A Synthesis of Functionalized Dihydro-1*H*-pyrroles from Nef-Isocyanide Adducts and Enamines

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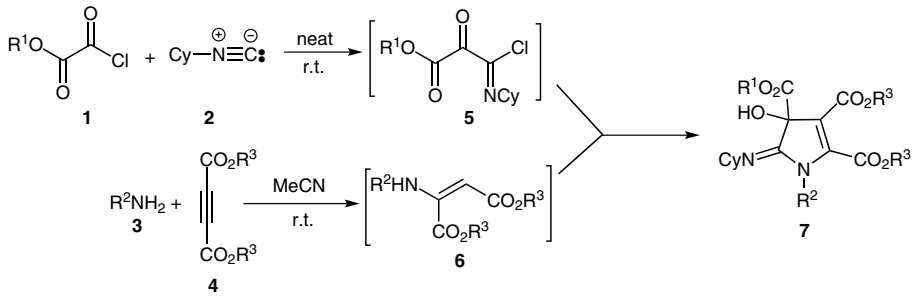
Abstract: α-Ketoimidoyl chlorides, obtained from α-addition of acyl chlorides onto alkyl isocyanides, are treated with enamines to afford 5-(alkylimino)-4-hydroxy-4,5-dihydro-1*H*-pyrrole-2,3,4-tricarboxylates and 2-(alkylimino)-3-hydroxy-2,3-dihydro-1*H*-pyrrole-3,4-dicarboxylates in good to excellent yields.

Key words: Nef-isocyanide adduct, enaminone, imidoyl chloride, pyrrole, chemoselective reaction

Nitrogen-containing heterocycles are of great importance in the pharmaceutical industry because they often exhibit interesting biological activities. Substituted pyrroles are important heterocycles with useful biological and physical properties.[1,2] For example, tetra- and penta-substituted pyrroles feature prominently in natural products, pharmaceuticals, agrochemicals, fluorescent dyes, and conducting polymers.[3,4] Thus, significant demand exists in drug discovery and other research programs for novel and structurally diverse pyrrole derivatives.

The unique properties of the isocyano group, which may function as both an electrophile and as a nucleophile, have turned these compounds into useful reagents for organic synthesis.[5] Beyond the classical multicomponent reactions,[6] the most important applications of isocyanides are in the synthesis of various heterocycles.[7] A number of isocyanide reactions have seen their potential largely unexplored, and this is probably the case with the Nef reaction; the α-addition of acyl chlorides onto isocyanides forming imidoyl chlorides.[8] Nef-type reactions could also be obtained with highly electrophilic acid derivatives such as trifluoroacetic anhydride[9] or acyl bromides, which are more reactive than the corresponding chlorides.[10,11] Intramolecular trapping of the Nef adducts with various nucleophiles have been reported.[12–15] The scope of the Nef reaction could be further extended by adding external trapping agents that are able to induce new cascade reactions.

One of the main problems of the Nef isocyanide reaction is the selectivity of the nucleophilic attack on the Nef adducts; either the imidoyl or the carbonyl function can be attacked, which may lead to isocyanide elimination. We anticipated that the use of the α-carboalkoxy substituent would make the ketone more electrophilic and reduce the chance of elimination of the isocyanide and consequent formation of trivial acylation derivatives. This modification was found to be successful. Thus, as part of our current studies on the development of new routes to heterocyclic systems,[16–18] we report a simple synthesis of functionalized 4,5-dihydro-1*H*-pyrroles from the reaction



1–4, 7	R^1	R^2	R^3	Yield (%) of 7
a	Me	Bn	Me	70
b	Me	4-$MeC_6H_4CH_2$	Me	72
c	Me	4-$MeOC_6H_4CH_2$	Me	70
d	Et	Bn	Me	76
e	Et	4-$MeC_6H_4CH_2$	Me	65
f	Et	allyl	Me	65
g	Et	*n*-Bu	Me	70
h	Et	Bn	Et	50

Scheme 1 Synthesis of compounds **7**

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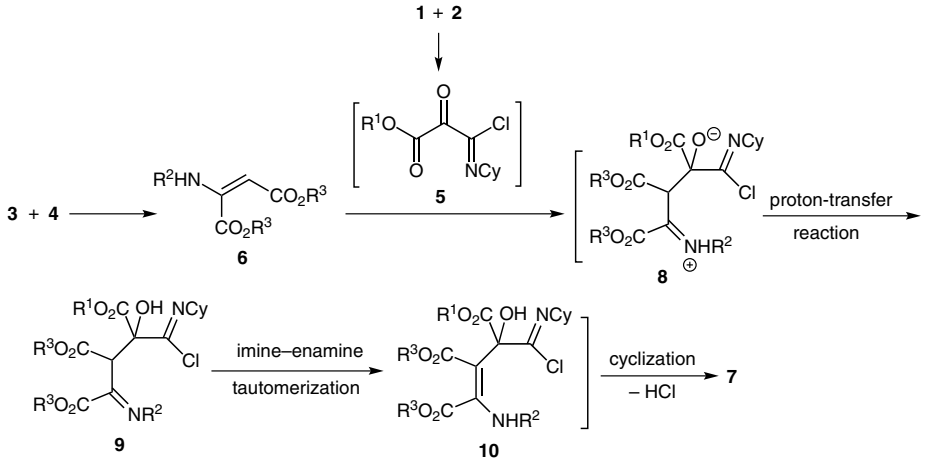
between α-ketoimidoyl chlorides and enaminones. As a result, the Nef-isocyanide adducts **5**, obtained from alkyl chloroglyoxalates **1** and alkyl isocyanides **2**, react with enaminones **6** (prepared from alkyl amines **3** and dialkyl acetylenedicarboxylates **4** at room temperature, in anhydrous MeCN), to afford trialkyl 1-alkyl-5-(alkylimino)-4,5-dihydro-4-hydroxy-1*H*-pyrrole-2,3,4-tricarboxylates **7** in 50–76% yields (Scheme 1).[19]

