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A facile reaction involving zwitterionic intermediates for the synthesis of 5-hydroxy-2*H*-pyrrol-2-one derivatives

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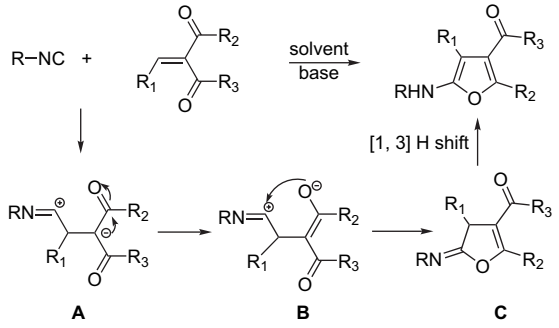
Abstract—The reaction of cyclohexyl isocyanide with various aldehydes and 1,3-dicarbonyl compounds catalyzed by piperidine is described. The protocol offers facile and efficient synthesis of 5-hydroxy-2*H*-pyrrol-2-one derivatives from readily available starting materials in high yields.

1. Introduction

The reaction of 1:1 zwitterionic species, generated in situ by the addition of different nucleophiles such as triphenylphosphine, pyridine, tertiary amines, and isocyanides to suitably activate π-systems has been investigated in detail.[1] These intermediates can be trapped by various substrates including aldehydes, 1,2-diones, *N*-tosylimines, and isocyanates.[2–5] The interception can either be a two-component or a multicomponent reaction.[6,7] This strategy has been successfully employed in the synthesis of various heterocyclic systems like aminofurans, pyrroles, iminolactones, and aminopyrans from readily available starting materials. Among them, the annulation reaction of isocyanides with dimethyl acetylenedicarboxylate (DMAD) has been well developed, but only a few reports on olefin-involved reactions exist in the literature. In the context of our recent observation that a facile reaction occurs between ammonium ylide and olefin in the presence of anhydrous K_2CO_3,[8] we planned to test a similar reaction between isocyanides and electron-deficient olefins for the construction of aminofuran derivatives via a zwitterion **A** mediated step, which was also based on the work of Yavari (Scheme 1).[9] In subsequent experiments, we found that the reaction was different from the report of Yavari and could not stop at the aminofuran formation step presumably due to the unstable character of the products. 5-Hydroxy-2*H*-pyrrol-2-one derivatives were finally formed just as the reaction reported by Quai and co-workers.[10] The results of our detailed investigations into this reaction are presented here.



Scheme 1.

2. Results and discussion

In order to increase the reactivity of the olefin, β-substituted olefin with two electron-withdrawing groups at the α-olefin carbon atom was used to test its reactivity. In an initial experiment, the reaction of cyclohexyl isocyanide **1** (Cy=cyclohexyl) with olefin **2a** in CH_2Cl_2 at reflux was first examined in the absence of any base or catalyst. Unfortunately, different from the former reaction reported by Yavari,[9] it did not yield any desired cyclization product even when we refluxed the reaction mixture for 12 h (Table 1, entry 1). Then, to elevate the reaction temperature, we used other high boiling point solvents such as toluene for this process. It was found that the reaction of cyclohexyl isocyanide **1** with olefin **2a** proceeded smoothly in toluene at 100 °C to afford 5-hydroxy-2*H*-pyrrol-2-one **3a** (not the desired 2-aminofuran derivative) in 57% yield (entry 3). The structure of **3a** was deduced from its IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic data. In addition, the NMR-based

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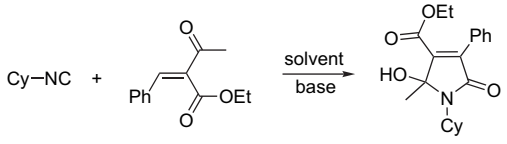
Table 1. Reaction of cyclohexyl isocyanide **1** with olefin **2a** under various conditions[a]



1 **2a** **3a**

Entry	Time/h	*T*/°C	Solvent	Base	Yield[b]/%
1	12	Reflux	CH_2Cl_2	—	0
2	12	rt	Toluene	—	0
3	36	100	Toluene	—	57
4	48	rt	Toluene	K_2CO_3	0
5	12	100	Toluene	K_2CO_3	59
6	12	rt	Toluene	Piperidine	0
7	12	100	Toluene	Piperidine	86
8	14	Reflux	CH_2Cl_2	Piperidine	Trace
9	24	100	Toluene	Pyridine	48
10	12	100	Toluene	Pyrrolidine	67

