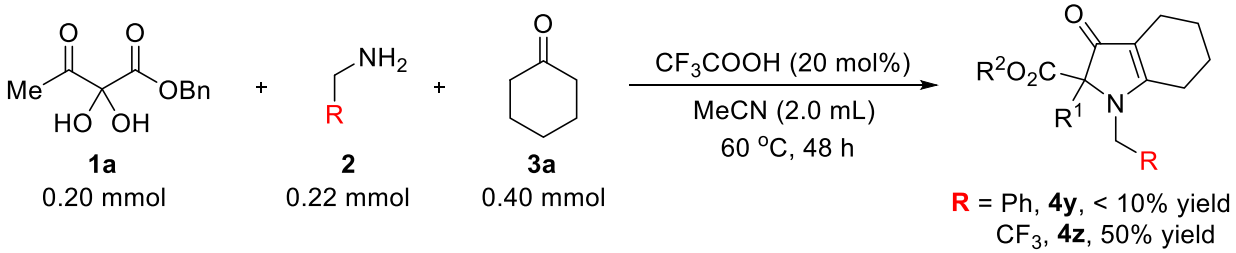
Aniline derivatives were then subjected to reactions with 2,2-dihydroxy-3-oxobutanoate and cycloheptanone (Scheme 4). Both electron-donating and electron-withdrawing groups on the phenyl ring gave the 1*H*-pyrrol-3(2*H*)-one products in similar yields. A series of substituents, including halide (**4n**-**4q**), methyl (**4r**, **4s**), methoxy (**4t**), nitro (**4u**), cyano (**4v**), and ethyl carboxylate group (**4w**), were all tolerated thus providing broad space for further modifications or late-stage synthesis. 1*H*-Indazol-5-amine also participated in the reaction and gave **4x** in 47% yield. Two aliphatic amines were tested (Scheme 5), the reaction of benzylamine was messy but the desired product **4y** can be detected by LC-MS (< 10% yield, see SI). 2,2,2-Trifluoroethan-1-amine gave **4z** in 50% yield.

Scheme 4. Investigation on the scope of aromatic amines. [a]



[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.22 mmol), **3a** (0.40 mmol), TFA (0.040 mmol), MeCN (2.0 mL), at 60 °C for 48 h; yields refer to isolated yields.

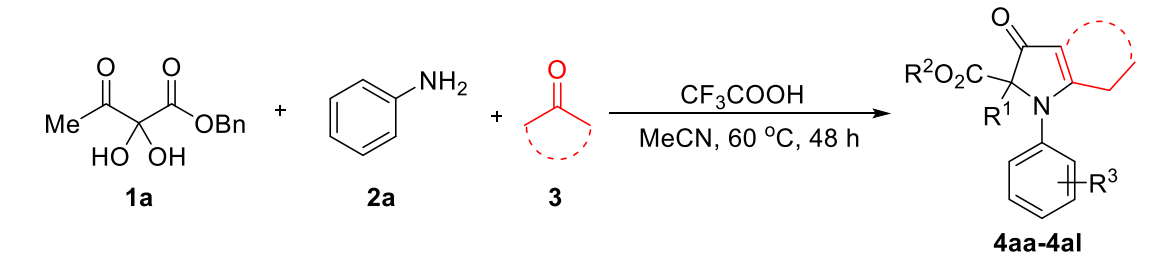
Scheme 5. Investigation on the reaction of aliphatic amines.

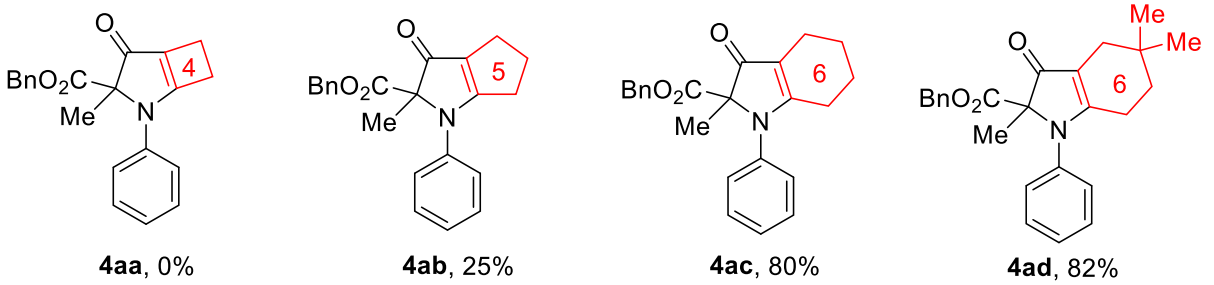


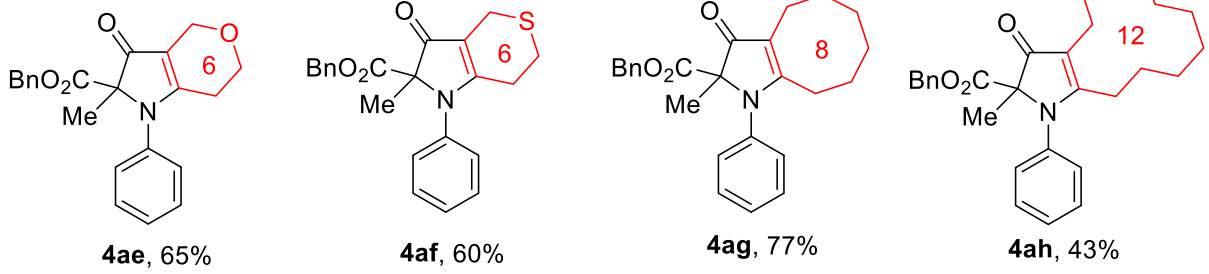
We were also attentive to structural variation of ketones since the scope of this modification greatly determines the utility of this three-component transformation (Scheme 6). Cyclobutanone did not give the desired product **4aa** probably due to ring tension in the four-membered ring which made the cyclization reaction too difficult. However, cyclopentanone did successfully participate in the