The structures of compounds **7a**–**h** were deduced from their IR and ^{1}H and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **7a** exhibited three single sharp lines that were readily recognized as arising from methoxy (δ = 3.60, 3.65 and 3.75 ppm) protons, together with characteristic multiplets for cyclohexyl, aryl, and benzylic protons. A fairly broad single peak was observed for the OH (δ = 4.16 ppm) proton. The ^{1}H-decoupled ^{13}C NMR spectrum of **7a** showed 21 distinct resonances, in agreement with the proposed structure. The mass spectrum of **7a** displayed the molecular ion peak (*m*/*z* 444). The ^{1}H and ^{13}C NMR spectra of **7b**–**h** are similar to those for **7a**, except for the alkyl and aryl groups.

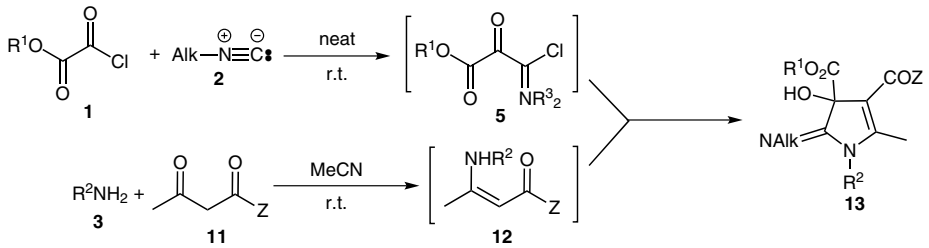
A plausible pathway may be advanced to rationalize product formation (Scheme 2). Presumably, the Nef-isocyanide adduct **5**, formed from acid chloride **1** and isocyanide **2**, is attacked by enaminoester **6** in a chemoselective manner, to furnish intermediate **8**, which undergoes an intramolecular proton-transfer reaction to afford **9**. This intermediate is converted into **7** by imine-enamine tautomerization and cyclization reaction.

To extend our knowledge of this transformation, we performed the reaction between Nef-isocyanide adduct **5** and enamines **12** derived from 2,4-pentanedione and β-keto ester **11** and primary alkylamines **3**. These reactions led to the formation of diethyl 1-benzyl-2-(alkylimino)-3-hydroxy-5-methyl-2,3-dihydro-1*H*-pyrrole-3,4-dicarboxylates (**13a**–**c**) and alkyl 4-acetyl-1-alkyl-2-(alkylimino)-3-hydroxy-5-methyl-2,3-dihydro-1*H*-pyrrole-3-carboxylates (**13d**–**i**) in 52–82% yields (Scheme 3). Compounds **13** were again fully characterized with their IR, ^{1}H NMR and ^{13}C NMR spectra.[19]

In conclusion, Nef-isocyanide adducts are employed in sequential reactions with enamines to afford functional-



Scheme 2 A plausible mechanism for the formation of compounds **7**



1,2,3,11,13	R^1	Alk	R^2	Z	Yield (%) of **13**
a	Et	Cy	Bn	OEt	78
b	Et	*t*-Bu	Bn	OEt	65
c	Et	1,1,3,3-tetramethylbutyl	Bn	OEt	52
d	Et	Cy	Bn	Me	75
e	Et	*t*-Bu	Bn	Me	70
f	Et	Cy	2-ClC$_6$H$_4$CH$_2$	Me	74
g	Et	Cy	Bu	Me	78
h	Me	Cy	Bn	Me	80
i	Et	Cy	4-MeC$_6$H$_4$CH$_2$	Me	82

Scheme 3 Synthesis of compounds **13**

ized 4-hydroxy-4,5-dihydro-1*H*-pyrroles and 3-hydroxy-2,3-dihydro-1*H*-pyrrole in a chemoselective manner, in good yields. Due to the presence of transformable functionalities in these products they are potentially valuable for further synthetic manipulations.