[a] All the reactions were carried out with 1.5 equiv of cyclohexyl isocyanide, 1.5 equiv of olefin **2a**, and 1.0 equiv of piperidine or 1.0 equiv of K_2CO_3.
[b] Isolated yields.

structure was further confirmed by its X-ray crystallographic analysis (Fig. 1).[11] Although a similar reaction was reported by Quai and co-workers, the reaction scope was very limited and the yield was very low (41–59%).[9] Considering that the process involved an enolization step, to facilitate the enolization we conducted the reaction in the presence of various bases with a view to increase the product yield and shorten the reaction time. Among the bases examined, piperidine was found to be the best (Table 1). The yield of the reaction increased from 57% to 86% by using piperidine as a base. At the same time, the reaction time was reduced markedly (from 36 to 12 h; entry 7). Some other weak bases were also tested, but the results were less efficient than that of piperidine. Thus, it is clear from the aforementioned experiments that the best yield of **3a** could be obtained by employing piperidine as a base and toluene as a solvent.

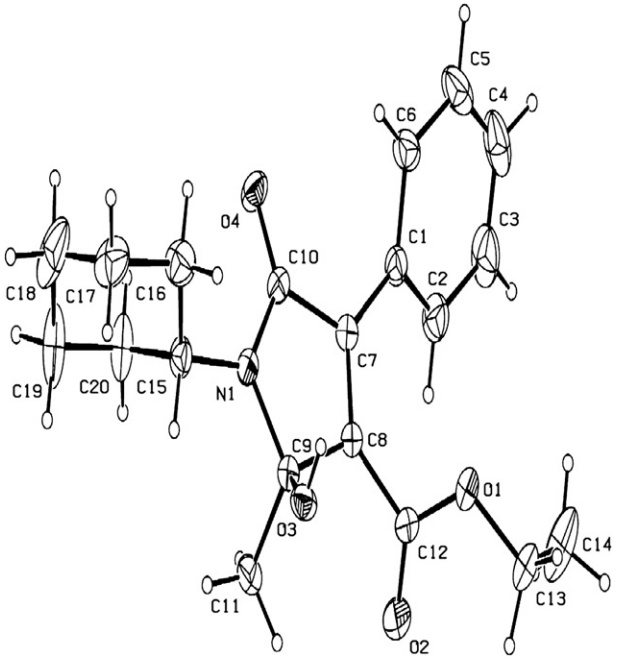
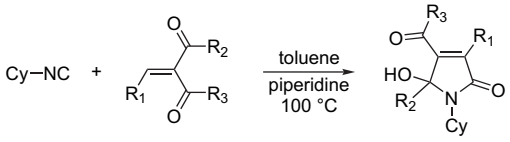


Figure 1. X-ray structure of **3a**.

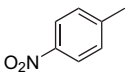
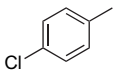
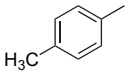
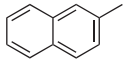
A number of β-substituted olefins with two electron-withdrawing groups at the α-olefin carbon atom were selected for the reaction under the optimized conditions and found to be efficient to afford 5-hydroxy-2*H*-pyrrol-2-one derivatives in excellent yields. The results are summarized in Table 2. It may be pointed out that olefins generated from aldehydes with electron-withdrawing substituent groups on the phenyl ring are more suitable for this reaction than those generated from aldehydes bearing electron-donating groups (Table 2, entry 5).

With these successful results in hand, we were encouraged to modify the reaction to make it more convenient and efficient. It was reported that the olefin **2** could be synthesized by the reaction of commercially available aldehydes with 1,3-dicarbonyl compounds in the presence of weak base, including amines such as pyridine, pyrrolidine, and piperidine or corresponding ammonium salts.[12,13] We surmised that a three-component reaction in one-pot might occur if cyclohexyl isocyanide, aldehyde, and 1,3-dicarbonyl compound are reacted together in the presence of piperidine. In subsequent investigations, we were pleased to find that aromatic aldehydes, regardless of electron-donating or electron-withdrawing substituents on the phenyl ring, participated in this process with high efficiency. 5-Hydroxy-2*H*-pyrrol-2-one derivatives **3** were obtained in good to excellent yields (Table 3, entries 1–14). It can be seen that electron-deficient aldehydes performed much better than their electron-rich counterparts. For example, the reaction of 4-methylbenzaldehyde and 3,4-(methylenedioxy)benzaldehyde gave lower

