Efficient One-Pot Synthesis of Polysubstituted Pyrroles

Alan R. Katritzky,*,‡ Tian-Bao Huang,‡ Michael V. Voronkov,‡,§ Mingyi Wang,‡ and Hartmuth Kolb§

Department of Chemistry, Center for Heterocyclic Compounds, University of Florida, Gainesville, Florida 32611-7200, and Coelacanth Corporation, 279 Princeton-Hightstown Road, East Windsor, New Jersey 08520

katritzky@chem.ufl.edu

Received July 31, 2000

Reactions of *N*-(benzotriazol-ylmethyl)thioamides **2a**−**e** and **3a**−**e** with various activated olefins gave the corresponding tri- and tetrasubstituted pyrroles in preparatively useful yields.

Polysubstituted pyrroles are common pharmacophores for numerous natural compounds including antibiotics and alkaloids.[1] Tetrasubstituted pyrroles are synthetic therapeutic agents with a wide spectrum of biological activity.[2a−d] The valuable and diverse biological properties of pyrroles make the development of efficient methods for the preparation of these compounds having a defined substitution pattern a focus of considerable synthetic effort.[3a−j]

Among various methods for the preparation of polysubstituted pyrroles,[1] 1,3-dipolar additions of acetylenes with azomethine ylides are the most widely used.[3e,4a−g] These methods are not always regioselective,[1,3e,4a−e] and the diversity of the desired pyrroles is limited by the small number of commercially available acetylenes. In our group, we previously prepared di- and trisubstituted pyrrole derivatives by 1,3-dipolar cycloaddition reactions of activated olefins with (i) *N*-(benzotriazol-ylmethyl) thioimidates RC(SMe)=NCH_2Bt,[3f] or (ii) benzotriazol-ylmethyl isocyanide $BtCH_2NC$,[3i] or (iii) benzotriazol-ylaryl-*N*-(arylmethylidene)aryl methanamine.[5] The presence of a benzotriazolyl group, together with the methylthio group as an additional leaving group in (i) or isonitrile group in (ii), advantageously allows for the highly regioselective cyclizations with disubstituted olefins, leading directly to the corresponding pyrroles. Since a wider variety of olefins is commercially available compared to that of acetylenes, this increases the potential diversity of the resulting polysubstituted pyrroles. We now extend this methodology to a one-pot preparation of tri- and tetrasubstituted pyrroles.

Discussion

The general one-pot sequence is depicted in Scheme 1. Thioamides **2a**−**e** and **3a**−**d** with a variety of R^1 and R^3 substituents are prepared from **1** via Mannich-type condensations in 90−96% yields.[3f,6a−c] Compounds **2a**−**e** and **3b**−**d** are crystalline, while **3a** was isolated as a sticky oil; none required column chromatography purification (Table 1). The compounds show a characteristic ^1H NMR signal in the 6.55−6.79 ppm range for the methylene protons of **2a**−**e** and in the 8.61−8.82 ppm range for the methine protons of **3a**−**d**.

2a−**e** and **3a**−**d** were treated with *t*-BuOK in THF at 0 °C, followed by the addition of MeI, and the corresponding *S*-methylthioamidates **4a**−**c**,**e** and **5a**,**c** were formed. The use of *n*-BuLi at −78 °C, LDA at −30 °C, or NaH at 0 °C, in THF, afforded inferior results. The intermediates **4a**−**c** and **5a**,**b** can be isolated and have significant shelf life. For compounds **2a**−**e** and **3a**−**d**, slow amide rotation results in two sets of carbon and proton signals in the corresponding NMR spectra.

Conversion of **4a**−**c** and **5a**,**b** into the desired pyrroles was achieved by an additional 3 equiv of *t*-BuOK and an activated olefin to the reaction mixture at 25 °C. A stoichiometric amount of base required longer reaction times and in some cases gave lower yields. The reaction was monitored by TLC, which indicated reaction completion within 0.15−2.0 h with the desired pyrrole **6a**−**e** being the sole product. The pure products were crystallized from ethanol or ethyl acetate. Pyrroles **6h**,**i**,**j** were isolated by column chromatography. While this procedure works well with aromatic and heterocyclic substituents, the introduction of alkyl substituents was not successful and gave only traces of the pyrroles **6f**, **6g**, and **7a**,**c**. Our experimental results are summarized in Table 2.