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(19) **Synthesis of 7 and 13; General Procedure:** To a magnetically stirred solution of alkylamine **3** (1 mmol) in anhydrous MeCN (2 mL), was added either dialkyl acetylenedicarboxylate **4** (1 mmol) or 1,3-dicarbonyl compound **11** (1 mmol). This solution was added to α-ketoimidoyl chloride **5** [obtained from the alkyl chloroglyoxalate **1** (1 mmol) and alkyl isocyanide **2** (1 mmol) at room temperature]. After completion of the reaction [ca. 6 h; reaction monitored by TLC (EtOAc–hexane, 1:5)], the cream precipitate was separated, washed with hexane–Et_2O, and neutralized with Et_3N in a mixture of H_2O–MeOH to the give product.
Trimethyl 1-Benzyl-5-(cyclohexylimino)-4,5-dihydro-4-hydroxy-1*H*-pyrrole-2,3,4-tricarboxylate (7a): Yield: 0.31 g (70%); cream powder; mp 124–126 °C. IR (KBr): 3431 (OH), 1749 (C=O), 1675 (C=N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = δ = 1.22–1.93 (m, 10 H, 5 CH_2), 3.05–3.10 (m, 1 H, CH), 3.60 (s, 3 H, MeO), 3.65 (s, 3 H, MeO), 3.75 (s, 3 H, MeO), 4.16 (br s, 1 H, OH), 4.63 (d, ^2J = 15.6 Hz, 1 H, CH_2N), 4.80 (d, ^2J = 15.6 Hz, 1 H, CH_2N), 7.17 (t, ^3J = 7.0 Hz, 2 H, 2 CH), 7.20 (t, ^3J = 7.0 Hz, 1 H, CH), 7.24 (d, ^3J = 7.0 Hz, 2 H, 2 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.9 (CH_2), 24.0 (CH_2), 25.5 (CH_2), 34.0 (CH_2), 34.5 (CH_2), 45.2 (CH), 51.2 (MeO), 52.8 (MeO), 53.3 (MeO), 57.5 (CH_2N), 77.3 (C-OH), 104.3 (C), 127.3 (2 CH), 128.1 (2 CH), 128.7 (CH), 136.4 (C), 150.6 (C), 152.8 (C=N), 161.6 (C=O), 161.9 (C=O), 170.7 (C=O). MS (EI): *m*/*z* (%) = 444 (2) $[M]^+$, 385 (48), 353 (65), 293 (15), 271 (30), 211 (35), 151 (5), 91 (100), 55 (15). Anal. Calcd. for $C_{23}H_{28}N_2O_7$ (444.19): C, 62.15; H, 6.35; N, 6.30. Found: C, 62.11; H, 6.27; N, 6.34.
Trimethyl 5-(Cyclohexylimino)-4,5-dihydro-4-hydroxy-1-(4-methylbenzyl)-1*H*-pyrrole-2,3,4-tricarboxylate (7b): Yield: 0.33 g (72%); cream powder; mp 114–116 °C. IR (KBr): 3430 (OH), 1751 (C=O), 1663 (C=N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21–1.72 (m, 10 H, 5 CH_2), 2.29 (s, 3 H, Me), 2.78 (br s, 1 H, OH), 3.63 (s, 3 H, MeO), 3.71 (s, 3 H, MeO), 3.77 (s, 3 H, MeO), 4.10–4.25 (m, 1 H, CH), 4.62 (d, ^2J = 15.5 Hz, 1 H, CH_2N), 4.78 (d, ^2J = 15.5 Hz, 1 H, CH_2N), 6.90–7.20 (m, 5 H, 5 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.9 (Me), 24.0 (2 CH_2), 25.5 (CH_2), 34.0 (CH_2), 34.5 (CH_2), 45.0 (CH), 51.2 (MeO), 52.8 (MeO), 53.3 (MeO), 57.5 (CH_2N), 77.2 (C-OH), 104.2 (C), 127.3 (2 CH), 128.9 (2 CH), 133.4 (C), 137.0 (C), 150.6 (C), 152.8 (C=N), 161.6 (C=O), 162.0 (C=O), 170.8 (C=O). MS (EI): *m*/*z* (%) = 458 (2) $[M]^+$, 399 (48), 367 (40), 293 (12), 239 (10), 211 (28), 151 (10), 105 (100), 79 (12), 55 (12). Anal. Calcd. for $C_{24}H_{30}N_2O_7$ (458.21): C, 62.87; H, 6.59; N, 6.11. Found: C, 62.81; H, 6.62; N, 6.19.
Trimethyl 5-(Cyclohexylimino)-4,5-dihydro-4-hydroxy-1-(4-methyloxybenzyl)-1*H*-pyrrole-2,3,4-tricarboxylate (7c): Yield: 0.33 g (70%); cream powder; mp 96–98 °C. IR (KBr): 3429 (OH), 1747 (C=O), 1664 (C=N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.24–1.74 (m, 10 H, 5 CH_2), 2.28 (s, 3 H, Me), 3.63 (s, 3 H, MeO), 3.73 (s, 3 H, MeO), 3.77 (s, 3 H, MeO), 3.78 (s, 3 H, MeO), 3.64–3.68 (m, 1 H, CH), 4.62 (d, ^2J = 15.4 Hz, 1 H, CH_2N), 4.64 (br s, 1 H, OH), 4.75 (d, ^2J = 15.4 Hz, 1 H, CH_2N), 6.80 (d, ^3J = 8.6 Hz, 2 H, 2 CH), 7.13 (d, ^3J = 8.6 Hz, 2 H, 2 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 24.1 (CH_2), 24.2 (CH_2), 25.7 (CH_2), 34.2 (CH_2), 34.7 (CH_2), 44.9 (CH), 51.4 (MeO), 53.0 (MeO), 53.5 (MeO), 55.2 (MeO), 57.7 (CH_2N), 76.6 (C-OH), 104.3 (C), 113.7 (2 CH), 128.7 (C), 128.8 (2 CH), 150.8 (C), 153.0 (C), 159.9 (C=N), 161.8 (C=O), 162.1 (C=O), 170.9 (C=O). MS (EI): *m*/*z* (%) = 474 (10) $[M]^+$, 415 (18), 383 (9), 293 (6), 211 (12), 136 (7), 151 (10), 121 (100), 83 (9), 55 (15). Anal. Calcd. for $C_{24}H_{30}N_2O_8$ (474.2): C, 60.57; H, 6.37; N, 5.90. Found: C, 60.68; H, 6.25; N, 5.83.
4-Ethyl 2,3-Dimethyl 1-benzyl-5-(cyclohexylimino)-4,5-dihydro-4-hydroxy-1*H*-pyrrole-2,3,4-tricarboxylate (7d): Yield: 0.35 g (76%); cream powder; mp 105–107 °C. IR (KBr): 3431 (OH), 1750 (C=O), 1667 (C=N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.18–1.75 (m, 10 H, 5 CH_2), 1.24 (t, ^3J = 7.0 Hz, 3 H, Me), 3.62 (s, 3 H, MeO), 3.69 (s, 3 H, MeO), 3.86–3.88 (m, 1 H, CH), 4.21 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 4.57 (d, ^2J = 15.8 Hz, 1 H, CH of CH_2N), 4.88 (br s, 1 H, OH), 5.91 (d, ^2J = 15.8 Hz, 1 H, CH of CH_2N), 7.23–7.29 (m, 5 H, 5 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.6 (Me), 23.5 (CH_2), 23.5 (CH_2), 25.0 (CH_2), 33.5 (CH_2), 34.0 (CH_2), 44.3 (CH), 49.9 (MeO), 51.7 (MeO), 56.8 (OCH_2), 61.6 (CH_2N), 76.6 (C-OH), 105.2 (C), 126.6 (2 CH), 126.7 (CH), 127.5 (2 CH), 136.3 (C), 150.4 (C), 154.8 (C=N), 161.4 (C=O), 161.8 (C=O), 169.1 (C=O). MS (EI): *m*/*z* (%) = 458 (2) $[M]^+$, 385 (60), 353 (80), 307 (10), 271 (37), 225 (17), 181 (10), 126 (12), 91 (100), 55 (18). Anal. Calcd. for $C_{24}H_{30}N_2O_7$ (458.21): C, 62.87; H, 6.59; N, 6.11. Found: C, 62.74; H, 6.27; N, 6.02.
4-Ethyl 2,3-Dimethyl 5-(cyclohexylimino)-4,5-dihydro-4-hydroxy-1-(4-methylbenzyl)-1*H*-pyrrole-2,3,4-tricarboxylate (7e): Yield: 0.31 g (65%); cream powder; mp 96–98 °C. IR (KBr): 3426 (OH), 1753 (C=O), 1665 (C=N) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.03 (t, ^3J = 7.1 Hz, 3 H, Me), 1.21–1.73 (m, 10 H, 5 CH_2), 2.27 (s, 3 H, Me), 3.60–3.70 (m, 1 H, CH), 3.61 (s, 3 H, MeO), 3.68 (s, 3 H, MeO), 4.21 (br s, 1 H, OH), 4.26 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 4.52 (d, ^2J = 15.6 Hz, 1 H, CH_2N), 4.86 (d, ^2J =

