Concise and Versatile Multicomponent Synthesis of Multisubstituted Polyfunctional Dihydropyrroles

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Tetra- and pentasubstituted polyfunctional dihydropyrroles have been concisely synthesized in high yields by two different processes of the one-pot multicomponent reactions (MCRs) of but-2-ynedioates **1**, amines **2**, and aldehydes **3** at room temperature or at 70 °C. The first one involves a domino hydroamination/nucleophilic addition/amidation-cyclization process and leads to the formation of tetrasubstituted polyfunctional dihydropyrroles **4**. The second undergoes hydroamination/amidation/intramolecular cyclization/imine-enamine tautomerization sequence and results in pentasubstituted products **5**. The structures of **4** and **5** were confirmed by single-crystal X-ray diffraction. These novel methodologies provide easy access to diversely multisubstituted polyfunctional dihydropyrrole libraries. The primary biological screening in vitro against HIV-1 has shown that 22 tested compounds have exhibited significant activity with IC_{50} in micromolar range (38−58 μM).

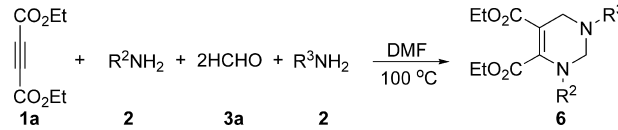
Introduction

Nitrogen heterocycles have been the subject of intense research because of their outstanding biological properties and wide range of applications to pharmaceutical compounds, agrochemicals and synthetic intermediates. For example, dihydropyrrol-2-ones have been used as the inhibitors of cardiac cyclic AMP phosphodiesterase,[1] HIV (human immunodeficiency virus) integrase,[2] and vascular endothelial growth factor receptors[3] and also as pesticides,[4] as well as useful intermediates.[5] Therefore, a diversity of methodologies has been developed for the synthesis of such nitrogen heterocycles.[6]

Recently we have reported a new, efficient methodology for the synthesis of tetrahydropyrimidines **6** via the MCRs of diethyl but-2-ynedioate **1a**, primary amines **2** and formaldehyde **3a** in excellent yields[7] (Scheme 1). Following the methodology, detailed investigation into expanding the scope of the MCRs for asymmetric alkynoates,[8] improving the method and studying the mechanism[9] have been undertaken on account of the importance of tetrahydropyrimidines on pharmaceutical and synthetic chemistry. To clarify the proposed reaction mechanism of the MCRs,[7] the mixture of **7b**, **2b**, and **3a** (molar ratio 1:1:1) was conducted for the preparation of Mannich-type reaction product **8** (Scheme 2). However, our attempt failed. It was very interesting that a mixture of diethyl 1,2,3,6-tetrahydro-1,3-diphenylpyrimidine-4,5-dicarboxylate **6bb** and ethyl 2,5-dihydro-5-oxo-1-phenyl-4-(phenylamino)-1H-pyrrole-3-carboxylate **4abb**[10] were detected (Scheme 2). As compared to dihydropyrrol-2-ones, **4abb** possess enamine and α,β-aminocarboxylate moieties, which are attractive targets in synthetic chemistry[11,12] for their importance of building nature and synthetic biologically active compounds, in addition to the useful dihydropyrrol-2-one scaffold. However, to the best of our knowledge, few studies have been performed on these polyfunctional dihydropyrroles because of a paucity of efficient synthetic routes.[13] The interesting and important moieties in **4abb** and the practical advantages associated with the use of dihydropyrrol-2-ones as bioactive compounds and synthetic intermediates encouraged us to explore new versatile method for the synthesis of such polyfunctional dihydropyrrole derivatives.

It is well-known that multicomponent reactions (MCRs) would be very beneficial from a synthetic standpoint for generating molecular complexity and diversity.[14] We noted that, although MCRs could be used to prepare multisubstituted pyrroles,[15] this kind of dihydropyrrol-2-ones with enamine and α,β-aminocarboxylate moieties have been synthesized via substitution reactions of corresponding hydroxyl dihydropyrrol-2-ones and amines.[13b−f] Herein, we disclose an efficient one-pot multicomponent synthesis of tetra- and pentasubstituted polyfunctional dihydropyrroles with good to excellent yields from but-2-ynedioates **1**, amines **2**, and aldehydes **3** at room

Scheme 1. Reported Methodology for the Synthesis of **6**[7]



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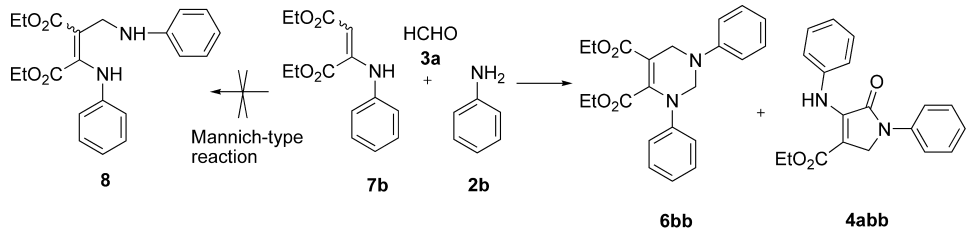
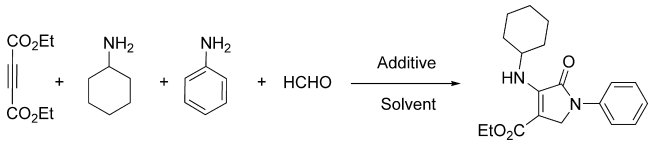
Scheme 2. Reaction of **7b**, **2b**, and **3a**



7b:2b:3a = 1:1:3, **6bb** in 98% yield

7b:2b:3a = 1:1:1, **6bb:4abb** = 44:56 in 80% yield

Table 1. Optimization of Reaction Conditions for the Synthesis of **4aab**[a]



1a **2a** **2b** **3a** **4aab**

entry	solvent	**2b**/equiv	**3a**/equiv	additive (equiv)	T/°C	t/h	yield/%[b]
1		4	1.5	AcOH (2)	rt	3	60
2	MeOH	4	1.5	AcOH (2)	rt	3	80
3	EtOH	4	1.5	AcOH (2)	rt	3	90
4	DMF	4	1.5	AcOH (2)	rt	6	85
5	EtOH	4	1.5		rt	24	trace
6	EtOH	4	1.5	Na_2CO_3 (2)	rt	24	
7	EtOH	4	1.5	Et_3N (2)	rt	24	
8	EtOH	4	1.5	AcOH (1)	rt	3	89
9	EtOH	4	1.5	AcOH (4)	rt	3	80
10	EtOH	4	1	AcOH (2)	rt	3	88
11	EtOH	4	2	AcOH (2)	rt	3	78
12	EtOH	4	1.5	AcOH (2)	70	0.5	92
13	EtOH	1.5	1.5	AcOH (2)	70	0.5	80
14	EtOH	2	1.5	AcOH (2)	70	0.5	92

[a] Reactions were run with the following steps: (1) **1a** (0.5 mmol) and **2a** (0.5 mmol) were added into 2 mL solvent and kept at room temperature for 10 min; (2) **2b**, **3a** and additive were added to the above mixture in sequence, and then stirred at rt/70 °C for desired time. [b] Isolated yields.

temperature or at 70 °C, and discussed the possible reaction mechanisms for the synthesis of **4** and **5**.

Results and Discussion

Synthesis of Tetrasubstituted Functional Dihydropyrroles. Our research began with the preparation of ethyl 4-(cyclohexylamino)-2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrrole-3-carboxylate **4aab**[13g] via four-component reaction of diethyl but-2-ynedioate **1a**, cyclohexylamine **2a**, formaldehyde **3a**, and aniline **2b**. We screened solvents, additives, reactant ratios, and reaction temperature for optimal reaction conditions (Table 1) and found that when **1a**/**2a**/**2b**/**3a**/AcOH = 1:1:2:1.5:2, **4aab** can be precipitated from reaction solution and obtained in 92% yield as white solid (entry 14). A single crystal of **4aab** was obtained by slow crystallization from ethanol or reaction solution, and its structure was established by single-crystal X-ray analysis (see Supporting Information for the crystal data of **4aab**).

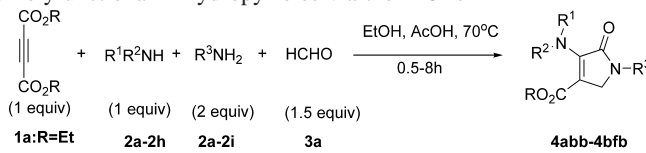
The addition order of reactants was also investigated, which indicated that the MCR was performed smoothly in similar yields by the different addition orders. Order 1: **2b**, **3a**, and AcOH were sequentially added into the mixture of **1a** and **2a** in solvent kept at room temperature for 10 min and then stirred at 70 °C for 30 min. Order 2: The mixture of **1a** and **2a** in solvent kept for 10 min at room temperature was added into the mixture of **2b**, **3a**, and AcOH in solvent kept for 10 min at room temperature and then stirred at 70 °C for 30 min. Order 3: **2b** and AcOH were added into the mixture of **1a** and **2a** in solvent kept at room temperature for 10 min and then stirred at 70 °C for 30 min; **3a** was added, and then, the mixture was stirred at 70 °C for 30 min.