Following these syntheses, we investigated *N*-acylation and *N*-alkylation of pyrroles. We found that quenching the reaction mixture containing **6b** with acetyl chloride resulted in formation of **6l** in 82% yield. Similarly, methyl iodide quenching of reaction mixtures containing **6e** and **6h** afforded **6m** and **6n** in 89% and 80% yield, respectively. Pyrrole **6p** was prepared from isolated **6j** by treatment with methyl iodide in THF in the presence of NaH.

In conclusion, we believe that this synthetic sequence is advantageous for the one-pot preparation of both tri- and tetrasubstituted pyrroles. This method provides at least four points of diversification, and it allows the introduction of ester, amide, sulfone, and various aryl and heterocyclic substituents. This procedure does not require harsh reaction conditions or difficult to handle reagents and can be easily scaled up to the preparation of gram quantities of pyrroles.

‡ University of Florida.

§ Coelacanth Corporation.

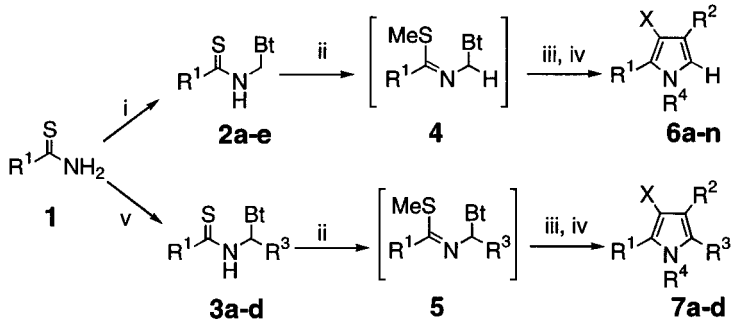
(1) Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon Press: Oxford; vol. 4, p 370 and references therein.

(2) (a) Huebsch, W.; Angerbauer, R.; Fey, P.; Bischoff, H.; Petzinna, D.; Schmidt, D.; Bayer A.-G. Ger. Offen. DE 3,726,528, Oct 27, 1988; Appl. Apr 14, 1987; *Chem. Abstr.* **1989**, *110*, 135079t. (b) Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G., Bergmann, A.; Granzer, E.; Kerekjarto, B.; Kesseler, K.; Krause, R.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 61. (c) Rosowsky, A.; Forsch, R. A.; Maran, R. G. *J. Med. Chem.* **1991**, *34*, 463. (d) Barrero, A. F.; Sanchez, J. F.; Oltra, J. E.; Teva, D.; Ferrol, R. R.; Elmerabet, J.; Del Moral, R. G.; Lucena, M. A.; O'Valle, F. *Eur. J. Med. Chem.* **1994**, *29*, 773.

(3) (a) Simmons, H. E.; Vest, R. D.; Vladuchick, S. A.; Webster, O. W. *J. Org. Chem.* **1980**, *45*, 5113. (b) Paine, J. B., III; Brough, J. R.; Buller, K. K.; Erikson, E. E. *J. Org. Chem.* **1987**, *52*, 3986. (c) Vedejs, E.; Grissom, J. W. *J. Org. Chem.* **1988**, *53*, 1876. (d) Eberlin, M. N.; Kascheres, C. *J. Org. Chem.* **1988**, *53*, 2084. (e) Ohno, M.; Komatsu, M.; Miyata, H.; Ohshiro, Y. *Tetrahedron Lett.* **1991**, *32*, 5813. (f) Katritzky, A. R.; Zhu, L.; Lang, H.; Denisko, O.; Wang, Z. *Tetrahedron* **1995**, *51*, 13271. (g) Barluenga, J.; Tomas, M.; Kouznetsov, V.; Suarez-Sobrino, A.; Rubio, E. *J. Org. Chem.* **1996**, *61*, 2185. (h) Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999. (i) Katritzky, A. R.; Cheng, D.; Musgrave, R. P. *Heterocycles* **1997**, *44*, 67. (j) Nakamura, M.; Hara, K.; Sakata, G.; Nakamura, E. *Org. Lett.* **1999**, *1*, 1505.

10.1021/jo001160w CCC: $19.00
Published on Web 11/16/2000

Scheme 1



i. $BtCH_2OH$, $PhCH_3$, 41-96%; ii. *t*-BuOK, THF, MeI, 0°C; iii. $R^2CH{=}CHX$, *t*-BuOK; iv. NaH, R^4X; v. BtH, R^3CHO, $PhCH_3$, 40-90%.