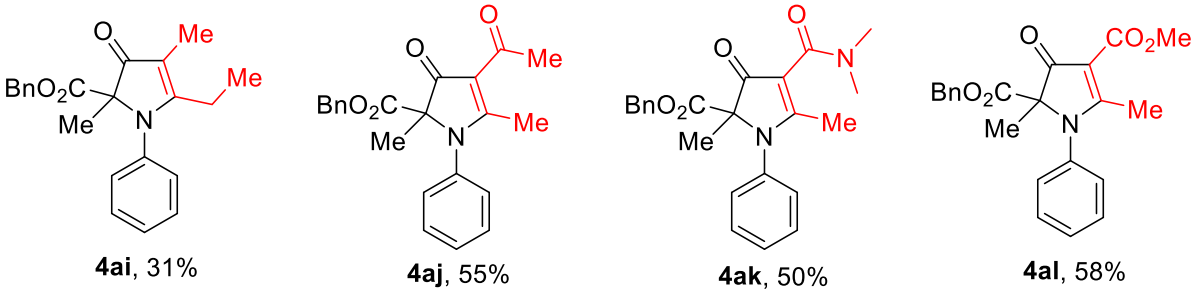
reaction, although the yield of its product (**4ab**) was only 25%. Several six-membered cyclic ketones, including aliphatic and heterocyclic substrates, were favored in this transformation, which give corresponding 1*H*-pyrrol-3(2*H*)-one products in good yields (**4ac**-**4af**). Medium ring and macrocyclic ketones, exemplified by cyclooctanone and cyclododecanone, gave the corresponding products in 77% and 43% yields, respectively (**4ag**, **4ah**). In order to further demonstrate the wide substrate scope of ketones, 3-pentanone, a representative non-cyclic ketone, gave product **4ai** in 31% yield. Acetylacetone, *N*,*N*-dimethylacetoacetamide and methyl acetoacetate also afford 1*H*-pyrrol-3(2*H*)-one products in moderate yields (**4aj**-**4al**) (un-optimized). These results suggest an extremely broad scope for this transformation.

Scheme 6. Investigation on the scope of ketones. [a]





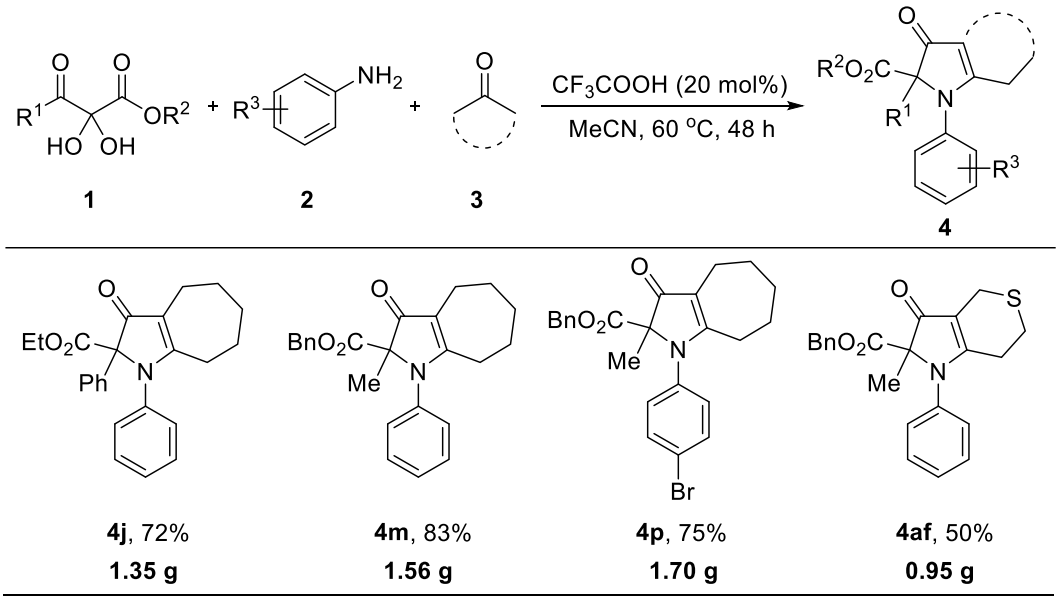




[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.22 mmol), **3** (0.40 mmol), TFA (0.040 mmol), MeCN (2.0 mL), at 60 °C for 48 h; yields refer to isolated yields.

Finally, we carried out gram-scale synthesis in order to further demonstrate that this method is practically useful (Scheme 7). When performed on a 5 mmol scale, no obvious drop of the yield was observed. Representative 2,3-diktoesters, one each with an aliphatic and aromatic ketone chain, gave reacting with aniline and cycloheptanone to give products **4j** and **4m**, respectively, in 80% and 83% yields. *p*-Bromoaniline was then used, and gave **4p** in 75% yield. Tetrahydro-4*H*-thiopyran-4-one was also tested, and **4af** was obtained in moderate yield.

Scheme 7. Gram-scale synthesis. [a]



[a] Reaction conditions: **1** (5.0 mmol), **2a** (5.5 mmol), **3** (10.0 mmol), TFA (1.0 mmol), MeCN (30 mL), at 60 °C for 48 h; yields refer to isolated yields.