Scope of Tetrasubstituted Polyfunctional Dihydropyrroles 4. The above optimal reaction conditions were proved suitable for the synthesis of a variety of tetrasubstituted functional dihydropyrroles **4** (Table 2). No matter whether R^1R^2NH were primary amines (entries 1−8, 10−12) or secondary amines (entry 9), whether R^1R^2NH and R^3NH_2 were the same (entries 1−5) or different (entries 6−12), whether aromatic (entries 1−4) or aliphatic (entry 5), the MCRs can be performed smoothly.

In a comprehensive study, we found that in the case of R^1 = H, the reactivity of **2** with different R^2 and R^3 in the MCRs presented an obvious rule. The activity order of **2** is: aliphatic R^2 and aromatic R^3 > aromatic R^2 and aromatic R^3 > aliphatic R^2 and aliphatic R^3 > aromatic R^2 and aliphatic R^3. The reaction time of the MCRs at 70 °C could prove this point: 0.5 h with 85−93% yields (Table 2, entries 6−8, 10−12), 4 h with 85−89% yields (entries 1−4), and 8 h with 86% yield (entry 5). It was particularly noteworthy to mention that when using **2** with aromatic R^2 and aliphatic R^3 instead of aliphatic R^2 and aromatic R^3 as reactants, such as aniline **2b** (R^2 = Ph) and benzyl aniline **2f** (R^3 = $PhCH_2$) or **2b** (R^2 = Ph) and *n*-propyl amine **2g** (R^3 = *n*-propyl), the reaction gave complex compounds despite using a variety of stoichiometries, higher temperature, and longer reaction time. According to these experimental results, the reactivity order of amines **2** with different R^2 in the MCRs is aliphatic R^2 > aromatic R^2 with electron-donating groups on phenyl ring > aromatic R^2> aromatic R^2 with electron-withdrawing groups on phenyl ring. The reactivity order is in good agreement with the basicity order of amines R^2NH_2.

It is interesting that the reactivity order of amines **2** with different R^3 in the MCRs is reversed as compared to that of amines **2** with different R^2. For instance, the reaction using amine **2** with R^2 = 4-$NO_2C_6H_4$− as substrate did not occur but that using amine **2** with R^3 = 4-$NO_2C_6H_4$− took place easily (Table 2, entry 10). In addition, no obvious influence was observed when R changed from ethyl to methyl in the MCRs (entries 6 and 11, 7 and 12).

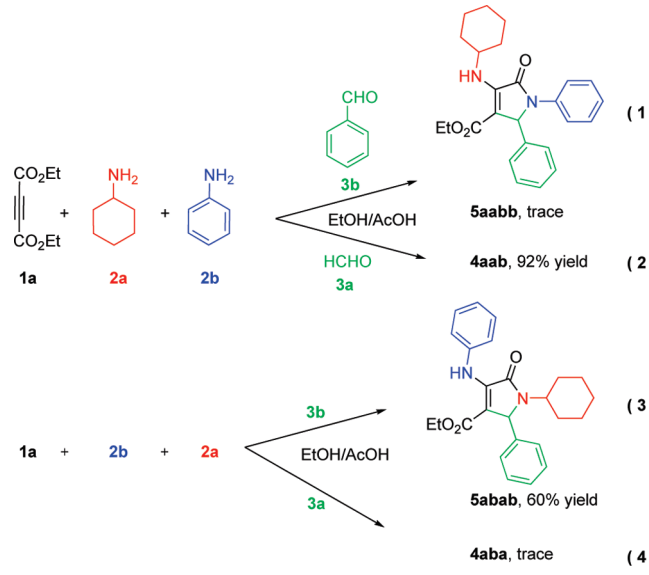
Table 2. Scope of Tetrasubstituted Polyfunctional Dihydropyrroles via the MCRs[a]



entry	R	R^1R^2NH	R^3NH_2	time (h)	product (yield %)[b]
1	Et **1a**		**2b**	4	**4abb**[12] 85
2	Et **1a**		**2c**	4	**4acc** 86
3	Et **1a**		**2d**	4	**4add** 87
4	Et **1a**		**2e**	4	**4aee**89
5	Et **1a**		**2f**	8	**4aff** 86
6	Et **1a**	**2a**	**2b**	0.5	**4aab**[13g] 92
7	Et **1a**	**2f**	**2b**	0.5	**4afb** 90
8	Et **1a**	*n*-$C_3H_7NH_2$ **2g**	**2b**	0.5	**4agb** 93
9	Et **1a**	**2h**[16]	**2b**	1	**4ahb** 90
10	Et **1a**	**2a**	**2i**	0.5	**4aai** 85
11	Me **1b**	**2a**	**2b**	0.5	**4bab** 93
12	Me **1b**	**2f**	**2b**	0.5	**4bfb** 89

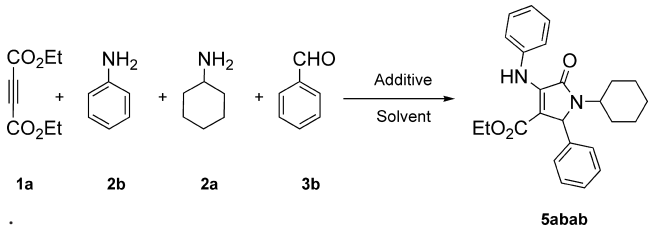
[a] All reactions were performed on 1 mmol scale. [b] Isolated yields.

Synthesis of Pentasubstituted Polyfunctional Dihydropyrroles. The synthesis of ethyl 4-(cyclohexylamino)-2,5-dihydro-5-oxo-1,2-diphenyl-1H-pyrrole-3-carboxylate **5aabb** under the above optimal reaction conditions via the MCRs of **1a**, **2a**, **2b**, and benzaldehyde **3b** was unsuccessful, which led to complex products (Reaction 1). In contrast to the synthesis of **5aabb**, ethyl 1-cyclohexyl-2,5-dihydro-5-oxo-2-phenyl-4-(phenylamino)-1H-pyrrole-3-carboxylate **5abab** was obtained in 60% yield when the addition order of **2a** and **2b** was changed (reaction 3). The structural influence of **2** on the synthesis of **5aabb** and **5abab** are completely reversed as compared to the cases of **4aab** and **4aba** (reactions 2 and 4). Based on these experimental results, we deduced that the synthetic conditions of **5abab** may be very different from that of **4aab**. Therefore, we screened additives, ratios of reactants, and temperature for the synthesis of **5abab** (Table 3). The results in Table 3 have proved our hypothesis. Two remarkable differences were found in comparing the reaction conditions of **4aab** and **5abab**, that are (1) excess of aldehyde **3b** instead of amine **2b** could increase the yield of product **5abab** (entries 6−8), and (2) **5abab** was afforded in higher yield under neutral or basic condition than that under acidic condition (entries 2, 4, 6), while little and no **4aab** was obtained under neutral and basic condition conditions respectively (Table 1, entries 5−7). The optimal conditions for the synthesis of **5abab** were **1a/2b/2a/3b** = 1:1:2:3 at 70 °C for 16 h (entry 11). A single crystal of **5abab** was obtained by slow crystallization from ethyl acetate and its structure was established by single-crystal X-ray analysis (Figure 1).



Scope of Pentasubstituted Polyfunctional Dihydropyrroles 5. With this optimal conditions in hands, a small library of 18 pentasubstituted polyfunctional dihydropyrroles

Table 3. Optimization of Reaction Conditions for the Synthesis of **5abab**[a]



1a **2b** **2a** **3b** **5abab**

entry	solvent	**2a**/equiv	**3b**/equiv	additive (equiv)	*T*/°C	*t*/h	**5abab**/%[b]
1	MeOH	2	3	AcOH (2)	70	6	68
2	EtOH	2	3	AcOH (2)	70	6	70
3	DMF	2	3	AcOH (2)	70	6	65
4	EtOH	2	3		70	6	76
5	EtOH	2	3	K_2CO_3 (2)	70	6	30
6	EtOH	2	3	$(Et)_3N$ (2)	70	6	75
7	EtOH	2	2		70	6	71
8	EtOH	2	1.5		70	6	59
9	EtOH	1.5	3		70	6	50
10	EtOH	3	3		70	6	74
11	EtOH	2	3		70	16	95
12	EtOH	2	3		rt	24	10

[a] Reactions were run with the following steps: (1) **1a** (0.5 mmol) and **2b** (0.5 mmol) were added into 2 mL solvent and kept at room temperature for 30 min; (2) **3b** and **2a** were added to the above reaction mixture in sequence, then stirred at rt or 70 °C for desired time. [b] Isolated yields.