15.6 Hz, 1 H, CH_2N), 7.03 (d, ^3J = 7.9 Hz, 2 H, 2 CH), 7.07 (d, ^3J = 7.9 Hz, 2 H, 2 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (Me), 21.0 (Me), 24.1 (CH_2), 24.2 (CH_2), 25.7 (CH_2), 34.2 (CH_2), 34.7 (CH_2), 45.0 (CH), 51.2 (MeO), 52.8 (MeO), 57.6 (OCH_2), 62.8 (CH_2N), 76.9 (C-OH), 104.6 (C), 127.4 (2 CH), 128.9 (2 CH), 133.6 (C), 137.0 (C), 150.7 (C), 153.1 (C=N), 161.8 (C=O), 162.0 (C=O), 170.3 (C=O). MS (EI): *m*/*z* (%) = 472 (2) $[M]^+$, 399 (34), 367 (34), 307 (10), 285 (14), 225 (15), 181 (5), 143 (4), 105 (100), 55 (12). Anal. Calcd. for $C_{25}H_{32}N_2O_7$ (472.22): C, 63.54; H, 6.83; N, 5.93. Found: C, 63.65; H, 6.73; N, 5.85.

4-Ethyl 2,3-Dimethyl 1-allyl-5-(cyclohexylimino)-4,5-dihydro-4-hydroxy-1*H*-pyrrole-2,3,4-tricarboxylate (7f): Yield: 0.26 g (65%); cream powder; mp 82–84 °C. IR (KBr): 3430 (OH), 1753 (C=O), 1666 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 (t, ^3J = 7.1 Hz, 3 H, Me), 1.23–1.68 (m, 10 H, 5 CH_2), 3.54–3.58 (m, 1 H, CH), 3.60 (s, 3 H, MeO), 3.84 (s, 3 H, MeO), 4.00–4.04 (m, 1 H, CH_2N), 4.06–4.08 (br s, 1 H, OH), 4.13–4.17 (m, 1 H, CH_2N), 4.22 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 5.05 (d, ^3J = 10.3 Hz, 1 H, H_2C=), 5.08 (d, ^2J = 17.1 Hz, 1 H, H_2C=), 5.65–5.72 (m, 1 H, =CH-). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8 (Me), 23.9 (CH_2), 24.0 (CH_2), 25.5 (CH_2), 34.0 (CH_2), 34.5 (CH_2), 44.0 (CH), 51.1 (MeO), 52.8 (MeO), 57.5 (OCH_2), 62.7 (CH_2N), 77.2 (C-OH), 104.2 (C), 116.8 (H_2C=), 131.7 (=CH-), 150.7 (C), 152.4 (C=N), 161.6 (C=O), 161.9 (C=O), 170.2 (C=O). MS (EI): *m*/*z* (%) = 408 (2) $[M]^+$, 355 (20), 303 (100), 253 (80), 221 (95), 166 (28), 126 (24), 105 (8), 55 (25). Anal. Calcd. for $C_{20}H_{28}N_2O_7$ (408.19): C, 58.81; H, 6.91; N, 6.86. Found: C, 58.71; H, 6.82; N, 6.83.