Table 2. Reaction of cyclohexyl isocyanide **1** with olefin **2** catalyzed by piperidine[a]

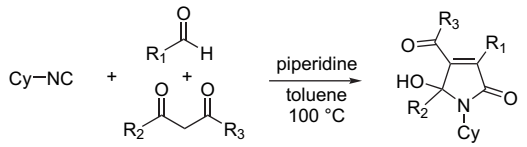


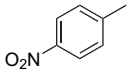
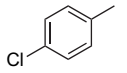
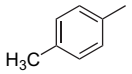
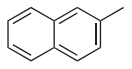
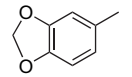
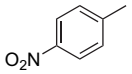
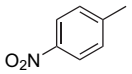
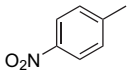
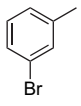
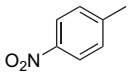
1 **2** **3**

Entry	R_1	R_2	R_3	Product	Yield[b]/%
1	Ph	CH_3	OEt	**3a**	86
2	Ph	CH_3	CH_3	**3b**	84
3		CH_3	CH_3	**3c**	90
4		CH_3	CH_3	**3d**	89
5		CH_3	CH_3	**3e**	63
6		CH_3	CH_3	**3f**	86

[a] All the reactions were carried out with 1.0 equiv of cyclohexyl isocyanide, 1.5 equiv of olefin **2**, and 1.0 equiv of piperidine at 100 °C for 12 h.
[b] Isolated yields.

Table 3. Three-component reaction of cyclohexyl isocyanide, aryl aldehydes, and 1,3-dicarbonyl compounds catalyzed by piperidine[a]



Entry	R_1	R_2	R_3	Product	Yield[b]/%
1	Ph	CH_3	OEt	**3a**	78
2	Ph	CH_3	CH_3	**3b**	74
3		CH_3	CH_3	**3c**	76
4		CH_3	CH_3	**3d**	74
5		CH_3	CH_3	**3e**	50
6		CH_3	CH_3	**3f**	74
7		CH_3	CH_3	**3g**	53
8		CH_3	OEt	**3h**	70
9		CH_3	OCH_3	**3i**	85
10		Ph	OEt	**3j**	81
11	Ph	CH_3	OCH_3	**3k**	86
12		CH_3	OEt	**3l**	77
13		CH_3	OEt	**3m**	72
14		Ph	Ph	**3n**	60
15	Ph	OEt	OEt	—	0
16	Ph	CN	OEt	—	0

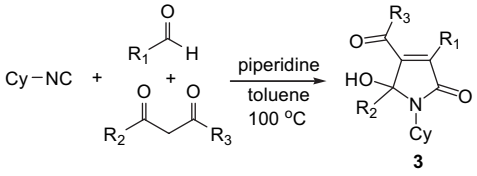
[a] All the reactions were carried out with 1.0 equiv of cyclohexyl isocyanide, 2.0 equiv of aryl aldehydes, 2.0 equiv of 1,3-dicarbonyl compounds, and 1.0 equiv of piperidine at 100 °C for 12 h.
[b] Isolated yields.

yields of the corresponding product than that of other aldehydes (entries 5 and 7). The position of the substituents on the aromatic ring has no significant effect on this transformation. Reactions of aromatic aldehydes such as 3-bromobenzaldehyde and the sterically congested 2-chlorobenzaldehyde could also provide the corresponding products in high yields (entries 12 and 13). Moreover, the equivalent of water simultaneously generated during the condensation reaction of aldehydes with 1,3-dicarbonyl compounds had no effect on the whole reaction process. The reaction was also tolerant to various 1,3-dicarbonyl compounds. A number of 1,3-diketones and β-ketoesters were tested in this reaction and the same good results were obtained (entries 1 and 8–14). Even for the sterically congested 1,3-diphenylpropane-1,3-dione, the corresponding product **3n** could be obtained in 60% yield (entry 14). Unfortunately, this reaction could not be used for malonates. When diethyl malonate or ethyl 2-cyanoacetate was employed, no cyclization product was detected (entries 15 and 16), presumably due to the difficulty in the enolization step of the carbonyl group during the reaction process.