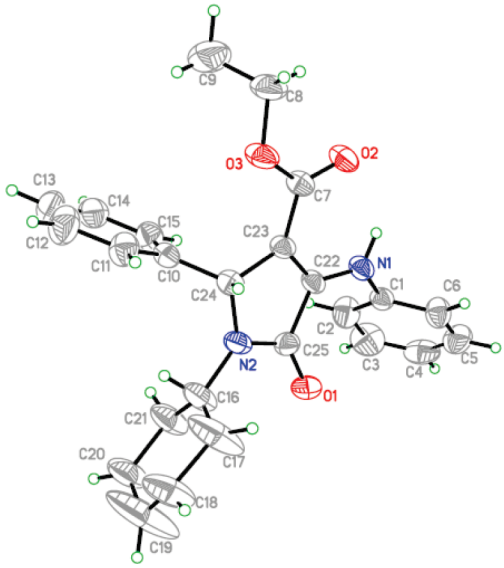


Figure 1. Single crystal structure of **5abab**.

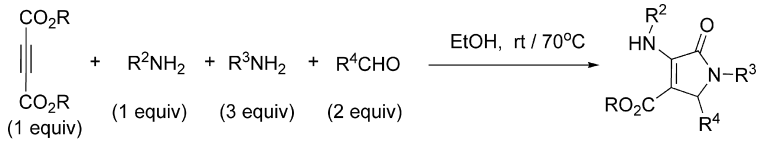
5 with structural diversity was rapidly generated using but-2-ynedioate **1a** and **1b**, a set of ten primary amines, R^2NH_2 and R^3NH_2, (**2a**−**2d**, **2f**−**2g**, and **2i**−**2l**, diversity points R^2 and R^3) and five aldehydes, R^4CHO, (**3b**−**3f**, diversity points R^4) (Table 4).

Replacement of **1a** with **1b** presented little influence on the MCRs (Comparing entries 6 and 18 in Table 4). Structure variation of primary amines **2**, however, showed great influence on the rates of the MCRs. Comparing the influence of **2** with different substituents R^2 and R^3 on the synthesis of **4** and **5**, two remarkable differences were observed. First, the rates of the MCRs for the synthesis of **5** were correlated with the structure of substituents R^2 and R^3 in **2** in a reverse order: aromatic R^2 and aliphatic R^3 > aliphatic R^2 and R^3 > aromatic R^2 and R^3 > aliphatic R^2 and aromatic R^3. Second, when using **2** with aliphatic R^2 and aromatic R^3 instead of aromatic R^2 and aliphatic R^3 as reactants, such as benzyl aniline **2f** (R^2 = benzyl) and aniline **2b** (R^3 = Ph) or *n*-propyl amine **2g** (R^2 = *n*- propyl) and **2b** (R^3 = Ph), the reaction gave complex results under the optimal reaction conditions. On the basis of the aforementioned results, we could further infer that the reactivity order of **2** with different R^2 in the MCRs for synthesis of **5** is: aromatic R^2 with electron-withdrawing substituents on phenyl ring > aromatic R^2 > aromatic R^2 with electron-donating groups on phenyl ring > aliphatic R^2 and that the reactivity order of **2** with different R^3 in the MCRs is contrary to that of **2** with different R^2. The following examples could confirm the orders. By using **2** with R^2 = 4-$NO_2C_6H_4$− as substrate, the reaction was carried out efficiently to produce **5** (entry 12); however, all attempts to synthesize **5** failed under different reaction conditions when using **2** with R^3 = 4-$NO_2C_6H_4$− as substrate. We also found that when using **2** with aromatic R^2 and R^3 as reactants, the MCRs afforded **5** with higher yields under acetic condition than that under neutral condition (entry 1).

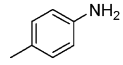
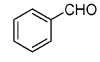
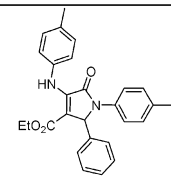
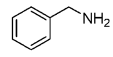
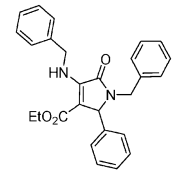
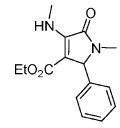
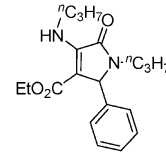
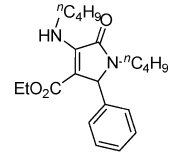
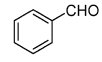
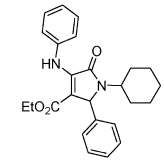
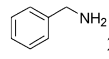
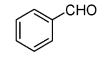
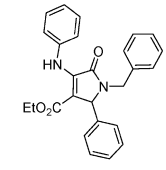
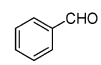
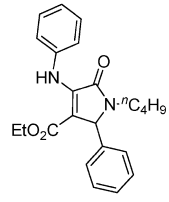
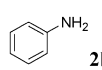
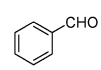
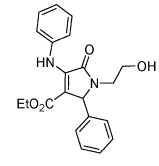
The reactivity of aldehyde **3** in the synthesis of **5** presented much more sensitive than that of primary amines **2**. It is of great interest that when using aromatic aldehydes **3** as substrates, the MCRs was completed at 70 °C in more than 16 h (Table 4, entries 1−14, 18). On the contrary, while employing aliphatic aldehydes **3** as substrates, the MCRs afforded the corresponding products in good to excellent yields at room temperature, but complex products at 70 °C (entries 15−17). The reactivity order of aldehydes **3** in the MCRs was increased by the variation of R^4 in **3**: aliphatic R^4 > aromatic R^4 with electron-donating substituents on phenyl ring > aromatic R^4 > aromatic R^4 with electron-withdrawing substituents on phenyl ring. Therefore, it was not surprising that we failed to synthesize **5** when using aldehydes **3** with R^4 = 4-$NO_2C_6H_4$− under the optimal reaction conditions.

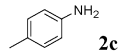
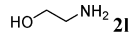
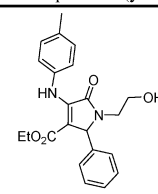
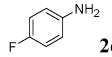
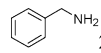
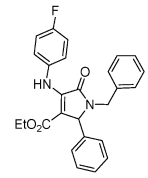
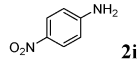
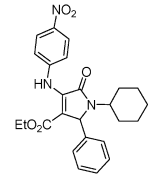
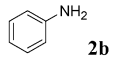
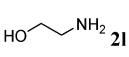
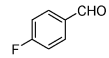
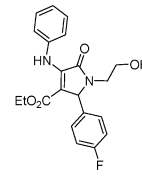
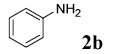
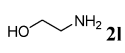
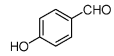
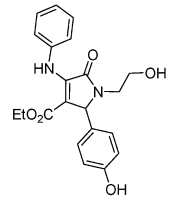
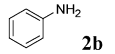
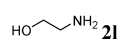
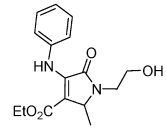
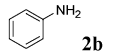
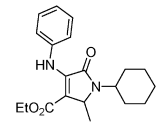
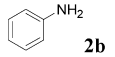
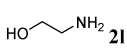
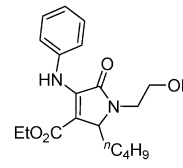
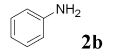
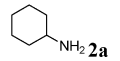
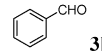
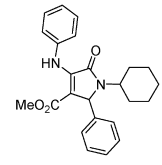
Possible Mechanism for the Synthesis of Multisubstituted Polyfunctional Dihydropyrroles. According to the results mentioned above, a possible mechanism for the synthesis of **4** was proposed, which contains three elementary steps: hydroamination, nucleophilic addition, and amidation−cyclization (Scheme 3). Our previous work proved that the hydroamination of **1a** and primary amines **2** were performed fast with the ratio of the products, *Z*- and *E*-isomers **7**, controlled by solvents,[9] which proved that the mixture of *Z*- and *E*-isomers **7** was obtained in ethanol solvent. Considering the great δ value of N−H in **7** (>9 ppm),[9] the fact that both of *Z*- and *E*-isomers **7** could lead to the same products **4,** and the fact that the reactions of *N*,*N*-disubstituted enamines **7** and imines **9** were limited to secondary aliphatic amines as substrates (Table 2, entry 9), we thought that **7** and **9** underwent a nucleophilic addition involved the transfer of lone electron pair on the nitrogen rather than Mannich-type reaction involved the transfer of $\sigma_{(C-H)}$ (dashed bond in Scheme 3) electron pair in **7** for it is obvious that the reactivitities of the MCRs are correlated with the electron density on the nitrogen instead of the reactivity of the

Table 4. Scope of Pentasubstituted Polyfunctional Dihydropyrroles **5** via the MCRs[a]