In order to look into the detail of reaction pathway, we tried to use LC-MS to detect possible reaction intermediates. Fortunately, although the key intermediate, diol **A** (Scheme 2), was formed in low concentration during the reaction, they were successfully detected (for details, see SI). The above investigations suggest that the three component reactions of 2,3-diketo esters, amines and ketones probably occur through the way that depicted in Scheme 2.

■ CONCLUSION

In conclusion, we have demonstrated that 2,3-diketo esters react with anilines and ketones in a one-pot process to afford 1*H*-pyrrol-3(2*H*)-one derivatives in good yields. This method can be easily scaled up and uses readily available starting materials. Its substrate scope allows easy access to a broad diversity of novel 1*H*-pyrrol-3(2*H*)-one derivatives.

■ EXPERIMENTAL SECTION

General Materials and Methods. Solvents and reagents (AR grade) were used without purification unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker-DMX 400 spectrometer. Chemical shifts are reported in ppm with the solvent signals as reference, and coupling constants (*J*) are given in Hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; ddd, doublet of doublet of doublets and brs, broad single. High resolution mass spectroscopic data of the products were collected on a Waters Micromass GCT instrument using EI (70 eV) or an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS using ESI. Melting points were obtained uncorrected from an Electrothermo Buchi M-560 device.

General procedure for the synthesis of 2,3-diketo esters.

1. Preparation of *α*-Diazo-*β*-keto esters:[23] A solution of *β*-keto ester (10 mmol, 1.0 equiv.) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (2.8 g, 12 mmol, 1.2 equiv.) in 75 mL of CH_3CN was added triethylamine (2.1 mL, 1.5 mmol, 1.5 equiv.) at 0 °C, and the resulting solution was stirred at room temperature for 8 hours during which time the corresponding sulfonamide precipitated as a white solid. The white precipitate was filtered, and the resulting solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2), eluting with petroleum and ethyl acetate to provide *α*-diazo-*β*-keto ester.

2. General Procedure for the Synthesis of 2,3-Diketo esters:[19f] A solution of *α*-diazo-*β*-keto esters (5.0 mmol, 1.0 equiv.) in 20 mL of solvent [CH_3CN:H_2O (9:1)] at 0 °C was added *tert*-butyl hypochlorite (0.61 mL, 5.5 mmol) dropwise over 30 min *via* syringe pump. The reaction was stirred for an additional 30 min at room temperature and then concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2), eluting with petroleum and ethyl acetate to provide 2,3-diketo esters as their monohydrates.

General procedure for the synthesis of 1*H*-pyrrol-3(2*H*)-ones.

A Schlenk tube with a magnetic stir bar charged with 2,3-diketo esters **1** (0.20 mmol), amines **2** (0.22 mmol, 1.1 equiv.), ketones **3** (0.40 mmol, 2.0 equiv.), trifluoroacetic acid (0.04 mmol, 0.2 equiv.), and 2 mL acetonitrile. The reaction mixture was then heated to 60 °C and stirred for 48 hours. The reaction mixture was then allowed to cool to ambient temperature and all of the volatiles were removed under vacuum, the crude product was purified on flash chromatography, eluding with petroleum/ethyl acetate, to provide 1*H*-pyrrol-3(2*H*)-ones.

General procedures for gram-scale reactions.

A Schlenk tube with a magnetic stir bar charged with 2,3-diketo esters **1** (5.0 mmol), amines **2** (5.5 mmol, 1.1 equiv.), ketones **3** (10.0 mmol, 2.0 equiv.), trifluoroacetic acid (1.0 mmol, 0.2 equiv.), and 30 mL acetonitrile. The reaction mixture was then heated to 60 °C and stirred for 48 hours. The reaction mixture was then allowed to cool to ambient temperature and all of the volatiles were removed under vacuum, the crude product was purified on flash chromatography, eluding with petroleum/ethyl acetate, to provide 1*H*-pyrrol-3(2*H*)-ones.

Methyl-methyl-3-oxo-1-phenyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4a)

45.4 mg (Brown solid, 76% yield); m.p. = 92.8-94.8 °C; TLC R_f = 0.45 (PE/EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H), 7.36-7.32 (m, 1H), 7.08-7.06 (m, 2H), 3.73 (s, 3H), 2.54-2.51 (m, 2H), 2.44-2.40 (m, 2H), 1.86-1.78 (m, 2H), 1.77-1.72 (m, 1H), 1.69-1.61 (m, 2H),

1.59-1.53 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3 , 179.8, 168.3, 137.7, 129.4, 128.2, 127.7, 112.6, 75.2, 53.0, 31.9, 29.8, 27.8, 26.0, 21.7, 19.4; HRMS (ESI−TOF) *m/z*: $[M+Na]^+$ Calcd for -$C_{18}H_{21}NO_3Na$ 322.1414; Found 322.1414.

Ethyl 2-methyl-3-oxo-1-phenyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4b)

47.0 mg (Orange liquid, 75% yield); TLC R_f = 0.27 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.38 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 4.16 (q, *J* = 7.0 Hz, 2H), 2.56-2.45 (m, 2H), 2.43-2.39 (m, 2H), 1.83-1.79 (m, 2H), 1.69-1.64 (m, 2H), 1.58-1.57 (m, 2H), 1.48 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 179.6, 167.7, 137.7, 129.4, 128.0, 127.5, 112.7, 75.2, 61.9, 31.9, 29.7, 27.8, 26.0, 21.7, 19.6, 19.2, 14.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{23}NO_3Na$ 336.1570; Found 336.1571.