4-Ethyl 2,3-Dimethyl 1-butyl-5-(cyclohexylimino)-4,5-dihydro-4-hydroxy-1*H*-pyrrole-2,3,4-tricarboxylate (7g): Yield: 0.30 g (70%); cream powder; mp 94–96 °C. IR (KBr): 3414 (OH), 1753 (C=O), 1660 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (t, ^3J = 7.3 Hz, 3 H, Me), 1.15–1.70 (m, 14 H, 7 CH_2), 1.21 (t, ^3J = 7.1 Hz, 3 H, CH_3), 3.32–3.37 (m, 1 H, CH), 3.86–3.55 (d, ^3J = 7.1 Hz, 2 H, CH_2N), 3.62 (s, 3 H, MeO), 3.91 (s, 3 H, MeO), 4.10 (br s, 1 H, OH), 4.20 (q, ^3J = 7.1 Hz, 2 H, OCH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6 (Me), 13.9 (Me), 19.5 (CH_2), 24.0 (CH_2), 24.1 (CH_2), 25.7 (CH_2), 30.3 (CH_2), 34.2 (CH_2), 34.7 (CH_2), 42.2 (CH), 51.1 (MeO), 53.1 (MeO), 57.7 (OCH_2), 62.7 (CH_2N), 77.3 (C-OH), 103.5 (C), 151.6 (C), 153.0 (C=N), 162.0 (C=O), 162.1 (C=O), 170.4 (C=O). MS (EI): *m*/*z* (%) = 424 (2) $[M]^+$, 351 (33), 319 (100), 287 (10), 263 (10), 237 (10), 182 (14), 142 (8), 126 (5), 57 (15). Anal. Calcd. for $C_{21}H_{32}N_2O_7$ (424.22): C, 59.42; H, 7.60; N, 6.60. Found: C, 59.46; H, 7.68; N, 6.72.

Triethyl 1-Benzyl-5-(cyclohexylimino)-4,5-dihydro-4-hydroxy-1*H*-pyrrole-2,3,4-tricarboxylate (7h): Yield: 0.25 g (50%); cream powder; mp 80–82 °C. IR (KBr): 3430 (OH), 1733 (C=O), 1672 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (t, ^3J = 7.1 Hz, 3 H, Me), 1.19 (t, ^3J = 7.1 Hz, 3 H, Me), 1.26 (t, ^3J = 7.1 Hz, 3 H, Me), 1.25–1.89 (m, 10 H, 5 CH_2), 3.60–3.66 (m, 1 H, CH), 4.11 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 4.15 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 4.23 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 4.57 (br s, 1 H, OH), 4.63 (d, ^2J = 15.8 Hz, 1 H, CH_2N), 4.90 (d, ^2J = 15.8 Hz, 1 H, CH_2N), 7.22–7.26 (m, 5 H, 5 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.0 (Me), 15.4 (Me), 15.6 (Me), 25.5 (CH_2), 25.6 (CH_2), 27.1 (CH_2), 35.6 (CH_2), 36.2 (CH_2), 46.6 (CH), 59.1 (OCH_2), 61.4 (OCH_2), 63.9 (OCH_2), 64.3 (CH_2N), 78.1 (C-OH), 105.9 (C), 128.7 (2 CH), 128.8 (2 CH), 129.7 (CH), 138.2 (C), 152.1 (C), 154.5 (C=N), 162.8 (C=O), 163.1 (C=O), 171.9 (C=O). MS (EI): *m*/*z* (%) = 486 (2) $[M]^+$, 413 (2), 367 (4), 299 (15), 207 (18), 178 (8), 105 (10), 91 (100), 77 (5), 52 (4). Anal. Calcd. for $C_{26}H_{34}N_2O_7$ (486.24): C, 64.18; H, 7.04; N, 5.76. Found: C, 64.12; H, 6.98; N, 5.73.

Diethyl 1-Benzyl-2-(cyclohexylimino)-2,3-dihydro-3-hydroxy-5-methyl-1*H*-pyrrole-3,4-dicarboxylate (13a): Yield: 0.33 g (78%); colorless solid; mp 85–87 °C. IR (KBr): 3357 (OH), 1729 (C=O), 1641 (C=O), 1604 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.20 –1.80 (m, 10 H, 5 CH_2), 1.24 (t, ^3J = 7.1 Hz, 3 H, Me), 1.30 (t, ^3J = 7.1 Hz, 3 H, Me), 2.31 (s, 3 H, Me), 2.29 (s, 3 H, Me), 3.63–3.72 (m, 1 H, CH), 4.13 (br s, 1 H, OH), 4.21 (m, 2 H, OCH_2), 4.27 (m, 2 H, OCH_2), 4.64 (d, ^2J = 16.1 Hz, 1 H, CH_2N), 5.05 (d, ^2J = 16.1 Hz, 1 H, CH_2N), 7.15–7.30 (m, 5 H, 5 CH of aryl). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.8 (Me), 14.1 (Me), 14.3 (Me), 24.3 (2 CH_2), 25.7 (CH_2), 34.3 (CH_2), 34.7 (CH_2), 43.8 (CH), 57.4 (OCH_2), 59.3 (OCH_2), 62.4 (CH_2N), 82.0 (C-OH), 103.6 (C), 126.4 (CH), 127.1 (CH), 128.5 (CH), 137.5 (CH), 154.2 (C), 160.6 (C=N), 163.8 (C=O), 171.5 (C=O). MS (EI): *m*/*z* (%) = 428 (2) $[M]^+$, 355 (72), 309 (100), 283 (12), 227 (60), 200 (10), 132 (19), 91 (94), 69 (54), 55 (51). Anal. Calcd. for $C_{24}H_{32}N_2O_5$ (428.23): C, 67.27; H, 7.53; N, 6.54. Found: C, 67.22; H, 7.46; N, 6.48.