1a:R=Et **2a-2j** **3b-3l** **2b-2f** **5accb-5bbab**
1b:R=Me

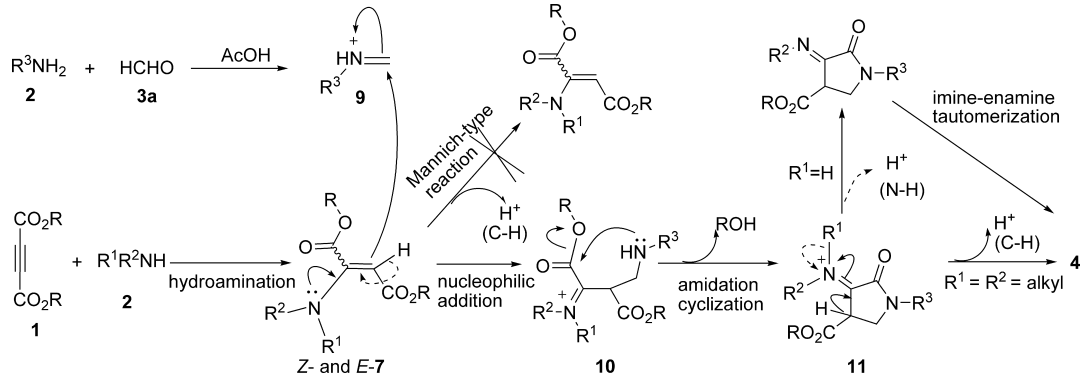
entry	R	R^2NH_2	R^3NH_2	R^4CHO	product (yield%)[b]
1	Et **1a**	 **2c**		 **3b**	 **5accb** 92
2	Et **1a**	 **2f**		 **3b**	 **5affb** 86
3	Et **1a**	CH_3NH_2 **2j**		 **3b**	 **5ajjb**[17] 86
4	Et **1a**	*n*-$C_3H_7NH_2$ **2g**		 **3b**	 **5aggb**92
5	Et **1a**	*n*-$C_4H_9NH_2$ **2k**		 **3b**	 **5akkb** 87
6	Et **1a**	 **2b**	 **2a**	 **3b**	 **5abab** 95
7	Et **1a**	 **2b**	 **2f**	 **3b**	 **5abfb** 87
8	Et **1a**	 **2b**	*n*-$C_4H_9NH_2$ **2k**	 **3b**	 **5abkb** 89
9	Et **1a**	 **2b**	 **2l**	 **3b**	 **5ablb** 94

entry	R	R^2NH_2	R^3NH_2	R^4CHO	product (yield%) [b]
10	Et **1a**	 **2c**	 **2l**	 **3b**	 **5aclb** 92
11	Et **1a**	 **2d**	 **2f**	 **3b**	 **5adfb**89
12	Et **1a**	 **2i**	 **2a**	 **3b**	 **5aiab** 88
13	Et **1a**	 **2b**	 **2l**	 **3c**	 **5ablc** 93
14	Et **1a**	 **2b**	 **2l**	 **3d**	 **5abld** 92
15[c]	Et **1a**	 **2b**	 **2l**	CH_3CHO **3e**	 **5able** 98
16[c]	Et **1a**	 **2b**	 **2a**	CH_3CHO **3e**	 **5abae** 92
17[c]	Et **1a**	 **2b**	 **2l**	n-C_4H_9CHO **3f**	 **5ablf** 60
18	Me **1b**	 **2b**	 **2a**	 **3b**	 **5bbab** 92

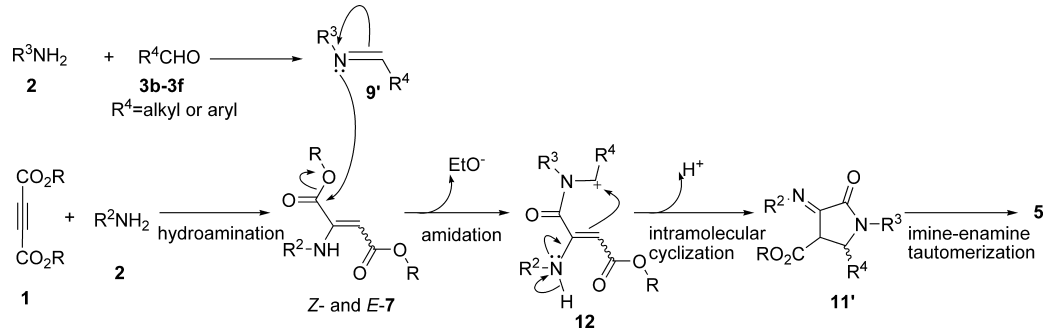
[a] All reactions were performed on 1 mmol scale without additives apart from the exception of entry 1 which with two equiv of AcOH. [b] Isolated yields. [c] Reactions were performed at room temperature.

hydrogen at $\sigma_{(C-H)}$ bond. The reactivity order of amines **2** in the MCRs for the synthesis of **4**, that is, **2** with aliphatic R^2 and aromatic R^3 > aromatic R^2 and R^3 > aliphatic R^2 and R^3 >aromatic R^2 and aliphatic R^3, suggested that the nucleophilic addition rather than the amidation was the rate-determining step because aliphatic R^2 and aromatic R^3 favored the nucleophilic addition rather than the amidation. Therefore, it is not difficult to understand why the ractivities

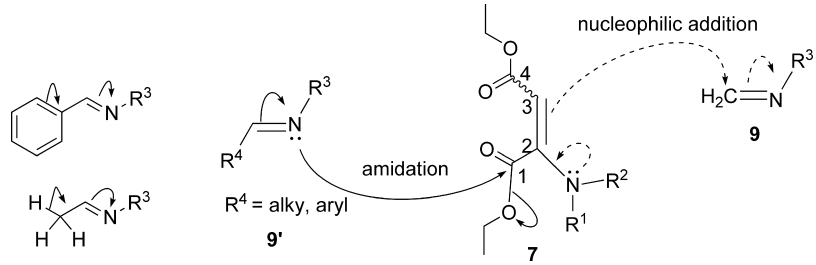
Scheme 3. Possible Mechanism for the Synthesis of Tetrasubstituted Polyfunctional Dihydropyrroles **4**



Scheme 4. Proposed Mechanism for the Synthesis of Pentasubstituted Polyfunctional Dihydropyrroles **5**



Scheme 5. Reactions of **7** and **9/9′** Occurred at Different Positions



of R^2 NH_2 and R^3 NH_2 shows reverse orders from the activity analysis of nucleophiles **7** and electrophiles **9**, and why the MCRs did not take place when using **2** with aromatic R^1 and R^2 as substrate, in which two phenyls greatly lowered the electron density on the nitrogen because of the conjugative effect of its lone electron pair with the phenyl rings so that the nucleophilic addition of **7** to **9** can not take place. The mechanism for the reaction of *N*,*N*-disubstituted enamines with arylsulfonyl isocyanate under neutral condition[18] is similar to that for synthesis of **4ahb**.

The greatly different reaction conditions and the reverse reactivity order of **2** indicated that the mechanism of the MCRs for the formation of **5** is different from that of **4**. The possible mechanism was depicted in Scheme 4, which included the following steps: hydroamination, amidation, intramolecular cyclization, and imine−enamine tautomerization.

The different mechanisms of the MCRs for the synthesis of **4** and **5** result from the different reactions took place between **7** and **9/9′** (Scheme 5). One of the notable features of **7** is the enhanced electron density on C_3 and O_1 owing to the conjugative effect of the lone electron pair on the nitrogen, which leads to higher nucleophilicity of C_3 and lower electrophilicity of C_4 other than C_1 (Scheme 5). Therefore, C_1 and C_3 become the electron-deficient and electron-rich reaction centers in **7**, respectively. On the other hand, imines **9/9′** have also two possible reaction centers, that is, the electron-poor carbon and the electron-rich nitrogen of the imines. Comparing **9** with **9′**, it is obvious that the reactivity of the carbon reaction center is lower, while the reactivity of the nitrogen reaction center is higher in **9′** than that in **9** because of the electron-donating and the spatial hindering effects derived from the substituent aryl or alkyl at the carbon. So **7** and **9** underwent an nucleophilic addition between electron-rich C_3 in **7** and the electron-deficient carbon of imine in **9**, three dashed arrows present the nucleophilic addition involved the transfer of the lone electron pair in nitrogen, while **7** and **9′** proceeded in an amidation between electron-deficient C_1 in **7** and the electron-rich nitrogen of imine in **9′**. It is obvious that acidic condition (activating **9** via formation of imine ions), electron-donating R^1 and R^2 substituents(increasing the electron density of C_3 in **7**), and electron-withdrawing R^3 group (decreasing the electron density of the carbon in **9**)are favorable for the nucleophilic addition of **7** to **9**, while neutral (keeping the nucleophilic activity of **9′**), electron-withdrawing R^1 and R^2

substituents (decreasing the electron density of C_1 in **7**), and electron-donating R^3 group (increasing the electron density of the nitrogen in **9′**) are favorable for the amidation of **7** and **9′** which are in excellent agreement with the experimental facts described above(with the exception of entry 1 in Table 4).

Conclusions

A total of 30 examples of tetra- and pentasubstituted polyfunctional dihydropyrroles with structure diversity were synthesized via MCRs in good to excellent yields from easily available but-2-ynedioates, amines and aldehydes. On the basis of the careful investigation into the effect of substrates, additives, reaction time, temperature on the reactions, the MCRs were proved to undergo two different mechanisms: for the synthesis of tetrasubstituted polyfunctional dihydropyrroles is a domino hydroamination/nucleophilic addition/amidation-cyclization process, and for the synthesis of pentasubstituted polyfunctional dihydropyrroles undergoes hydroamination/amidation/intramolecular cyclization/imine-enamine tautomerization sequence. It should be mentioned that as the development of our previous work on the research of *N*-substituted pyrrole activities anti-HIV-1,[19] the primary evaluated experiments anti-HIV-1 in vitro for 22 compounds of these polyfunctional dihydropyrrole derivatives are described in patent,[20] in which significant biological activities were observed.