To explore the scope of this reaction further, we extended it to aliphatic aldehydes also. The reaction was found to be general and efficient. In the reaction of cyclohexyl isocyanide, 1,3-dicarbonyl compounds with various aliphatic aldehydes, the corresponding 5-hydroxy-2*H*-pyrrol-2-one derivatives were obtained in excellent yields (Table 4, entries 2–6). Only for short chain aldehyde such as propionaldehyde, the yield is somewhat low (entry 1). It is worth noting that only a very few examples exist in the literature on 5-hydroxy-2*H*-pyrrol-2-one synthesis using aliphatic aldehydes as substrates.

The reaction mechanism for the formation of 5-hydroxy-2*H*-pyrrol-2-one **3** is considered analogous to the reported mechanism of Quai.[10]

Table 4. Three-component reaction of cyclohexyl isocyanide, aliphatic aldehydes, and 1,3-dicarbonyl compounds catalyzed by piperidine[a]



Entry	R_1	R_2	R_3	Product	Yield[b]/%
1	CH_3CH_2	CH_3	CH_3	**3o**	48
2	$(CH_3)_2CH$	CH_3	CH_3	**3p**	74
3	$CH_3CH_2CH_2$	CH_3	CH_3	**3q**	76
4	$CH_3(CH_2)_4CH_2$	CH_3	CH_3	**3r**	81
5	$(CH_3)_2CH$	CH_3	OEt	**3s**	84
6	$CH_3(CH_2)_4CH_2$	CH_3	OCH_3	**3t**	75

[a] All the reactions were carried out with 1.0 equiv of cyclohexyl isocyanide, 2.0 equiv of aliphatic aldehydes, 2.0 equiv of 1,3-dicarbonyl compounds, and 1.0 equiv of piperidine at 100 °C for 12 h.
[b] Isolated yields.

3. Conclusion

In summary, we have successfully developed a facile general method for the synthesis of 5-hydroxy-2*H*-pyrrol-2-one derivatives via weak base catalyzed multicomponent reactions. The process takes advantages including (1) the simultaneous formation of several bonds in only one operation step, (2)

simple and easily available starting materials, and (3) metal-free and mild conditions. It is conceivable that the efficient multicomponent reactions described herein will find application in the synthesis of heterocyclic compounds. Our further studies will focus on the development of related transformations and the application of this method to the preparation of 5-hydroxy-2*H*-pyrrol-2-one containing natural products.

4. Experimental

4.1. General

All reagents were used directly as obtained commercially unless otherwise noted. Melting points were determined on a microscopic apparatus and were uncorrected. Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ using TMS as internal standard on a Varian Mercury Plus 300BB MHz NMR spectrometer. Nicolet NEXUS 670 FTIR spectrometer was used for IR spectra. HRMS spectra were obtained with a Bruker APEX II instrument. Flash column chromatography was performed using 200–300 mesh silica gel and mixture of petroleum ether and ethyl acetate (v/v=10:1) was used for elution.

4.2. Typical procedure for the reaction of cyclohexyl isocyanide 1 with olefin 2 catalyzed by piperidine

A mixture of cyclohexyl isocyanide (0.5 mmol), olefin **2** (0.75 mmol), and piperidine (0.5 mmol) in 4 mL dry toluene was heated at 100 °C for 12 h. The solvent and most of the piperidine were evaporated under reduced pressure and the residue was purified by flash chromatography on silica column to give final products.

4.3. Typical procedure for the three-component reaction of cyclohexyl isocyanide, aryl aldehydes, and 1,3-dicarbonyl compounds catalyzed by piperidine

A mixture of cyclohexyl isocyanide (0.5 mmol), aryl aldehydes (1.0 mmol), 1,3-dicarbonyl compounds (1.0 mmol), and piperidine (0.5 mmol) in 4 mL dry toluene was heated at 100 °C for 12 h. The solvent and most of the piperidine were evaporated under reduced pressure and the residue was purified by flash chromatography on silica column to give final products.