Pentyl 2-methyl-3-oxo-1-phenyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4c) 59.0 mg (Yellow liquid, 83% yield); TLC R_f = 0.35 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (m, 2H), 7.33-7.29 (m, 1H), 7.06 (d, *J* = 7.3 Hz, 2H), 4.17-4.06 (m, 2H), 2.5-2.52 (m, 2H), 2.47 (ddd, *J* = 15.2 Hz, 7.4 Hz, 4.0 Hz, 1H), 1.86-1.79 (m, 2H), 1.69-1.59 (m, 6H), 1.48 (s, 3H), 1.31-1.27 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 179.5, 167.8, 137.8, 129.4, 128.0, 127.4, 112.8, 75.2, 66.0, 32.0, 29.7, 28.1, 27.9, 27.8, 26.0, 22.2, 21.7, 19.1, 14.0; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{29}NO_3Na$ 378.2040; Found 378.2040.

Isobutyl 2-methyl-3-oxo-1-phenyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2- carboxylate (4d) 48.5 mg (Orange liquid, 71% yield); TLC R_f = 0.38 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.40-7.36 (m, 2H), 7.33-7.29 (m, 1H), 7.05 (d, *J* = 7.4 Hz, 2H), 3.97 (dd, *J* = 10.5 Hz, 6.6 Hz, 1H), 3.84 (dd, *J* = 10.5 Hz, 6.6 Hz, 1H), 2.55-2.52 (m, 2H), 2.49 (ddd, *J* = 15.2 Hz, 9.0 Hz, 2.6 Hz, 1H), 2.34 (ddd, *J* = 15.2 Hz, 9.0 Hz, 2.6 Hz, 1H), 1.96-1.77 (m, 3H), 1.69-1.53 (m, 4H), 1.46 (s, 3H), 0.91 (d, *J* = 4.3 Hz, 3H), 0.90 (d, *J* = 4.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 179.5, 167.8, 137.7, 129.4, 127.9, 127.4, 112.9, 75.2, 71.7, 32.0, 29.7, 27.8, 26.1, 21.7, 19.0, 19.0, 18.9; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{27}NO_3Na$ 364.1883; Found 364.1883.

2-Methoxyethyl 2-methyl-3-oxo-1-phenyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4e) 41.2 mg (Orange liquid, 60% yield); TLC R_f = 0.30 (PE/EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.34-7.29 (m, 1H), 7.13 (d, *J* = 7.3 Hz, 2H), 4.33-4.30 (m, 1H), 4.22-4.17 (m, 1H), 3.61-3.53 (m, 2H), 3.36 (s, 3H), 2.53-2.49 (m, 2H), 2.46-2.38 (m, 2H), 1.84-1.79 (m, 2H), 1.69-1.65 (m, 2H), 1.61-1.55 (m, 2H), 1.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 179.9, 167.7, 137.6, 129.4, 128.3, 127.7, 112.4, 75.2, 70.2, 64.8, 58.9, 31.9, 29.7, 27.8, 25.9, 21.7, 19.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{25}NO_4Na$ 366.1676; Found 366.1676.

Methyl 2-ethyl-3-oxo-1-phenyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4f) 53.2 mg (Yellow solid, 85% yield); m.p. = 92.7-94.8 °C; TLC R_f = 0.27 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (m, 2H), 7.33-7.29 (m, 1H), 7.07 (d, *J* = 7.4 Hz, 2H), 3.67 (s, 3H), 2.62-2.60 (m, 2H), 2.50 (ddd, *J* = 15.3 Hz, 8.2 Hz, 2.2 Hz, 1H), 2.44-2.34 (m, 2H), 2.01-1.94 (m, 1H), 1.92-1.85 (m, 1H), 1.81-1.73 (m, 2H), 1.69-1.57 (m, 2H), 1.52-1.44 (m, 1H), 0.78 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 181.0, 167.9, 137.7, 129.3, 127.4, 127.2, 114.9, 79.3, 52.7, 32.0, 29.7, 27.9, 26.4, 25.1, 21.7, 6.8; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{23}NO_3Na$ 336.1570; Found 336.1572.

Ethyl 3-oxo-1-phenyl-2-propyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4g) 56.6 mg (Yellow solid, 83% yield); m.p. = 75.9-77.5 °C; TLC R_f = 0.36 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.29 (m, 2H), 7.32-7.29 (m, 1H), 7.06-7.04 (m, 2H), 4.11 (q, *J* = 11.6 Hz, 2H), 2.65-2.55 (m, 2H), 2.48-2.33 (m, 3H), 1.91-1.79 (m, 3H), 1.77-1.70 (m, 1H), 1.66-1.60 (m, 2H), 1.54-1.49 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4, 180.6, 167.3, 137.7, 129.3, 127.3, 127.0, 114.7, 79.0, 61.9, 34.0, 32.0, 29.7, 27.9, 26.4, 21.7, 15.6, 14.0; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{27}NO_3Na$ 364.1883; Found 364.1883.

Ethyl 2-isopropyl-3-oxo-1-phenyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2- carboxylate (4h) 45.7 mg (Yellow liquid, 67% yield); TLC R_f = 0.32 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H), 7.34-7.30 (m, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 4.24-4.16 (m 2H), 2.82-2.75 (m, 1H), 2.53-2.51 (m, 2H), 2.48-2.35 (m, 2H), 1.86-1.78 (m, 2H), 1.75-1.58 (m, 3H), 1.54-1.46 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 167.3, 139.0, 129.2, 128.4, 127.4, 114.0, 82.0, 61.8, 32.7, 32.0, 29.6, 28.0, 26.2, 21.6, 17.5, 15.6, 14.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{27}NO_3Na$ 364.1883; Found 364.1884.