Experimental Section

General Procedure for the Synthesis of 4 (A). Primary amines **2** (2 mmol), 38% **3a** (120 mg, 1.5 mmol), and AcOH (120 mg, 2 mmol) were dropwise added into the mixture of EtOH (4 mL), **1** (1 mmol) and primary or secondary aliphatic amines **2** (1 mmol) kept at room temperature for 10−30 min in sequence, followed with stirring at 70 °C for desired time (monitored by TLC). After completion of the reactions, the product mixture was purified by preparative TLC with *n*-hexane/ethyl acetate (10:1−1:1) as eluent to afford the desired products in 85−93% yields (Table 2, entries 5−12).

General Procedure for the Synthesis of 4 (B). Primary aromatic amines **2** (4 mmol), 38% **3a** (120 mg, 1.5 mmol), and AcOH (120 mg, 2 mmol) were dropwise added into the mixture of EtOH (4 mL), **1** (1 mmol) and primary aromatic amines **2** (1 mmol) kept at room temperature for 30−60 min in sequence, followed the same steps described in general procedure A to afford the desired products in 85−89% yields (Table 2, entries 1−4).

General Procedure for the Synthesis of 5 (C). Aldehydes **3b**−**3f** (3 mmol) and primary aliphatic amines **2** (2 mmol) were dropwise added into the mixture of EtOH (4 mL), **1** (1 mmol) and **2** (1 mmol) kept at room temperature for 30−60 min in sequence, followed with stirring at rt or 70 °C for desired time (monitored by TLC). After completion of the reactions, the product mixture was purified by preparative TLC with *n*-hexane/ethyl acetate (10:1−1:1) as eluent to afford the desired products in 60−98% yields (Table 4, entries 2−18).

General Procedure for the Synthesis of 5 (D). Aldehyde **3b** (3 mmol), primary aromatic amine **2c** (2 mmol), and AcOH (120 mg, 2 mmol) were dropwise added into the mixture of EtOH (4 mL), **1a** (1 mmol), and **2c** (1 mmol) kept at room temperature for 30 min in sequence, followed the same steps described in general procedure C to afford the desired product **5accb** in 92% yield (Table 4, entry 1).

Characterization Data for Compounds 4. (1). Ethyl 2,5-Dihydro-5-oxo-1-phenyl-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (4abb): 85% yield, white solid, mp = 138−140 °C; IR (KBr) ν_{max} = 3299, 2976, 1681, 1631, 1450, 1304, 1291, 1130, 756, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00(s, 1H), 7.79(d, J = 7.6 Hz, 2H), 7.41−7.12(m, 8H), 4.53(s, 2H), 4.19(q, J = 7.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H)ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 164.6, 164.0, 142.6, 138.8, 138.7, 129.2, 128.4, 125.1, 124.6, 122.6, 119.3, 103.6, 60.4, 48.4, 14.2 ppm; MS (ESI) *m*/*z* 323(M + H^+, 98), 277 (100); Anal. Calcd for $C_{19}H_{18}N_2O_3$ C, 70.79; H, 5.63; N, 8.69; Found C, 70.96; H, 5.53; N, 8.51.

(2). Ethyl 4-(*p*-Tolylamino)-2,5-dihydro-5-oxo-1-*p*-tolyl-1*H*-pyrrole-3-carboxylate(4acc): 86% yield, yellow solid, mp = 131−132 °C; IR (KBr) ν_{max} = 3290, 2981, 1691, 1642, 1558, 1538, 1455, 1300, 1271, 1115, 802, 759 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ = 7.96(s, 1H), 7.64(d, J = 8.4 Hz, 2H), 7.16(d, J = 8.4 Hz, 2H), 7.09(d, J = 8.0 Hz, 2H), 7.01(d, J = 8.4 Hz, 2H), 4.47(s, 2H), 4.18(q, J = 7.2 Hz, 2H), 2.32(s, 3H), 2.31(S, 3H), 1.20(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 164.7, 163.8, 143.3, 136.3, 136.2, 134.8, 134.4, 129.6, 129.0, 123.0, 119.3, 102.4, 60.2, 48.4, 21.0, 20.9, 14.2 ppm; MS (ESI) *m*/*z* 351(M + H^+, 100), 305 (76); Anal. Calcd for $C_{21}H_{22}N_2O_3$ C, 71.98; H, 6.33; N, 7.99; Found C, 71.90; H, 6.45; N, 8.02.

(3). Ethyl 4-(4-Fluorophenylamino)-1-(4-fluorophenyl)-2,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylate (4add): 87% yield, white solid, mp = 172−173 °C; IR (KBr) ν_{max} = 3302, 2968, 1708, 1690, 1621, 1458, 1304, 1222, 1119, 831, 759 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ = 7.72(s, 1H), 7.71−7.68(m, 2H), 7.11−6.96(m, 6H), 4.48(s, 2H), 4.21(q, J = 7.2 Hz, 2H), 1.24(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 164.6, 163.6, 161.2(d, J = 100 Hz, 1C), 158.8(d, J = 108 Hz, 1C), 143.2, 134.7, 134.5, 124.9, 124.8, 121.2, 121.1,116.0, 115.7, 115.2, 115.0, 102.9, 60.4, 48.4, 14.2 ppm; MS (ESI) *m*/*z* 359(M + H^+, 81), 313 (100); Anal. Calcd for $C_{19}H_{16}F_2N_2O_3$ C, 63.68; H, 4.50; F, 10.60; N, 7.82; Found C, 63.75; H, 4.71; N, 7.78, F, 10.71.

(4). Ethyl 4-(4-Bromophenylamino)-1-(4-bromophenyl)-2,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylate (4aee): 89%, white solid, mp = 169−171 °C; IR (KBr) ν_{max} = 3290, 2980, 1699, 1640, 1587, 1491, 1454, 1383, 1223, 1195, 823, 758 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ = 8.00(s, 1H), 7.67−6.97(m, 8H), 4.47(s, 2H), 4.22(q, J = 7.2 Hz, 2H), 1.24(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 164.4, 163.6, 142.6, 137.7, 137.6, 132.2, 131.4, 124.3, 120.6, 118.0, 117.6, 104.4, 60.6, 48.1, 14.2 ppm; MS (ESI) *m*/*z* 481(M + H^+, 30), 435 (100); Anal. Calcd for $C_{19}H_{16}Br_2N_2O_3$ C, 47.53; H, 3.36; Br, 33.28; N, 5.83; Found C, 47.45; H, 3.42; Br, 33.31; N, 5.79.

(5). Ethyl 1-Benzyl-4-(benzylamino)-2,5-dihydro-5-oxo-1*H*-pyrrole-3-carboxylate (4aff): 86% yield, yellow oil; IR (KBr) ν_{max} = 3337, 3062, 3029, 2979, 1691, 1627, 1539, 1452, 1324, 1290, 1137, 763, 699 cm^{-1}; ^1H NMR(400 MHz,

$CDCl_3$) δ = 7.38−7.27(m, 10H), 5.15(s, 1H), 5.14(s, 1H), 4.66(s, 2H), 4.17(q, J = 7.2 Hz, 2H), 3.89(s, 2H), 1.25(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 165.6, 165.4, 146.7, 139.6, 136.5, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.5, 127.3, 122.7, 98.3, 59.6, 47.0, 46.7, 46.4, 14.4 ppm; MS (ESI) m/z 351(M + H^+, 42), 305 (100); Anal. Calcd for $C_{21}H_{22}N_2O_3$ C, 71.98; H, 6.33; N, 7.99; Found C, 71.96; H, 6.43; N, 7.92.

(6). Ethyl 4-(Cyclohexylamino)-2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrrole-3-carboxylate (4aab): 96% yield, white solid, mp = 107−108 °C; IR (KBr) ν_{max} = 3431, 2928, 2854, 1700, 1628, 1511, 1390, 1290, 1142, 761, 691 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$) δ = 7.69(d, J = 8.4 Hz, 2H), 7.33−7.29(m, 2H), 7.11−7.07(m, 1H), 4.56(brs, 1H), 4.31(s, 2H), 4.19(q, J = 7.2 Hz, 2H), 1.99−1.95(m, 2H), 1.72−1.35(m, 5H), 1.27(t, J = 7.2 Hz, 3H), 1.21−1.32(m, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 165.2, 164.4, 138.8, 129.0, 128.8, 124.8, 119.3, 96.3, 59.6, 50.6, 48.0, 34.7, 25.5, 24.6, 19.1, 14.5 ppm; MS (ESI) m/z 329(M + H^+, 100), 283 (23); Anal. Calcd for $C_{19}H_{24}$ N_2O_3 C, 69.49; H, 7.37; N, 8.53; Found C, 69.53; H, 7.41; N, 8.50.