4.4. Typical procedure for the three-component reaction of cyclohexyl isocyanide, aliphatic aldehydes, and 1,3-dicarbonyl compounds catalyzed by piperidine

To a mixture of 1,3-dicarbonyl compounds (1.0 mmol) and piperidine (0.5 mmol) in 3 mL dry toluene at −15 to −10 °C, a solution of aliphatic aldehydes (1.0 mmol) in 1 mL dry toluene was added slowly and the mixture was stirred at −10 °C for 12 h. Then, the resulting solution was allowed to warm to rt and a solution of cyclohexyl isocyanide (0.5 mmol) in 1 mL dry toluene was added. The reaction mixture was heated at 100 °C for 12 h. The solvent and most of the piperidine were evaporated under reduced pressure and the residue was purified by flash chromatography on silica column to give final products.

4.4.1. Ethyl 1-cyclohexyl-2-hydroxy-2-methyl-5-oxo-4-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (3a). White solid, mp 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.54–7.35 (m, 5H), 4.21 (q, J=6.9 Hz, 2H), 3.45–3.37 (m, 2H), 2.37–1.18 (m, 10H), 1.75 (s, 3H), 1.15 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.0, 164.0, 141.2, 141.0, 129.7, 129.3, 127.9, 127.6, 88.7, 61.4, 52.5, 30.0, 29.8, 26.2, 25.2, 23.6, 13.7. HRMS calcd for $C_{20}H_{25}NO_4$: (M+H) 344.1856, found: 344.1862. IR (KBr): 3325, 2936, 1680, 1644 cm^{-1}.

4.4.2. 4-Acetyl-1-cyclohexyl-5-hydroxy-5-methyl-3-phenyl-1*H*-pyrrol-2(5*H*)-one (3b). White solid, mp 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.46–7.43 (m, 5H), 3.78 (br, 1H), 3.44–3.36 (m, 1H), 2.35–1.20 (m, 10H), 2.10 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=199.7, 166.4, 147.9, 140.8, 129.7, 129.5, 128.3, 89.2, 52.4, 30.6, 29.8, 26.2, 25.1, 23.9. HRMS calcd for $C_{19}H_{23}NO_3$: (M+H) 314.1751, found: 314.1752. IR (KBr): 3267, 2937, 1668, 1641 cm^{-1}.

4.4.3. 4-Acetyl-1-cyclohexyl-5-hydroxy-5-methyl-3-(4-nitrophenyl)-1*H*-pyrrol-2(5*H*)-one (3c). Yellow solid, mp 195–197 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.30 (d, J=8.7 Hz, 2H), 7.64 (d, J=8.7 Hz, 2H), 3.54 (br, 1H), 3.46–3.37 (m, 1H), 2.33–1.20 (m, 10H), 2.15 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=198.7, 165.4, 150.3, 148.4, 137.6, 136.4, 130.6, 123.5, 89.5, 52.7, 30.9, 29.9, 26.2, 25.1, 23.7. HRMS calcd for $C_{19}H_{22}N_2O_5$: (M+H) 359.1601, found: 359.1606. IR (KBr): 3330, 2924, 1670, 1644 cm^{-1}.

4.4.4. 4-Acetyl-3-(4-chlorophenyl)-1-cyclohexyl-5-hydroxy-5-methyl-1*H*-pyrrol-2(5*H*)-one (3d). White solid, mp 180–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.39 (dd, J=9, 9 Hz, 4H), 3.78 (br, 1H), 3.39–3.34 (m, 1H), 2.32–1.23 (m, 10H), 2.12 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=199.8, 166.3, 148.8, 139.3, 136.4, 131.2, 129.0, 128.4, 89.5, 52.7, 31.0, 30.2, 26.5, 25.4, 24.1. HRMS calcd for $C_{19}H_{22}ClNO_3$: (M+H) 348.1361, found: 348.1361. IR (KBr): 3263, 2932, 1667, 1645 cm^{-1}.

4.4.5. 4-Acetyl-1-cyclohexyl-5-hydroxy-5-methyl-3-*p*-tolyl-1*H*-pyrrol-2(5*H*)-one (3e). White solid, mp 156 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.31 (d, J=8.4 Hz, 2H), 7.24 (d, J=8.1 Hz, 2H), 3.68–3.57 (br, 1H), 3.45–3.34 (m, 1H), 2.40–1.19 (m, 10H), 2.39 (s, 3H), 2.12 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=199.9, 166.6, 147.3, 141.0, 140.1, 129.6, 129.1, 126.8, 89.1, 52.4, 30.5, 29.9, 26.2, 25.2, 24.0, 21.4. HRMS calcd for $C_{20}H_{25}NO_3$: (M+H) 328.1907, found: 328.1910. IR (KBr): 3388, 2930, 1672, 1641 cm^{-1}.