Methyl 2-cyclopropyl-3-oxo-1-phenyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4i) 45.4 mg (Yellow solid, 70% yield); m.p. = 101.6-103.3 °C; TLC R_f = 0.27 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.33 (m, 3H), 7.16-7.14 (m, 2H), 3.78 (m, 3H), 2.56-2.48 (m, 2H), 2.40 (ddd, *J* = 15.5 Hz, 8.1 Hz, 2.4 Hz, 1H), 2.30 (ddd, *J* = 15.5 Hz, 8.1 Hz, 2.4 Hz, 1H), 1.88-1.82 (m, 1H), 1.79-1.71 (m, 2H), 1.68-1.59 (m, 2H), 1.47-1.39 (m, 2H), 1.18-1.11 (m, 1H), 0.67-0.59 (m, 1H), 0.34-0.26 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 180.5, 168.5, 138.1, 129.3, 128.6, 127.7, 113.5, 77.3, 53.0, 31.9, 29.9, 27.9, 26.1, 21.6, 13.9, 1.9, 0.5; HRMS

(ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{23}NO_3Na$ 348.1570; Found 348.1571.

Ethyl 3-oxo-1,2-diphenyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4j) 57.8 mg (Yellow liquid, 77% yield); TLC R_f = 0.32 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.28 (m, 5H), 7.25-7.20 (m, 3H), 6.92-6.90 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.69-2.55 (m, 2H), 2.52-2.41 (m, 2H), 1.85-1.82 (m, 2H), 1.79-1.74 (m, 1H), 1.70-1.63 (m, 2H), 1.61-1.51 (m, 1H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 180.5, 166.6, 138.2, 135.3, 128.8, 128.5, 128.3, 127.9, 127.1, 113.6, 82.4, 62.2, 32.0, 30.1, 27.9, 26.2, 21.9, 14.0; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{25}NO_3Na$ 398.1727; Found 398.1729.

Benzyl 2-methyl-3-oxo-1-phenyl-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4m)

66.8 mg (Yellow solid, 89% yield); m.p. = 82.8-84.2 °C; TLC R_f = 0.27 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 8H), 6.92-6.90 (m, 2H), 5.21 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 2.51-2.44 (m, 3H), 2.38 (ddd, *J* = 15.3 Hz, 7.6 Hz, 3.9 Hz, 1H), 1.85-1.77 (m, 2H), 1.66-1.55 (m, 4H), 1.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 179.7, 167.6, 137.5, 135.4, 129.3, 128.5, 128.3, 128.1, 128.0, 127.5, 112.8, 75.1, 67.4, 31.9, 29.7, 27.8, 26.0, 21.7, 19.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{25}NO_3Na$ 398.1727; Found 398.1726.

Benzyl 1-(4-fluorophenyl)-2-methyl-3-oxo-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4n) 68.4 mg (Yellow solid, 87% yield); m.p. = 74.6-76.3 °C; TLC R_f = 0.59 (PE/EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 6.97-6.93 (m, 2H), 6.90-6.88 (m, 2H), 5.22 (d, *J* = 12.3 Hz, 1H), 5.09 (d, *J* = 12.3 Hz, 1H), 2.49-2.33 (m, 4H), 1.83-1.77 (m, 2H), 1.64-1.55 (m, 4H), 1.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 179.5, 167.3, 161.6 (d, *J* =

249.4 Hz), 135.3, 133.4 (d, J = 3.2 Hz), 130.2 (d, J = 8.7 Hz), 128.6, 128.4, 128.3, 116.3 (d, J = 22.7 Hz), 112.6, 75.1, 67.4, 31.8, 29.5, 27.7, 25.9, 21.7, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{24}NO_3FNa$ 416.1632; Found 416.1631.

Benzyl 1-(4-chlorophenyl)-2-methyl-3-oxo-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4o) 68.7 mg (Yellow liquid, 84% yield); TLC R_f = 0.33 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.34 (m, 3H), 7.31-7.29 (m, 2H), 7.22 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 2.49-2.42 (m, 3H), 2.40-2.33 (m, 1H), 1.85-1.77 (m, 2H), 1.65-1.56 (m, 4H), 1.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 179.2, 167.3, 136.1, 135.3, 133.2, 129.5, 129.3, 128.6, 128.4, 128.3, 113.4, 75.0, 67.5, 31.8, 29.6, 27.6, 25.9, 21.7, 19.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{24}NO_3ClNa$ 432.1337; Found 432.1335.

Benzyl 1-(4-bromophenyl)-2-methyl-3-oxo-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4p) 71.6 mg (Brown liquid, 79% yield); TLC R_f = 0.33 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.34 (m, 5H), 7.30-7.27 (m, 2H), 6.76 (d, J = 8.7 Hz, 2H), 5.21 (d, J = 12.3 Hz, 1H), 5.07 (d, J = 12.3 Hz, 1H), 2.48-2.42 (m, 3H), 2.39-2.33 (m, 1H), 1.83-1.78 (m, 2H), 1.65-1.55 (m, 4H), 1.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 179.2, 167.3, 136.6, 135.2, 132.5, 129.5. 128.6, 128.4, 128.3, 121.1, 113.5, 75.0, 67.5, 31.8, 29.7, 27.6, 25.9, 21.7, 19.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{24}NO_3BrNa$ 476.0832; Found 476.0832.

Benzyl 1-(4-iodophenyl)-2-methyl-3-oxo-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4q) 77.2 mg (Yellow liquid, 77% yield); TLC R_f = 0.37 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.6 Hz, 2H), 7.36-7.34 (m, 3H), 7.30-7.27 (m, 2H), 6.63 (d, J = 8.6 Hz, 2H), 5.21 (d, J = 12.3 Hz, 1H), 5.08 (d, J = 12.3 Hz, 1H), 2.49-2.42 (m, 3H), 2.40-2.33 (m, 1H),

1.85-1.75 (m, 2H), 1.65-1.56 (m, 4H), 1.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 179.1, 167.3, 138.5, 137.4, 135.3, 129.7, 128.6, 128.4, 128.3, 113.6, 92.4, 75.0, 67.5, 31.8, 29.7, 27.6, 25.9, 21.7, 19.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{24}NO_3INa$ 524.0693; Found 524.0692.