Diethyl 1-Benzyl-2-(*tert*-butylimino)-2,3-dihydro-3-hydroxy-5-methyl-1*H*-pyrrole-3,4-dicarboxylate (13b): Yield: 0.26 g (65%); colorless crystals; mp 80–82 °C. IR (KBr): 3373 (OH), 1749 (C=O), 1656 (C=O), 1612 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, ^3J = 7.1 Hz, 3 H, Me), 1.23 (t, ^3J = 7.1 Hz, 3 H, Me), 1.24 (s, 9 H, CMe_3), 2.35 (s, 3 H, Me), 4.10–4.28 (m, 4 H, 2 OCH_2), 4.43 (br s, 1 H, OH), 4.58 (d, ^2J = 15.8 Hz, 1 H, CH_2N), 5.10–5.19 (d, ^2J = 15.8 Hz, 1 H, CH_2N), 7.20–7.35 (m, 5 H, 5 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.2 (Me), 14.0 (Me), 14.4 (Me), 31.0 (CMe_3), 51.9 (CMe_3), 59.5 (OCH_2), 62.2 (OCH_2), 62.5 (CH_2N), 77.9 (C-OH), 102.1 (C), 126.6 (CH), 127.1 (CH), 128.5 (CH), 138.5 (CH), 160.1 (C), 161.2 (C=N), 164.5 (C=O), 172.0 (C=O). MS (EI): *m*/*z* (%) = 402 (10) $[M]^+$, 329 (74), 283 (79), 227 (100), 181 (22), 131 (28), 91 (83), 57 (55). Anal. Calcd. for $C_{22}H_{30}N_2O_5$ (402.22): C, 65.65; H, 7.51; N, 6.96. Found: C, 65.71; H, 7.62; N, 7.03.

Diethyl 1-Benzyl-2,3-dihydro-3-hydroxy-5-methyl-2-(1,1,3,3-tetramethylbutylimino)-1*H*-pyrrole-3,4-dicarboxylate (13c): Yield: 0.24 g (52%); yellow oil. IR (KBr): 3393 (OH), 1743 (C=O), 1676 (C=O), 1608 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (s, 3 H, CMe_2), 1.27 (t, ^3J = 7.1 Hz, 3 H, Me), 0.98 (s, 3 H, CMe_2), 1.23 (m, 3 H, Me), 1.25 (s, 9 H, CMe_3), 1.26 (m, 3 H, Me), 1.40 (d, ^2J = 12.1 Hz, 1 H, CH_2), 1.43 (d, ^2J = 12.1 Hz, 1 H, CH_2), 1.90 (s, 3 H, Me), 4.08 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 4.12 (br s, 1 H, OH), 4.20 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 4.58 (d, ^3J = 16.4 Hz, 1 H, CH_2N), 5.22 (d, ^3J = 16.4 Hz, 1 H, CH_2N), 7.15–7.35 (m, 5 H, 5 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.2 (Me), 14.1 (Me), 14.6 (Me), 29.7 (CMe_3), 31.4 (CMe_2), 31.6 (CMe_2), 31.9 (CH_2), 51.8 (CMe_3), 55.8 (CMe_2), 58.6 (OCH_2), 59.2 (OCH_2), 62.0 (CH_2N), 79.0 (C-OH), 103.1 (C), 126.2 (CH), 126.7 (CH), 127.3 (CH), 138.1 (CH), 160.0 (C), 161.7 (C=N), 164.2 (C=O), 171.3 (C=O). MS (EI): *m*/*z* (%) = 458 (5) $[M]^+$, 385 (11), 341 (14), 273 (24), 227 (31), 196 (27), 172 (26), 147 (37), 131 (22), 91 (100). Anal. Calcd. for $C_{26}H_{38}N_2O_5$ (458.28): C, 68.10; H, 8.35; N, 6.11. Found: C, 68.05; H, 8.29; N, 6.17.