(7). Ethyl 4-(Benzylamino)-2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrrole-3-carboxylate (4afb): 90% yield, white solid, mp = 130−132 °C; IR (KBr) ν_{max} = 3300, 2936, 1685, 1630, 1537, 1494, 1389, 1324, 1271, 1120, 748, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75−7.73(m, 2H), 7.40−7.15(m, 8H), 5.09(s, 2H), 4.41(s, 2H), 4.22(q, J = 7.2 Hz, 2H), 1.29(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$): δ = 164.6 (The ester and amide carbonyl carbon peaks overlap), 139.5, 138.8, 129.1, 128.7, 127.5, 127.4, 125.1, 119.5, 59.9, 48.1, 46.8, 14.5 ppm; MS (ESI) m/z 337(M + H^+, 100), 291 (49); Anal. Calcd for $C_{20}H_{20}$ N_2O_3 C, 71.41; H, 5.99; N, 8.33; Found C, 71.48; H, 5.92; N, 8.29.

(8). Ethyl 2,5-Dihydro-5-oxo-1-phenyl-4-(propylamino)-1*H*-pyrrole-3-carboxylate (4agb): 93% yield, white solid, mp = 78−79 °C; IR (KBr) ν_{max} = 3337, 2960, 2873, 1699, 1636, 1598, 1499, 1459, 1390, 1261, 1205, 1118, 761, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72(d, J = 8.0 Hz, 2H), 7.37−7.33(m, 2H), 7.13(t, J = 7.2 Hz, 1H), 4.36(s, 2H), 4.22(q, J = 7.2 Hz, 2H), 3.79(q, J = 6.8 Hz, 2H), 1.62−1.57(m, 2H), 1.30(t, J = 7.2 Hz, 3H), 0.95(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.3, 164.6, 138.8, 129.0, 124.9, 119.4, 96.5, 59.7, 48.0, 44.7, 24.5, 14.5, 11.1 ppm; MS (ESI) m/z 289(M + H^+, 49), 243 (100); Anal. Calcd for $C_{16}H_{20}$ N_2O_3 C, 66.65; H, 6.99; N, 9.72; Found C, 66.59; H, 6.87; N, 9.78.

(9). Ethyl 4-(Dibutylamino)-2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrrole-3-carboxylate (4ahb): 90% yield, yellow oil; IR (KBr) ν_{max} = 2958, 2870, 1697, 1602, 1500, 1461, 1391, 1266, 1198, 1104, 757, 690 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$) δ = 7.76−7.74(m, 2H), 7.40−7.36(m, 2H),.7.17−7.15(m, 1H), 4.42(s, 2H), 4.24(q, J = 7.2 Hz, 2H), 3.69 (t, J = 7.2 Hz, 4H), 1.56−1.50(m, 4H), 1.34−1.28(m, 7H), 0.91 (t, J = 7.2 Hz, 6H)ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 166.1, 162.8, 147.2, 139.0, 129.0, 124.8, 119.6, 103.7, 59.9, 51.1, 49.0, 30.3, 19.9, 14.5, 14.0 ppm; MS (ESI) m/z 359(M + H^+, 100), 313(15); Anal. Calcd for $C_{21}H_{30}N_2O_3$ C, 70.36; H, 8.44; N, 7.81; Found C, 70.25; H, 8.51; N, 7.90.

(10). Ethyl 4-(Cyclohexylamino)-2,5-dihydro-1-(4-nitrophenyl)-5-oxo-1*H*-pyrrole-3-carboxylate (4aai): 85% yield, yellow solid, mp = 149.5−150.5 °C; IR (KBr) ν_{max} = 3444, 2927, 2854, 1705, 1680, 1632, 1508, 1333, 1276, 1109, 851, 763 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$) δ = 8.27−8.24(m, 2H), 8.01−7.98 (m, 2H), 4.55(brs, 1H), 4.45(s, 2H), 4.27(q, J = 7.2 Hz, 2H), 2.02−1.98(m, 2H), 1.76−1.40(m, 5H), 1.34(t, J = 7.2 Hz, 3H), 1.24−1.21(m, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 165.1 (the ester and amide carbonyl carbon peaks overlap), 144.3, 143.8, 125.0, 118.3, 97.0, 60.0, 50.8, 47.8, 34.7, 25.4, 24.6, 14.5 ppm; MS (ESI) m/z 374(M + H^+, 100), 328 (23); Anal. Calcd for $C_{19}H_{23}$ N_3O_5 C, 61.11; H, 6.21; N, 11.25; Found C, 61.21; H, 6.28; N, 11.21.

(11). Methyl 4-(Cyclohexylamino)-2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrrole-3-carboxylate (4bab). 93% yield, white solid, mp = 94−95 °C; IR (KBr) ν_{max} = 3320, 2929, 2853, 1700,1630, 1598, 1499, 1459, 1389, 1305,1258, 1205, 1118, 759, 688 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$) δ = 7.75−7.73(m, 2H), 7.40−7.36(m, 2H), 7.19−7.15(m, 1H), 4.60(brs, 1H), 4.39(s, 2H), 3.77(s, 3H), 2.03−1.18(m, 10H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 165.8, 164.5, 138.9, 129.2, 125.2, 121.0, 119.6, 117.8, 95.9, 68.7, 51.1, 48.2, 34.9, 25.6, 24.8 ppm; MS (ESI) m/z 315(M + H^+, 100), 283 (5); Anal. Calcd for $C_{18}H_{22}$ N_2O_3 C, 68.77; H, 7.05; N, 8.91; Found C, 68.63; H, 7.12; N, 8.83.

(12). Methyl 4-(Benzylamino)-2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrrole-3-carboxylate (4bfb): 89% yield, white solid, 140−141 °C; IR (KBr) ν_{max} = 3310, 2929, 2853, 1704,1684, 1642, 1541, 1496, 1372, 1272, 1204, 985, 924, 756, 700 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$) δ = 7.76−7.74(m, 2H), 7.41−7.19(m, 8H), 5.12(s, 1H), 5.11(s, 1H), 4.43(s, 2H), 3.78(s, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 165.6, 164.6, 139.5, 138.8, 129.3, 128.8, 127.6, 127.5, 125.3, 119.6, 97.5, 51.2, 48.2, 46.8 ppm; MS (ESI) m/z 323(M + H^+, 100), 291 (34); Anal. Calcd for $C_{19}H_{18}$ N_2O_3 C, 70.79; H, 5.63; N, 8.69; Found C, 70.83; H, 5.69; N, 8.72.

Characterization Data for Compounds 5. (1). Ethyl 4-(*p*-Tolylamino)-2,5-dihydro-5-oxo-2-phenyl-1-*p*-tolyl-1*H*-pyrrole-3-carboxylate (5accb): 90% yield, white solid, mp = 156−158 °C; IR (KBr) ν_{max} = 3032, 2983, 2924, 1709, 1632, 1515, 1450, 1393, 1290, 1211, 1110, 1035, 834, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.15 (brs, 1 H), 7.33−7.16 (m, 7H), 7.11−7.00 (m, 6H), 5.75(s, 1H), 3.99(q, J = 7.2 Hz, 2H), 2.31(s, 3H), 2.21(s, 3H), 0.99(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.5, 163.9, 142.6, 137.1, 136.0, 135.3, 134.4, 134.0, 129.4, 129.0, 128.3, 128.0, 127.7, 123.0, 122.7, 108.8, 63.2, 60.1, 21.0, 20.9, 13.8 ppm; MS (ESI) m/z 427(M + H^+, 80), 381 (100); Anal. Calcd for $C_{27}H_{26}N_2O_3$ C, 76.03; H, 6.14; N, 6.57; Found C, 76.31; H, 6.09; N, 6.61.

(2). Ethyl 1-Benzyl-4-(benzylamino)-2,5-dihydro-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (5affb): 86% yield, white solid, mp = 104−106 °C; IR (KBr) ν_{max} = 3329, 3030, 2980, 1696, 1673, 1625, 1493, 1454, 1362, 1284, 1213, 1089, 1028, 761, 699 cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$) δ = 7.40−7.09(m, 15H), 5.18(brs, 2H), 5.13(d, J = 14.8 Hz, 1H), 4.89(s, 1H), 3.98−3.88(m, 2H), 3.52(d, J = 14.8 Hz, 1H), 0.96(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$)

δ = 165.4 (the ester and amide carbonyl carbon peaks overlap.), 139.5, 137.1, 136.7, 128.8, 128.4, 128.2, 128.0, 127.7, 127.6, 127.4, 60.9, 59.4, 43.9, 18.5, 14.0 ppm; MS (ESI) *m/z* 427(M + H^+, 100), 381 (30); Anal. Calcd for $C_{27}H_{26}N_2O_3$ C, 76.03; H, 6.14; N, 6.57; Found C, 76.15; H, 6.18; N, 6.63.