Benzyl 2-methyl-3-oxo-1-(*p*-tolyl)-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2- carboxylate (4r) 56.8 mg (Brown liquid, 73% yield); TLC R_f = 0.30 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 7.08 (d, *J* = 8.2 Hz, 2H), 5.21 (d, *J* = 12.4 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 2.50-2.44 (m, 3H), 2.41-2.37 (m, 1H), 2.35 (s, 3H), 1.85-1.77 (m, 2H), 1.64-1.57 (m, 4H), 0.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 179.9, 167.6, 137.6, 135.4, 134.7, 129.9, 128.5, 128.2, 128.1, 128.0, 112.2, 75.1, 67.3, 31.9, 29.6, 27.8, 25.9, 21.7, 21.1, 19.0; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{27}NO_3Na$ 412.1883; Found 412.1883.

Benzyl 2-methyl-3-oxo-1-(*m*-tolyl)-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2- carboxylate (4s) 52.9 mg (Yellow solid, 68% yield); m.p. = 93.3-94.8 °C; TLC R_f = 0.33 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.34 (m, 5H), 7.18-7.14 (m, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.71-6.70 (m, 2H), 5.23 (d, *J* = 12.4 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 2.51-2.45 (m, 3H), 2.41-2.35 (m, 1H), 2.24 (s, 3H), 1.86-1.78 (m, 2H), 1.66-1.59 (m, 4H), 1.49 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 179.8, 167.6, 139.4, 137.4, 135.4, 129.0, 128.5, 128.5, 128.3, 128.2, 125.0, 112.6, 75.1, 67.4, 31.9, 29.7, 27.8, 26.0, 21.8, 21.3, 19.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{27}NO_3Na$ 412.1883; Found 412.1883.

Benzyl 1-(4-methoxyphenyl)-2-methyl-3-oxo-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4t) 53.5 mg (Yellow liquid, 66% yield); TLC R_f = 0.48 (PE/EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 5.20 (d, *J*

= 12.4 Hz, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 3.79 (s, 3H), 2.49-2.32 (m, 4H), 1.85-1.73 (m, 2H), 1.63-1.56 (m, 4H), 1.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 180.1, 167.5, 158.9, 135.4, 129.8, 129.8, 128.5, 128.3, 128.2, 114.4, 111.7, 75.2, 67.3, 55.5, 31.9, 29.5, 27.9, 25.9, 21.7, 19.0; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{27}NO_4Na$ 428.1832; Found 428.1834.

Benzyl 2-methyl-1-(4-nitrophenyl)-3-oxo-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4u) 62.2 mg (Yellow liquid, 74% yield); TLC R_f = 0.31 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.0 Hz, 2H), 7.34-7.32 (m, 3H), 7.28-7.25 (m, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 5.24 (d, *J* = 12.2 Hz, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 2.62 (t, *J* = 5.6 Hz, 2H), 2.48 (ddd, *J* = 15.4 Hz, 7.0 Hz, 4.1 Hz, 1H), 2.39 (ddd, *J* = 15.4 Hz, 7.0 Hz, 4.1 Hz, 1H), 1.91-1.82 (m, 2H), 1.72-1.65 (m, 2H), 1.62-1.57 (m, 2H), 1.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.0, 177.7, 167.0, 145.1, 143.8, 135.0, 128.6, 128.6, 128.5, 126.1, 124.8, 117.0, 75.0, 67.8, 31.7, 30.1, 27.1, 26.1, 21.8, 19.6; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{24}H_{24}N_2O_5Na$ 443.1577; Found 443.1577.

Benzyl 1-(4-cyanophenyl)-2-methyl-3-oxo-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4v) 56.8 mg (Yellow liquid, 71% yield); TLC R_f = 0.57 (PE/EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.6 Hz, 2H), 7.36-7.33 (m, 3H), 7.28-7.26 (m, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.22 (d, *J* = 12.2 Hz, 1H), 5.07 (d, *J* = 12.2 Hz, 1H), 2.57 (t, *J* = 5.6 Hz, 2H), 2.47 (ddd, *J* = 15.4 Hz, 7.0 Hz, 3.8 Hz, 1H), 2.37 (ddd, *J* = 15.4 Hz, 7.0 Hz, 3.8 Hz, 1H), 1.87-1.80 (m, 2H), 1.70-1.63 (m, 2H), 1.61-1.56 (m, 2H), 1.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 178.1, 167.1, 142.0, 135.0, 133.2, 128.6, 128.6, 128.4, 126.9, 118.2, 116.2, 109.8, 74.9, 67.8, 31.8, 30.0, 27.2, 26.0, 21.7, 19.5; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{24}N_2O_3Na$ 423.1679; Found 423.1679.

Benzyl 1-(4-(ethoxycarbonyl)phenyl)-2-methyl-3-oxo-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4w) 58.1 mg (Yellow liquid, 65% yield); TLC R_f = 0.31 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.6 Hz, 2H), 7.35-7.28 (m 5H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.20 (d, *J* = 12.3 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.56 (t, *J* = 5.6 Hz, 2H), 2.47 (ddd, *J* = 15.4 Hz, 7.1 Hz, 3.6 Hz, 1H), 2.38 (ddd, *J* = 15.4 Hz, 7.1 Hz, 3.6 Hz, 1H), 1.84-1.79 (m, 2H), 1.69-1.56 (m, 4H), 1.50 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 178.8, 167.3, 165.7, 141.8, 35., 130.7, 128.6, 128.6, 128.4, 128.2, 126.5, 114.9, 75.0, 67.6, 61.2, 31.9, 29.9, 27.4, 26.0, 21.8, 19.3, 14.4; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{27}H_{29}NO_5Na$ 470.1938; Found 470.1938.