4.4.6. 4-Acetyl-1-cyclohexyl-5-hydroxy-5-methyl-3-(naphthalen-2-yl)-1*H*-pyrrol-2(5*H*)-one (3f). Pale yellow solid, mp 162–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.99 (s, 1H), 7.88–7.44 (m, 6H), 3.86–3.79 (br, 1H), 3.46–3.38 (m, 1H), 2.37–1.20 (m, 10H), 2.08 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=199.9, 166.4, 148.5, 140.1, 133.5, 132.7, 129.7, 128.4, 128.0, 127.6,

127.1, 126.5, 126.4, 89.2, 52.3, 30.7, 29.8, 26.1, 25.1, 23.8. HRMS calcd for $C_{23}H_{25}NO_3$: (M+H) 364.1907, found: 364.1903. IR (KBr): 3271, 2929, 1668, 1644 cm^{-1}.

4.4.7. 4-Acetyl-3-(benzo[*d*][1,3]dioxol-5-yl)-1-cyclohexyl-5-hydroxy-5-methyl-1*H*-pyrrol-2(5*H*)-one (3g). Pale yellow solid, mp 151–152 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=7.0 (s, 1H), 6.88 (dd, J=8.1, 8.1 Hz, 2H), 6.02 (s, 2H), 3.51–3.35 (m, 2H), 2.37–1.20 (m, 10H), 2.17 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=199.8, 166.5, 149.2, 147.8, 124.4, 123.4, 109.9, 108.4, 101.5, 89.1, 52.5, 30.5, 29.9, 26.3, 25.2, 24.0. HRMS calcd for $C_{20}H_{23}NO_5$: (M+H) 358.1649, found: 358.1651. IR (KBr): 3433, 2936, 1686, 1652 cm^{-1}.

4.4.8. Ethyl 1-cyclohexyl-2-hydroxy-2-methyl-4-(4-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (3h). White solid, mp 161–163 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=8.23 (d, J=8.7 Hz, 2H), 7.67 (d, J=9.0 Hz, 2H), 4.24 (q, J=6.9 Hz, 2H), 3.47 (s, 1H), 3.44–3.38 (m, 1H), 2.34–1.24 (m, 10H), 1.79 (s, 3H), 1.18 (t, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=165.0, 162.9, 148.0, 143.4, 139.4, 136.0, 130.9, 122.7, 89.0, 61.9, 52.7, 29.9, 29.8, 26.2, 25.0, 23.6, 13.7. HRMS calcd for $C_{20}H_{24}N_2O_6$: (M+H) 389.1707, found: 389.1710. IR (KBr): 3290, 2933, 1679, 1654 cm^{-1}.

4.4.9. Methyl 1-cyclohexyl-2-hydroxy-2-methyl-4-(4-nitrophenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (3i). White solid, mp 172–174 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=8.24 (d, J=9.3 Hz, 2H), 7.66 (d, J=8.7 Hz, 2H), 3.77 (s, 3H), 3.47–3.39 (m, 1H), 3.31 (br, 1H), 2.34–1.20 (m, 10H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=164.9, 163.4, 148.0, 143.0, 139.8 135.9, 130.8, 122.8, 89.0, 52.7, 52.5, 29.9, 29.8, 26.2, 25.1, 23.6. HRMS calcd for $C_{19}H_{22}N_2O_6$: (M+H) 375.1551, found: 375.1554. IR (KBr): 3291, 2936, 1678, 1656 cm^{-1}.

4.4.10. Ethyl 1-cyclohexyl-2-hydroxy-4-(4-nitrophenyl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (3j). White solid, mp 165 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=8.26 (d, J=9 Hz, 2H), 7.79 (d, J=8.7 Hz, 2H), 7.52–7.39 (m, 5H), 4.25 (br, 1H), 4.06 (q, J=7.2 Hz, 2H), 3.23–3.15 (m, 1H), 2.15–0.87 (m, 10H), 0.99 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.0, 162.6, 148.2, 143.3, 139.3, 136.6, 135.7, 131.1, 129.0, 128.6, 125.8, 122.8, 91.2, 61.9, 53.6, 30.2, 29.0, 26.0, 25.1, 13.5. HRMS calcd for $C_{25}H_{26}N_2O_6$: (M+H) 451.1864, found: 451.1870. IR (KBr): 3301, 2947, 1682, 1648 cm^{-1}.