(3). Ethyl 2,5-Dihydro-1-methyl-4-(methylamino)-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (5ajjb): 86% yield, white solid, mp = 129−131 °C; IR (KBr) ν_{max} = 2986, 2927, 1703, 1698, 1635, 1452, 1424, 1390, 1341, 1290, 1222, 1137, 1096, 1037, 920, 832 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ = 7.30−7.12(m, 5H), 4.92(s, 1H), 3.98−3.94(m, 2H), 3.38(s, 3H), 2.72(s, 3H), 1.00(t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 165.6 (The ester and amide carbonyl carbon peaks overlap.), 137.5, 128.3, 128.0, 127.6, 102.7, 63.8, 59.2, 30.1, 27.5, 14.0 ppm; MS (ESI) *m/z* 275(M + H^+, 100), 229 (40); Anal. Calcd for $C_{15}H_{18}N_2O_3$ C, 65.68; H, 6.61; N, 10.21; Found C, 65.73; H, 6.56; N, 10.38.

(4). Ethyl 2,5-Dihydro-5-oxo-2-phenyl-1-propyl-4-(propylamino)-1*H*-pyrrole-3-carboxylate (5aggb): 92% yield, yellow oil; IR (KBr) ν_{max} = 3333, 3030, 2964, 2933, 2864, 1698, 1672, 1540, 1456, 1343, 1218, 1075, 760, 701 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ = 7.32−7.13(m, 5H), 5.04(s, 1H), 4.01−3.97(m, 2H), 3.87(brs, 2H), 3.63−3.60(m, 1H), 2.61−2.60(m, 1H), 1.67−1.45(m, 4H), 1.05−0.97(m, 6H), 0.83(t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 165.5 (the ester and amide carbonyl carbon peaks overlap.), 137.8, 128.3, 128.0, 127.7, 102.7, 61.8, 59.2, 44.4, 42.0, 24.6, 21.4, 14.1, 11.3, 11.1 ppm; MS (ESI) *m/z* 331(M + H^+, 100), 285 (15); Anal. Calcd for $C_{19}H_{26}N_2O_3$ C, 69.06; H, 7.93; N, 8.48; Found C, 69.26; H, 7.98; N, 8.41.

(5). Ethyl 1-Butyl-4-(butylamino)-2,5-dihydro-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (5akkb): 87% yield, yellow oil; IR (KBr) ν_{max} = 3332, 3062, 2959, 2931, 2872, 1769, 1698, 1673, 1626, 1451, 1368, 1279, 1213, 1075, 1106, 760, 701 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ = 7.32−7.13(m, 5H), 5.03(s, 1H), 4.01−3.95(m, 2H), 3.90(brs, 2H), 3.69−3.65(m, 1H), 2.60−2.59(m, 1H), 1.61−1.25(m, 8H), 1.02(t, *J* = 7.2 Hz, 3H), 0.95(t, *J* = 7.2 Hz, 3H), 0.86(t, *J* = 7.2 Hz, 3H)ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 165.3 (the ester and amide carbonyl carbon peaks overlap.), 137.8, 128.3, 127.9, 127.7, 102.6, 61.7, 59.2, 42.3, 40.0, 33.4, 30.1, 20.0, 19.8, 14.0, 13.8, 13.6 ppm; MS (ESI) *m/z* 359(M + H^+, 100), 313 (35); Anal. Calcd for $C_{21}H_{30}N_2O_3$ C, 70.36; H, 8.44; N, 7.81; Found C, 70.29; H, 8.51; N, 7.78.

(6). Ethyl 1-Cyclohexyl-2,5-dihydro-5-oxo-2-phenyl-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (5abab): 95% yield, white solid, mp = 140−142 °C; IR (KBr) ν_{max} = 3261, 3030, 2932, 2855, 1696, 1632, 1597, 1536, 1498, 1452, 1366, 1211, 1121, 1076, 752, 695 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ = 8.09(s, 1H), 7.33−7.09(m, 10H), 5.20(s, 1H), 3.94−3.89(m, 2H), 3.71−3.65(m, 1H), 1.76−1.06(m, 10H), 0.91(t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 164.8, 164.4, 142.7, 138.9, 138.0, 128.3, 128.2, 128.1, 128.0, 124.4, 122.6, 109.7, 61.8, 59.8, 54.3, 30.9, 30.6, 26.0, 25.8, 25.2, 13.8 ppm; MS (ESI) *m/z* 405(M + H^+, 100), 359 (95); Anal. Calcd for $C_{25}H_{28}N_2O_3$ C, 74.23; H, 6.98; N, 6.93; Found C, 74.28; H, 6.87; N, 6.97.

(7). Ethyl 1-Benzyl-2,5-dihydro-5-oxo-2-phenyl-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (5abfb): 87% yield, yellow oil; IR (KBr) ν_{max} = 3274, 3030, 2926, 1702, 1629, 1597, 11495, 1454, 1350, 1211, 752, 698 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ = 8.28(s, 1H), 7.36−7.13(m, 15H), 5.14(d, *J* = 14.8 Hz, 1H), 4.96(s, 1H), 3.98−3.86(m, 2H), 3.53(d, *J* = 14.8 Hz, 1H), 0.91(t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 164.6(The ester and amide carbonyl carbon peaks overlap.), 143.0, 138.6, 136.6, 136.4, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.7, 124.6, 122.7, 109.6, 61.2, 59.9, 44.1, 13.7 ppm; MS (ESI) *m/z* 413(M + H^+, 100), 367 (35); Anal. Calcd for $C_{26}H_{24}N_2O_3$ C, 75.71; H, 5.86; N, 6.79; Found C, 75.83; H, 5.89; N, 6.81.

(8). Ethyl 1-Butyl-2,5-dihydro-5-oxo-2-phenyl-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (5abkb): 89% yield, white solid, mp = 101−102 °C; IR (KBr) ν_{max} = 3264, 3062, 2959, 2931, 2781, 1702, 1630, 1597, 1539, 1496, 1210, 11146, 752, 700 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ = 8.20(s, 1H), 7.36−7.10(m, 10H), 5.17(s, 1H), 3.98−3.93(m, 2H), 3.73−3.70(m, 1H), 2.66−2.65(m, 1H), 1.48−1.43(m, 2H), 1.28−1.23(m, 2H), 0.94(t, *J* = 7.2 Hz, 3H), 0.86(t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 164.7, 164.5, 143.0, 138.8, 136.8, 128.6, 128.4, 128.3, 127.8, 124.5, 122.6, 109.2, 62.2, 59.9, 40.3, 30.2, 20.0, 13.8, 13.7 ppm; MS (ESI) *m/z* 379(M + H^+, 100), 333 (75); Anal. Calcd for $C_{23}H_{26}N_2O_3$ C, 72.99; H, 6.92; N, 7.40; Found C, 72.79; H, 6.86; N, 7.35.

(9). Ethyl 2,5-Dihydro-1-(2-hydroxyethyl)-5-oxo-2-phenyl-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (5ablb): 94% yield, yellow solid, mp = 117−118 °C; IR (KBr) ν_{max} = 3445, 3199, 3058, 2980, 2911, 1702, 1627, 1590, 1539, 1493, 1442, 1374, 1290, 1221, 1095, 827, 754, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.22(s, 1H), 7.34−7.08(m, 10H), 5.28(s, 1H), 3.93(q, *J* = 7.2 Hz, 2H), 3.69−3.56(m, 3H), 3.15(brs, 1H), 2.94−2.88(m, 1H), 0.92(t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 164.4, 142.7, 138.7, 136.4, 128.6, 128.43, 128.37, 127.8, 124.5, 122.6, 110.1, 63.5, 60.9, 59.95, 44.1, 13.8 ppm; MS (ESI) *m/z* 367(M + H^+, 100), 321 (35); Anal. Calcd for $C_{21}H_{22}N_2O_4$ C, 68.84; H, 6.05; N, 7.65; Found C, 68.76; H, 6.13; N, 7.58.

(10). Ethyl 4-(*p*-Tolylamino)-2,5-dihydro-1-(2-hydroxyethyl)-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (5aclb): 92% yield, lemon solid, mp = 127−128 °C; IR (KBr) ν_{max} = 3509, 3321, 2926, 1691, 1628, 1516, 1443, 1370, 1283, 1212, 1077, 811, 760, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.20(s, 1H), 7.33−7.01(m, 9H), 5.26(s, 1H), 3.96−3.90(m, 2H), 3.67−3.56(m, 3H), 3.25(brs, 1H), 2.91−2.88(m, 1H), 2.30(s, 3H), 0.92(t, *J* = 7.2 Hz, 3H)ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.9, 164.5, 143.2, 136.6, 136.0, 134.3, 129.0, 128.6, 128.4, 127.9, 122.9, 109.2, 63.4, 60.9, 59.9, 44.0, 20.9, 13.8 ppm; MS (ESI) *m/z* 381(M + H^+, 100), 335 (53); Anal. Calcd for $C_{22}H_{24}N_2O_4$ C, 69.46; H, 6.36; N, 7.36; Found C, 69.53; H, 6.41; N, 7.39.