Benzyl 1-(1*H*-indazol-5-yl)-2-methyl-3-oxo-1,2,3,4,5,6,7,8-octahydrocyclohepta[*b*]pyrrole-2-carboxylate (4x) 39.0 mg (Yellow solid, 47% yield); TLC R_f = 0.25 (PE/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (brs, 1H), 7.97 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.33-7.30 (m, 6H), 6.95 (d, *J* = 8.8 Hz, 1H), 5.26 (d, *J* = 12.2 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 2.52-2.40 (m, 4H), 1.82-1.81 (m, 2H), 1.64-1.57 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 180.8, 167.6, 139.1, 135.4, 134.8, 130.3, 128.6, 128.4, 127.5, 123.4, 121.0, 112.0, 110.9, 75.6, 67.5, 31.9, 29.6, 27.9, 25.9, 21.7, 19.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{25}N_3O_3Na$ 438.1788; Found 438.1789.

Benzyl 2-methyl-3-oxo-1-(2,2,2-trifluoroethyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carboxylate (4z)

36.8 mg (Yellow liquid, 50% yield); TLC R_f = 0.42 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (m, 5H), 5.17 (q, *J* = 12.5 Hz, 2H), 3.99-3.88 (m, 1H), 3.67-3.57 (m, 1H), 2.48 (t, *J* = 5.8

Hz, 2H), 2.23 (t, *J* = 5.7 Hz, 2H), 1.88-1.78 (m, 2H), 1.73-1.61 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 175.5, 167.2, 135.3, 128.6, 128.3, 127.7, 123.6 (q, *J* = 281.0 Hz), 108.7, 74.8, 67.8, 45.8 (q, *J* = 35.5 Hz), 24.2, 22.0, 21.6, 18.9, 18.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.95; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{20}NO_3F_3Na$ 390.1293; Found 390.1296.

Benzyl 2-methyl-3-oxo-1-phenyl-1,2,3,4,5,6-hexahydrocyclopenta[*b*]pyrrole-2-carboxylate (4ab)

17.4 mg (Brown liquid, 25% yield); TLC R_f = 0.52 (PE/EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.33 (m, 4H), 7.31-7.24 (m, 3H), 7.18-7.15 (m, 1H), 6.91-6.89 (m, 2H), 5.26 (d, *J* = 12.4 Hz, 1H), 5.18 (d, *J* = 12.4 Hz, 1H), 2.92-2.72 (m, 2H), 2.60-2.50 (m, 2H), 2.47-2.39 (m, 2H), 1.67 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.0, 185.3, 167.5, 138.0, 135.3, 129.5, 128.5, 128.3, 128.2, 125.5, 122.4, 116.6, 82.2, 67.7, 28.8, 27.6, 22.2, 19.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{21}NO_3Na$ 370.1414; Found 370.1415.

Benzyl 2-methyl-3-oxo-1-phenyl-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carboxylate (4ac)[19d] 57.8 mg (Yellow liquid, 80% yield); TLC R_f = 0.27 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 9H), 7.00-6.98 (m, 2H), 5.22 (d, *J* = 12.4 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 2.37-2.27 (m, 4H), 1.79-1.67 (m, 4H), 1.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6, 175.2, 167.6, 137.1, 135.4, 129.3, 128.2, 128.1, 128.0, 127.6, 107.5, 75.0, 67.4, 25.5, 22.2, 22.1, 19.0, 19.0.

Benzyl 2,5,5-trimethyl-3-oxo-1-phenyl-2,3,4,5,6,7-hexahydro-1*H*-indole-2-carboxylate (4ad)

63.8 mg (Yellow solid, 82% yield); m..p. = 60.2-62.0 °C; TLC R_f = 0.35 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 8H), 7.00-6.97 (m, 2H), 5.20 (d, *J* = 12.4 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 2.34-2.31 (m, 2H), 2.17 (d, *J* = 15.7 Hz, 1H), 2.09 (d, *J* = 15.7 Hz, 1H), 1.56 (s, 3H),

1.53 (t, *J* = 6.5 Hz, 2H), 1.02 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 174.3, 167.6, 137.3, 135.3, 129.4, 128.5, 128.3, 128.2, 128.1, 127.6, 107.3, 75.5, 67.4, 35.0, 32.8, 29.5, 28.0, 27.6, 22.7, 18.9; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{27}NO_3Na$ 412.1883; Found 412.1885.

Benzyl 2-methyl-3-oxo-1-phenyl-1,2,3,4,6,7-hexahydropyrano[4,3-*b*]pyrrole-2-carboxylate (4ae) 47.2 mg (Yellow liquid, 65% yield); TLC R_f = 0.32 (PE/EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 8H), 7.00-6.98 (m, 2H), 5.25 (d, *J* = 12.3 Hz, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 4.52 (s, 2H), 3.96-3.90 (m, 1H), 3.83-3.77 (m, 1H), 2.53 (dt, *J* = 17.9 Hz, 6.0 Hz, 1H), 2.45 (dt, *J* = 17.9 Hz, 6.0 Hz, 1H), 1.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7, 171.9, 167.1, 136.4, 135.2, 129.5, 126, 128.4, 128.3, 127.9, 127.6, 105.4, 75.4, 67.7, 63.2, 62.5, 261, 18.8; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{21}NO_4Na$ 386.1363; Found 386.1362.