4.4.11. Methyl 1-cyclohexyl-2-hydroxy-2-methyl-5-oxo-4-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (3k). White solid, mp 155 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=7.49–7.35 (m, 5H), 3.71 (s, 3H), 3.42–3.39 (m, 2H), 2.32–1.27 (m, 10H), 1.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.2, 164.8, 141.6, 141.3, 130.0, 129.8, 129.7, 128.1, 89.1, 52.9, 52.5, 30.3, 30.2, 26.6, 25.5, 24.0. HRMS calcd for $C_{19}H_{23}NO_4$: (M+H) 330.1700, found: 330.1705. IR (KBr): 3311, 2927, 1673, 1653 cm^{-1}.

4.4.12. Ethyl 4-(2-chlorophenyl)-1-cyclohexyl-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (3l). White solid, mp 143–144 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=7.43–7.25 (m, 4H), 4.12 (q, J=6.9 Hz, 2H), 3.54 (s, 1H), 3.45–3.37 (m, 1H), 2.36–1.19 (m, 10H), 1.01 (t, J=6.9 Hz, 3H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=165.2, 162.7, 143.9, 140.8, 133.1, 130.6, 129.8, 129.4, 129.0, 126.0, 89.0, 61.3, 52.5, 39.9, 39.8, 26.2, 25.1, 23.9, 13.3. HRMS calcd for $C_{20}H_{24}ClNO_4$: (M+H) 378.1467, found: 378.1472. IR (KBr): 3327, 2933, 1677, 1645 cm^{-1}.

4.4.13. Ethyl 4-(3-bromophenyl)-1-cyclohexyl-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (3m). White solid, mp 114–115 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=7.65 (s, 1H), 7.53–7.22 (m, 3H), 4.22 (q, J=7.2 Hz, 2H), 3.70 (s, 3H), 3.44–3.36 (m, 1H), 2.36–1.23 (m, 10H), 1.74 (s, 3H), 1.18 (t, J=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=165.4, 163.4, 142.1, 139.5, 132.6, 132.1, 131.2, 129.1, 128.3, 121.4, 88.7, 61.6, 52.4, 29.8, 29.7, 26.1, 25.0, 23.5, 13.6. HRMS calcd for $C_{20}H_{24}BrNO_4$: (M+H) 422.0961, found: 422.0958. IR (KBr): 3286, 2933, 1721, 1673 cm^{-1}.

4.4.14. 4-Benzoyl-1-cyclohexyl-5-hydroxy-3-(4-nitrophenyl)-5-phenyl-1*H*-pyrrol-2(5*H*)-one (3n). Pale yellow solid, mp 102–104 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=8.02–7.10 (m, 14H), 5.08 (br, 1H), 3.31–3.23 (m, 1H), 2.34–0.78 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 194.3, 166.8, 149.3, 147.8, 136.2, 135.7, 134.6, 134.4, 130.7, 129.2, 129.1, 128.7, 128.5, 126.1, 123.1, 92.4, 53.8, 30.2, 29.4, 26.1, 26.0, 25.1. HRMS calcd for $C_{29}H_{26}N_2O_5$: (M+Na) 505.1734, found: 505.1735. IR (KBr): 3375, 2933, 1698, 1660 cm^{-1}.

4.4.15. 4-Acetyl-1-cyclohexyl-3-ethyl-5-hydroxy-5-methyl-1*H*-pyrrol-2(5*H*)-one (3o). White solid, mp 119–120 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=3.70 (br, 1H), 3.36–3.28 (m, 1H), 2.60–0.82 (m, 15H), 2.49 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=197.2, 167.2, 147.0, 146.0, 89.4, 52.2, 30.8, 29.9, 26.2, 25.2, 24.1, 18.6, 13.1. HRMS calcd for $C_{15}H_{23}NO_3$: (M+Na) 288.1570, found: 288.1573. IR (KBr): 3295, 2934, 1676, 1652 cm^{-1}.