Ethyl 4-Acetyl-1-benzyl-2-(cyclohexylimino)-2,3-dihydro-3-hydroxy-5-methyl-1*H*-pyrrole-3-carboxylate (13d): Yield: 0.29 g (75%); cream powder; mp 110–112 °C. IR (KBr): 3243 (OH), 1749 (C=O), 1686 (C=O), 1615 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15–1.75 (m, 10 H, 5 CH_2), 1.28 (t, ^3J = 7.2 Hz, 3 H, Me), 2.19 (s, 3 H, Me), 2.29 (s, 3 H, Me), 3.74–3.75 (m, 1 H, CH), 4.16–4.29 (m, 2 H, OCH_2), 4.40 (br s, 1 H, OH), 4.63 (d, ^2J = 16.2 Hz,

1 H, CH_2N), 5.13 (d, ^2J = 16.5 Hz, 1 H, CH_2N), 7.20 (d, ^3J = 7.2 Hz, 2 H, 2 CH), 7.24 (t, ^3J = 7.2 Hz, 1 H, CH), 7.28 (d, ^3J = 7.2 Hz, 2 H, 2 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8 (Me), 14.9 (Me), 25.0 (CH_2), 25.1 (CH_2), 26.6 (CH_2), 30.1 (Me), 35.1 (CH_2), 35.6 (CH_2), 44.8 (CH), 58.1 (OCH_2), 63.4 (CH_2N), 78.9 (C-OH), 116.6 (C), 127.3 (CH), 128.1 (CH), 129.5 (CH), 138.1 (CH), 155 (C), 160.1 (C=N), 172.5 (C=O), 191.9 (C=O). MS (EI): *m*/*z* (%) = 398 (2) $[M]^+$, 325 (100), 283 (4), 243 (45), 229 (10), 201 (12), 106 (15), 91 (96), 79 (14), 58 (45). Anal. Calcd. for $C_{23}H_{30}N_2O_4$ (398.22): C, 69.62; H, 8.06; N, 7.11. Found: C, 69.74; H, 8.14; N, 7.18.

Ethyl 4-Acetyl-1-benzyl-2-(*tert*-butylimino)-2,3-dihydro-3-hydroxy-5-methyl-1*H*-pyrrole-3-carboxylate (13e): Yield: 0.26 g (70%,); cream powder; mp 115–117 °C. IR (KBr): 3395 (OH), 1738 (C=O), 1687 (C=O), 1572 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (t, ^3J =7.1 Hz, 3 H, Me), 1.28 (s, 9 H, CMe_3), 2.21 (s, 3 H, Me), 2.29 (s, 3 H, Me), 3.70 (br s, 1 H, OH), 4.12–4.30 (m, 2 H, OCH_2), 4.58 (d, ^2J = 16.1 Hz, 1 H, CH_2N), 5.23 (d, ^2J = 16.1 Hz, 1 H, CH_2N), 7.22 (d, ^3J = 7.7 Hz, 2 H, 2 CH), 7.23 (d, ^3J = 7.7 Hz, 2 H, 2 CH), 7.28 (d, ^3J = 7.7 Hz, 2 H, 2 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (Me), 14.3 (Me), 29.4 (Me), 30.9 (CMe_3), 41.2 (CMe_3), 55.0 (OCH_2), 61.8 (CH_2N), 78.4 (C-OH), 114.2 (C), 126.4 (CH), 126.7 (CH), 126.9 (CH), 128.5 (CH), 137.6 (C), 149.8 (C), 158.9 (C=N), 171.1 (C=O), 190.9 (C=O). MS (EI): *m*/*z* (%) = 372 (22) $[M]^+$, 299 (25), 243 (100), 195 (40), 149 (23), 117 (38), 106 (98), 106 (70), 90 (98), 79 (18), 57 (35). Anal. Calcd. for $C_{21}H_{28}N_2O_4$ (372.2): C, 67.72; H, 7.58; N, 7.52. Found: C, 67.81; H, 7.64; N, 7.58.

Ethyl 4-Acetyl-1-(2-chlorobenzyl)-2-(cyclohexylimino)-2,3-dihydro-3-hydroxy-5-methyl-1*H*-pyrrole-3-carboxylate (13f): Yield: 0.32 g (74%); cream powder; mp 109–111 °C. IR (KBr): 3272 (OH), 1750 (C=O), 1651 (C=O), 1543 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11–1.97 (m, 10 H, 5 CH_2), 1.27 (d, ^3J =7.1 Hz, 3 H, Me), 2.18 (s, 3 H, Me), 2.24 (s, 3 H, Me), 3.74 (br s, 1 H, OH), 3.90–4.18 (m, 1 H, CH), 4.16–4.30 (m, 2 H, OCH_2), 4.74 (d, ^2J = 17.1 Hz, 1 H, CH_2N), 5.08 (d, ^2J = 17.1 Hz, 1 H, CH_2N), 7.09–7.36 (m, 4 H, 4CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7 (Me), 14.0 (Me), 23.7 (Me), 23.8 (CH_2), 25.2 (CH_2), 28.8 (Me), 33.7 (CH_2), 34.2 (CH_2), 41.2 (CH), 56.7 (OCH_2), 62.1 ((CH_2N), 77.5 (C-OH), 115.5 (C), 126.6 (CH), 126.7 (CH), 127.9 (CH), 129.0 (CH), 131.6 (C), 133.9 (C), 153.6 (C), 158.6 (C=N), 171.1 (C=O), 190.8 (C=O). MS (EI): *m*/*z* (%) = 432 (2) $[M]^+$, 359 (100), 301 (14), 277 (70), 228 (20), 148 (55), 127 (98), 106 (78), 89 (65), 77 (35), 55 (24). Anal. Calcd. for $C_{23}H_{29}ClN_2O_4$ (432.18): C, 63.81; H, 6.75; N, 6.47. Found: C, 63.89; H, 6.83; N, 6.5.