Benzyl 2-methyl-3-oxo-1-phenyl-1,2,3,4,6,7-hexahydrothiopyrano[4,3-*b*]pyrrole-2- carboxylate (4af)[19d] 45.5 mg (Orange liquid, 60% yield); TLC R_f = 0.27 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 8H), 7.00 (dd, *J* = 7.9 Hz, 1.6 Hz, 2H), 5.25 (d, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 3.52 (d, *J* = 15.6 Hz, 1H), 3.41 (d, *J* = 15.6 Hz, 1H), 2.89-2.72 (m, 2H), 2.58 (t, *J* = 5.7 Hz, 2H), 1.56 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 173.7, 167.1, 136.4, 135.2, 129.6, 128.6, 128.6, 128.4, 128.3, 128.3, 104.4, 74.3, 67.6, 27.6, 24.8, 21.2, 18.9.

Benzyl 2-methyl-3-oxo-1-phenyl-2,3,4,5,6,7,8,9-octahydro-1*H*-cycloocta[*b*]pyrrole-2-carboxylate (4ag) 59.9 mg (Orange liquid, 77% yield); TLC R_f = 0.27 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.26 (m, 8H), 6.97 (dd, *J* = 7.9 Hz, 1.5 Hz, 2H), 5.24 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H), 2.59-2.48 (m, 2H), 2.48-2.39 (m, 1H), 2.29-2.18 (m, 1H), 1.70-1.46 (m,

10H), 1.42-1.33 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 177.5, 167.6, 137.2, 135.2, 129.4, 129.2, 128.6, 128.5, 128.4, 128.1, 110.2, 74.8, 67.52, 29.82, 28.1, 26.2, 25.3, 25.2, 20.8, 18.7; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{25}H_{27}NO_3Na$ 412.1883; Found 412.1884.

Benzyl 2-methyl-3-oxo-1-phenyl-2,3,4,5,6,7,8,9,10,11,12,13-dodecahydro-1*H*-cyclododeca[*b*]pyrrole-2-carboxylate (4ah) 38.3 mg (Orange liquid, 43% yield); TLC R_f = 0.54 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (m, 1H), 7.36-7.30 (m, 7H), 7.02-6.91 (m, 2H), 5.23 (d, *J* = 12.2 Hz, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 2.67-2.55 (m, 1H), 2.44-2.31 (m, 2H), 2.27-2.18 (m, 1H), 1.77-1.70 (m, 1H), 1.65-1.48 (m, 2H), 1.40 (s, 3H), 1.39-1.12 (m, 13H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8, 176.9, 167.9, 138.2, 135.2, 129.4, 128.6, 128.5, 128.3, 127.6, 127.0, 111.0, 74.0, 67.5, 26.0, 25.9, 25.6, 24.2, 24.1, 23.7, 23.5, 23.2, 21.8, 20.2, 18.5; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{29}H_{35}NO_3Na$ 468.2509; Found 468.2512.

Benzyl 5-ethyl-2,4-dimethyl-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4ai) 21.6 mg (Orange liquid, 31% yield); TLC R_f = 0.27 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 8H), 6.97 (dd, *J* = 7.8 Hz, 1.7 Hz, 2H), 5.26 (d, *J* = 12.3 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H), 2.51-2.36 (m, 2H), 1.82 (s, 3H), 1.50 (s, 3H), 1.02 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1, 178.3, 167.6, 137.4, 135.4, 129.4, 128.9, 128.5, 128.3, 128.0, 104.9, 74.6, 67.4, 20.4, 18.9, 11.7, 6.7; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{23}NO_3Na$ 372.1570; Found 372.1571.

Benzyl 4-acetyl-2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4aj) 39.9 mg (Orange liquid, 55% yield); TLC R_f = 0.23 (PE/EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.32 (m, 8H), 6.99 (d, *J* = 7.3 Hz, 2H), 5.31 (d, *J* = 12.2 Hz, 1H), 5.12 (d, *J* = 12.2 Hz, 1H),

2.51 (s, 3H), 2.45 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 192.9, 182.0, 165.7, 135.0, 134.8, 129.9, 129.7, 128.7, 128.6, 109.9, 76.9, 68.1, 30.2, 18.8, 16.7; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{21}NO_4Na$ 386.1363; Found 386.1363.

Benzyl 4-(dimethylcarbamoyl)-2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate (4ak) 39.2 mg (Yellow liquid, 50% yield); m.p. = 120.2-122.2 °C; TLC R_f = 0.26 (PE/EtOAc/MeOH = 15:15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.29 (m, 8H), 7.02 (d, *J* = 7.3 Hz, 2H), 5.19 (s, 2H), 3.01 (s, 3H), 2.95 (s, 3H), 2.24 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4, 179.5, 166.4, 165.0, 135.8, 134.8, 129.8, 129.2, 128.7, 128.7, 128.6, 106.7, 75.9, 67.9, 38.5, 35.2, 18.5, 15.3; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$Calcd for $C_{23}H_{24}N_2O_4Na$ 415.1628; Found 415.1628.

2-Benzyl 4-methyl 2,5-dimethyl-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrole-2,4-dicarboxylate (4al) 44.0 mg (Yellow liquid, 58% yield); TLC R_f = 0.31 (PE/EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.30 (m, 8H), 6.99 (d, *J* = 7.4 Hz, 2H), 5.32 (d, *J* = 12.1 Hz, 1H), 5.06 (d, *J* = 12.1 Hz, 1H), 3.86 (s, 3H), 2.44 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 182.0, 165.7, 164.7, 135.2, 134.8, 129.9, 129.6, 128.8, 128.7, 128.7, 128.7, 101.1, 76.7, 68.1, 51.2, 18.9, 16.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{22}H_{21}NO_5Na$ 402.1312; Found 402.1312.

■ ASSOCIATED CONTENT

Supproting Imformation

Proton, carbon, HRMS data and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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