(11). Ethyl 4-(4-Fluorophenylamino)-1-benzyl-2,5-dihydro-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (5adfb): 89% yield, yellow solid, mp = 174−176 °C; IR (KBr) ν_{max} = 3159, 2978, 2917, 1677,1471, 1412, 1365, 1303, 1218, 1082, 772, 698 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ =

7.35−7.10(m, 10H), 5.19(d, J = 14.8 Hz, 1H), 4.88−4.84(m, 5H), 4.08−4.03(m, 2H), 3.54(d, J = 14.8 Hz, 1H), 1.05(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR(100 MHz, $CDCl_3$) δ = 165.2, 163.7, 157.4, 136.3, 134.5, 128.8, 128.5, 127.90, 127.86, 127.5, 122.3, 113.3, 61.0, 59.7, 44.0, 13.8 ppm; MS (ESI) m/z 431(M + H^+, 100), 385 (63); Anal. Calcd for $C_{26}H_{23}FN_2O_3$ C, 72.54; H, 5.39; F, 4.41; N, 6.51; Found C, 72.58; H, 5.43; F, 4.47; N, 6.60.

(12). Ethyl 4-(4-Nitrophenylamino)-1-cyclohexyl-2,5-dihydro-5-oxo-2-phenyl-1*H*-pyrrole-3-carboxylate (5aiab): 88% yield, yellow solid, mp = 160−161 °C; IR (KBr) ν_{max} = 3433, 3242, 3086, 2928, 2855, 1684, 1637, 1590, 1551, 1507, 1437, 1337, 1211 1112, 849, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.48 (s, 1H), 8.18−8.15(m, 2H), 7.35−7.22(m, 7H), 5.25(s, 1H), 4.02−3.96(m, 2H), 3.68(t, J = 3.2 Hz, 1H), 1.78−1.52(m, 7H), 1.19−1.12(m, 3H), 0.98 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.2, 163.9, 145.0, 143.0, 141.7, 136.7, 128.5, 128.4, 127.9, 124.5, 120.5, 115.0, 62.0, 60.5, 54.6, 30.8, 30.6, 25.9, 25.8, 25.1, 13.8 ppm; MS (ESI) m/z 450(M + H^+, 100), 404(60); Anal. Calcd for $C_{25}H_{27}N_3O_5$ C, 66.80; H, 6.05; N, 9.35; Found C, 66.83; H, 6.12; N, 9.23.

(13). Ethyl 2-(4-Fluorophenyl)-2,5-dihydro-1-(2-hydroxyethyl)-5-oxo-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (5ablc): 93%, yellow solid, mp = 134−135 °C; IR (KBr) ν_{max} = 3540, 3422, 3267, 3063, 2934, 1689, 1631, 1597, 1504, 1440, 1343, 1291, 1201, 1042, 844, 826, 757, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (brs, 1H), 7.28−6.98(m,9H),5.27(s,1H),3.96−3.91(m,2H),3.68−3.57(m, 3H), 2.91−2.86(m, 2H), 0.93(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.8, 164.3, 163.9, 161.4, 142.7, 138.6, 132.2, 129.6, 129.5, 128.4, 124.6, 122.6, 115.7, 115.5, 109.7, 62.7, 60.9, 60.0, 43.9, 13.8 ppm; MS (ESI) m/z 385(M + H^+, 100), 339 (30); Anal. Calcd for $C_{21}H_{21}FN_2O_4$ C, 65.62; H, 5.51; F, 4.94; N, 7.29; Found C, 65.69; H, 5.48; F, 4.97; N, 7.35.

(14). Ethyl 2,5-Dihydro-1-(2-hydroxyethyl)-2-(4-hydroxyphenyl)-5-oxo-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (5abld): 92% yield, yellow solid, mp = 117−119 °C; IR (KBr) ν_{max} = 3279, 2932, 1692, 1629, 1597, 1538,1496, 1074, 831, 754, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (s, 1H), 7.36−7.10(m, 9H), 5.33(s, 1H), 3.96(q, J = 7.2 Hz, 2H), 3.74−3.68(m, 1H), 3.63−3.57(m, 2H), 3.22(brs, 1H), 2.94−2.88(m, 1H), 0.94(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.9, 164.4, 142.7, 138.8, 136.5, 128.6, 128.4, 127.9, 124.4, 122.5, 110.1, 63.4, 60.8, 60.0, 43.9, 13.8 ppm; MS (ESI) m/z 383(M + H^+, 100), 337 (40); Anal. Calcd for $C_{21}H_{22}N_2O_5$ C, 65.96; H, 5.80; N, 7.33; Found C, 65.91; H, 5.76; N, 7.28.

(15). Ethyl 2,5-Dihydro-1-(2-hydroxyethyl)-2-methyl-5-oxo-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (5able): 98% yield, yellow oil; IR (KBr) ν_{max} = 3415, 3307, 2978, 2934, 1685, 1628, 1597,, 1536, 1498, 1438, 1373, 1283, 1226, 1078, 859, 766, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 1H), 7.26−7.22(m, 2H), 7.08−7.05(m, 3H),4.31(q,J=6.4Hz,1H),4.17−4.11(m,2H),3.80−3.71(m, 3H), 3.33−3.29(m, 1H), 2.80(brs, 1H), 1.41(d, J = 6.4 Hz, 3H), 1.15(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.4, 164.9, 142.8, 138.8, 128.3, 124.3, 122.5, 110.6, 61.3, 60.1, 55.2, 43.8, 17.9, 14.1 ppm; MS (ESI) m/z 305(M + H^+, 5), 359 (100); Anal. Calcd for $C_{16}H_{20}N_2O_4$ C, 63.14; H, 6.62; N, 9.20; Found C, 63.21; H, 6.71; N, 9.32.

(16). Ethyl 1-Cyclohexyl-2,5-dihydro-2-methyl-5-oxo-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (5abae): 92% yield, yellow solid, mp = 138−139 °C; IR (KBr) ν_{max} = 3449, 3282, 2928, 2858, 1673, 1643, 1595, 1540, 1496, 1373, 1261, 759, 662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00(s, 1H), 7.29−7.25(m, 2H), 7.10−7.06(m, 3H), 4.30(q, J = 6.4 Hz, 1H), 4.13(q, J = 7.2 Hz, 2H), 3.70−3.65(m, 1H), 1.91−1.31(m, 13H), 1.14(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.8, 164.1, 142.8, 139.1, 128.2, 124.2, 122.4, 109.5, 59.9, 54.2, 54.0, 31.1, 30.4, 26.1, 25.9, 25.4, 19.9, 14.1 ppm; MS (ESI) m/z 343(M + H^+, 30), 297(100); Anal. Calcd for $C_{20}H_{26}N_2O_3$ C, 70.15; H, 7.65; N, 8.18; Found C, 70.21; H, 7.59; N, 8.22.

(17). Ethyl 2-Butyl-2,5-dihydro-1-(2-hydroxyethyl)-5-oxo-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (5ablf): 60% yield, yellow oil; IR (KBr) ν_{max} = 3305, 2930, 1686, 1627, 1597, 1498, 1442, 1376, 1273, 1225, 1078, 751, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 1H), 7.25−7.21(m, 2H), 7.07−7.03(m, 3H), 4.45(t, J = 3.2 Hz, 1H), 4.17−4.09(m, 2H), 3.84−3.77(m, 1H), 3.72−3.69(m, 2H), 3.21−3.15(m, 1H), 2.17−2.08(m, 1H), 1.86−1.77(m, 1H), 1.27−1.20(m, 2H), 1.30(t, J=7.2 Hz, 3H), 0.98−0.88(m, 2H), 0.83(t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.1, 164.8, 143.2, 139.0, 128.3, 124.2, 122.3, 108.5, 61.0, 60.1, 58.6, 43.7, 28.2, 23.6, 22.5, 14.1, 13.9 ppm; MS (ESI) m/z 347(M + H^+, 100), 301(32); Anal. Calcd for $C_{19}H_{26}N_2O_4$ C, 65.87; H, 7.56; N, 8.09; Found C, 65.79; H, 7.61; N, 8.02.

(18). Methyl 1-Cyclohexyl-2,5-dihydro-5-oxo-2-phenyl-4-(phenylamino)-1*H*-pyrrole-3-carboxylate (5bbab): 92% yield, white solid, mp = 175.5−176.5 °C; IR (KBr): ν_{max} = 3341, 2932, 2854, 1770, 1697, 1631, 1596, 1539, 1452, 1373, 1273, 753, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (s, 1H), 7.33−7.09(m, 10H), 5.19(s, 1H), 3.69−3.63(m, 1H), 3.43(s, 3H), 1.79−1.48(m, 6H), 1.16−0.94(m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.8, 164.6, 142.8, 138.8, 137.9, 128.3, 128.2, 127.9, 124.6, 122.8, 109.2, 61.8, 54.3, 50.9, 30.9, 30.6, 26.0, 25.8, 25.2 ppm; MS (ESI) m/z 391(M + H^+, 100), 359(40); Anal. Calcd for $C_{24}H_{26}N_2O_3$ C, 73.82; H, 6.71; N, 7.17; Found C, 73.69; H, 6.83; N, 7.23.

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Supporting Information Available. Experimental procedures, crystallographic data for **4aab**, **5abab**, and **5accb**, spectroscopic data for **4abb**−**4bfb** and **5accb**−**bbab**, and copies of ^{1}H NMR and ^{13}C NMR spectra for **4abb**−**4bfb** and **5accb**−**5bbab**. This material is available free of charge via the Internet at http://pubs.acs.org.

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