Ethyl 4-Acetyl-1-buyl-2-(cyclohexylimino)-2,3-dihydro-3-hydroxy-5-methyl-1*H*-pyrrole-3-carboxylate (13g): Yield: 0.28 g (78%); cream powder; mp 124–126 °C. IR (KBr): 3240 (OH), 1749 (C=O), 1661 (C=O), 1600 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.99 (t, ^3J = 7.2 Hz, 3 H, Me), 1.26 (t, ^3J = 7.2 Hz, 3 H, Me), 1.20–1.86 (m, 14 H, 7 CH_2), 2.33 (s, 3 H, Me), 2.58 (s, 3 H, Me), 3.54–3.70 (m, 1 H, CH), 3.93 (d, ^2J = 16.0 Hz, 1 H, CH_2N), 4.20 (br s, 1 H, OH), 4.28 (d, ^2J = 16.0 Hz, 1 H, CH_2N), 4.30–4.35 (m, 2 H, OCH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8 (Me), 14.9 (Me), 25.0 CH_2), 25.1 (CH_2), 26.6 (CH_2), 30.1 (Me), 35.1 (CH_2), 35.6 (CH_2), 44.8 (CH), 58.1 (OCH_2), 63.4 (CH_2N), 78.9 (C-OH), 116.6 (C), 127.3 (CH), 128.1 (CH), 129.5 (CH), 138.1 (CH), 155 (C), 160.1 (C=N), 172.5 (C=O), 191.9 (C=O). MS (EI): *m*/*z* (%) = 364 (2) $[M]^+$, 291 (100), 236 (10), 210 (96), 183 (10), 154 (15), 127 (10), 98 (20), 84 (18), 67 (25), 57 (59). Anal. Calcd. for $C_{20}H_{32}N_2O_4$ (364.24): C, 65.91; H, 8.85; N, 7.69. Found: C, 65.93; H, 8.89; N, 7.64.

Methyl 4-Acetyl-1-benzyl-2-(cyclohexylimino)-2,3-dihydro-3-hydroxy-5-methyl-1*H*-pyrrole-3-carboxylate (13h): Yield: 0.31 g (80%); cream powder; mp 98–100 °C. IR (KBr): 3279 (OH), 1737 (C=O), 1673 (C=O), 1566 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10–2.15 (m, 10 H, 5 CH_2), 1.96 (s, 3 H, Me), 2.26 (s, 3 H, Me), 3.74 (br s, 1 H, OH), 3.85 (s, 3 H, OMe), 3.92–4.08 (m, 1 H, CH), 5.08 (d, ^2J = 16.5 Hz, 1 H, CH_2N), 5.12 (d, ^2J = 16.5 Hz, 1 H, CH_2N), 7. 20–7.26 (m, 5 H, 5 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.7 (Me), 26.0 (CH_2), 26.1 (CH_2), 26.7 (CH_2), 31.2 (Me), 33.3 (CH_2), 33.4 (CH_2), 49.0 (CH), 56.1 (OCH_2), 59.1 (CH_2N), 83.0 (C-OH), 123.4 (C), 128.0 (CH), 126.7 (CH), 129.6 (CH), 129.0 (CH), 130.4 (C), 134.8 (C), 157.2 (C), 167.5 (C=N), 168.5 (C=O), 194.1 (C=O). MS (EI): *m*/*z* (%) = 384 (2) $[M]^+$, 291 (100), 229 (34), 209 (14), 164 (12), 127 (20), 99 (35), 83 (50), 70 (25), 55 (96). Anal. Calcd. for $C_{23}H_{30}N_2O_4$ (398.22): C, 69.32; H, 7.59; N, 7.03. Found: C, 69.33; H, 7.62; N, 6.64.

Ethyl 4-acetyl-2-(cyclohexylimino)-2,3-dihydro-3-hydroxy-5-methyl-1-(4-methylbenzyl)-1*H*-pyrrole-3-carboxylate (13i): Yield: 0.34 g (82%); cream powder; mp 124–126 °C. IR (KBr): 3250 (OH), 1748 (C=O), 1662 (C=O), 1610 (C=N) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15–2.07 (m, 10 H, 5 CH_2), 1.20 (t, ^3J =7.1 Hz, 3 H, Me), 2.22 (s, 3 H, Me), 2.26 (s, 3 H, Me), 2.33 (s, 3 H, Me), 3.64 (br s, 1 H, OH), 3.90–3.93 (m, 1 H, CH), 4.10–4.32 (m, 2 H, OCH_2), 4.89 (d, ^2J = 16.3 Hz, 1 H, CH_2N), 5.91 (d, ^2J = 16.3 Hz, 1 H, CH_2N), 7.03 (d, ^3J = 7.8 Hz, 2 H, 2 CH), 7.07 (d, ^3J = 7.8 Hz, 2 H, 2 CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.7 (Me), 15.3 (Me), 22.4 (Me), 25.7 (CH_2), 25.8 (CH_2), 31.1 (Me), 31.2 (CH_2), 32.2 (CH_2), 48.2 (CH), 59.0 (OCH_2), 65.1 (CH_2N), 82.9 (C-OH), 123.3 (C), 127.9 (CH), 130.8 (CH), 130.9 (C), 139.3 (C), 157.2 (C), 167.4 (C=N), 168.1 (C=O), 194.0 (C=O). MS (EI): *m*/*z* (%) = 412 (22) $[M]^+$, 339 (100), 297 (24), 257 (22), 204 (23), 120 (60), 105 (97), 84 (60), 67 (30), 56 (47). Anal. Calcd. for $C_{24}H_{32}N_2O_4$ (412.24): C, 69.88; H, 7.82; N, 6.79. Found: C, 69.82; H, 7.87; N, 6.72.