4.4.16. 4-Acetyl-1-cyclohexyl-5-hydroxy-3-isopropyl-5-methyl-1*H*-pyrrol-2(5*H*)-one (3p). White solid, mp 141–142 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=3.39 (br, 1H), 3.37–3.29 (m, 1H), 3.15–3.08 (m, 1H), 2.50 (s, 3H), 2.31–1.19 (m, 16H), 1.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=199.2, 166.7, 147.2, 147.0, 89.0, 52.1, 32.0, 30.1, 30.0, 26.8, 26.3, 25.2, 23.8, 20.3, 20.0. HRMS calcd for $C_{16}H_{25}NO_3$: (M+Na) 302.1727, found: 302.1730. IR (KBr): 3315, 2941, 1679, 1655 cm^{-1}.

4.4.17. 4-Acetyl-1-cyclohexyl-5-hydroxy-5-methyl-3-propyl-1*H*-pyrrol-2(5*H*)-one (3q). White solid, mp 64–66 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=3.72 (br, 1H), 3.40–3.31 (m, 1H), 3.58–0.86 (m, 17H), 2.52 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=197.3, 167.4, 146.5, 145.7, 89.4, 52.2, 30.8, 29.9, 27.1, 26.2, 25.2, 24.2, 22.4, 14.3. HRMS calcd for $C_{16}H_{25}NO_3$: (M+Na) 302.1727, found: 302.1725. IR (KBr): 3335, 2923, 1669, 1619 cm^{-1}.

4.4.18. 4-Acetyl-1-cyclohexyl-3-hexyl-5-hydroxy-5-methyl-1*H*-pyrrol-2(5*H*)-one (3r). White solid, mp 82–84 °C; ^1H NMR (300 MHz, $CDCl_3$): δ=3.67 (br, 1H), 3.39–3.31

(m, 1H), 3.58–0.85 (m, 23H), 2.51 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=197.2, 167.4, 146.1, 89.4, 52.2, 31.4, 30.8, 30.0, 29.9, 29.6, 29.0, 26.2, 25.4, 25.2, 24.2, 22.4, 14.0. HRMS calcd for $C_{19}H_{31}NO_3$: (M+Na) 344.2196, found: 344.2192. IR (KBr): 3327, 2932, 1672, 1626 cm^{-1}.

4.4.19. Ethyl 1-cyclohexyl-2-hydroxy-4-isopropyl-2-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (3s). White solid, mp 76–77 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.33 (q, J=7.2 Hz, 2H), 3.38–3.15 (m, 3H), 2.31–1.19 (m, 19H), 1.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.5, 164.0, 150.5, 139.8, 88.6, 61.3, 52.3, 30.0, 26.3, 26.0, 25.2, 23.9, 20.0, 19.8, 14.1. HRMS calcd for $C_{17}H_{27}NO_4$: (M+Na) 332.1832, found: 332.1828. IR (KBr): 3408, 2939, 1690, 1642 cm^{-1}.

4.4.20. Methyl 1-cyclohexyl-4-hexyl-2-hydroxy-2-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (3t). White solid, mp 80–81 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.88 (s, 3H), 3.35–3.31 (m, 1H), 2.99 (br, 1H), 2.60–0.84 (m, 23H), 1.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.0, 164.0, 149.0, 139.6, 88.9, 52.3, 52.0, 31.4, 30.0, 29.4, 28.4, 26.3, 25.2, 24.9, 23.9, 22.5, 14.0. HRMS calcd for $C_{19}H_{31}NO_4$: (M+Na) 360.2145, found: 360.2144. IR (KBr): 3385, 2928, 1681, 1650 cm^{-1}.

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References and notes

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11. Crystal data for **3a** have deposited in CCDC as deposition number 635732: $C_{20}H_{25}NO_4$, MW=343.41, T=294(2) K, λ=0.71073 Å, monoclinic space group $P2(1)/n$, a=13.8351(4) Å, b=9.8237(3) Å, c=14.0206(4) Å, α=90.00, β=95.2280(10), γ=90.00, V=1897.64(10) Å^3, Z=4, D_c=1.202 mg m^{-3}, μ=0.083 mm^{-1}, $F(000)$=736, crystal size 0.28×0.25×0.20 mm, independent reflections 4042 [R (int)=0.0298], reflections collected 10,912, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 1.016, final R indices [$I>2\sigma(I)$] R_1=0.0531, wR_2=0.1272, R indices (all data) R_1=0.0914, wR_2=0.1464, extinction coefficient 0.0068(13), largest diff. peak and hole 0.321 and −0.196 eÅ^{-3}.
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