Table 1. *N*-(Benzotriazol-ylmethyl)thioamides 2 and 3

entry	R^1	R^3	mp (°C)	yield, %
2a	C_6H_5	H	205−206	96
2b	2-C_4H_3O	H	142−143	41
2c	3-pyridyl	H	162−164	60
2d	4-pyridyl	H	154−156	95
2e	4-$MeOC_6H_4$	H	178−180	91
3a	Me	C_6H_5	−	40
3b	C_6H_5	2,4-$Cl_2C_6H_3$	173−175	92
3c	4-ClC_6H_4	4-$CH_3C_6H_4$	152−154	90
3d	C_6H_5	*i*-Pr	194−195	42

Table 2. Tri- and Tetrasubstituted Pyrroles 6 and 7

entry	R^1	R^2	R^3	R^4	X	yield, %
6a	C_6H_5	C_6H_5	H	H	CN	99
6b	C_6H_5	C_6H_5	H	H	$SO_2C_6H_5$	90
6c	3-Py	CO_2Me	H	H	CO_2Me	60
6d	C_6H_5	2-C_4H_3S	H	H	COC_6H_4	96
6e	C_6H_5	C_6H_5	H	H	CO_2Et	99
6f	C_6H_5	Me	H	H	$CO_2Si(Me)_2t$-Bu	−
6g	C_6H_5	Me	H	H	CO_2Et	−
6h	C_6H_5	2-C_4H_3O	H	H	CO_2H	63
6i	2-C_4H_3O	C_6H_5	H	H	CO_2Et	65
6j	C_6H_5	CF_3	H	H	CO_2Et	20
6k	4-$MeOC_6H_4$	C_6H_5	H	H	CO_2Et	87
6l	C_6H_5	C_6H_5	H	Ac	$SO_2C_6H_5$	82
6m	C_6H_5	C_6H_5	H	Me	CO_2Et	89
6n	C_6H_5	2-C_4H_3O	H	Me	CO_2H	80
6o	2-C_4H_3O	C_6H_5	H	Me	CO_2Et	85
6p	C_6H_5	CF_3	H	Me	CO_2Et	67[a]
7a	C_6H_5	C_6H_5	*i*-Pr	H	CO_2Et	−
7b	C_6H_5	C_6H_5	2,4-$Cl_2C_6H_3$	H	CN	63
7c	Me	C_6H_5	C_6H_5	H	CO_2Et	−

[a] **6m**, **6n**, **6o**, and **6p** were prepared by treating isolated **6e**, **6h**, **6i**, and **6j** with (i) NaH in THF at RT, and (ii) MeI in THF, disparately.

Experimental Section

General Methods. Melting points were determined on a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). THF was distilled from sodium/benzophenone under nitrogen immediately prior to use. All reactions with air-sensitive compounds were carried out under an argon or nitrogen atmosphere. *t*-BuOK was purchased from Acros. Compounds **2a** and **3d** were prepared according to literature procedures.[4f,6c]

General Procedure for the Synthesis of *N*-(Benzotriazol-ylmethyl)thioamides 2b−e and 3a−c. A mixture of a thioamide **1** (20 mmol) and 1-(hydroxymethyl)benzotriazole (20 mmol), or benzotriazole (2.39 g, 20 mmol) and an aldehyde (20 mmol) for **3a**−**c**, in toluene (50 mL) with a catalytic amount of *p*-toluenesulfonic acid (0.019 g, 0.1 mmol) was refluxed for 24 h. The water formed was removed with a Dean−Stark trap. The mixture was cooled to room temperature and kept refrigerated overnight. Products **2b**−**e** and **3b**,**c** were obtained by filtration as crystalline compounds. Compound **3a** was isolated by column chromatography.

***N*-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-2-furancarbothioamide (2b)**: yellow needles, mp 142−143 °C; ^1H NMR δ 6.07 (s, 0.5H), 6.17 (s,1.5H), 6.60 (t, 1H, J = 1.8 Hz), 7.30 (t, 1H, J = 5.0 Hz), 7.44 (t, 1H, J = 8.1 Hz), 7.55−7.61 (m, 1H), 7.73 (d, 1H, J = 3.6 Hz), 7.92 (d, 1H, J = 8.4 Hz), 8.04 (d, 1H, J = 8.4 Hz), 9.93 (br s, 1H); ^{13}C NMR δ 56.1 112.2, 114.3, 119.6, 120.3, 125.2, 126.7, 128.7, 133.7, 146.6, 153.0, 185.4. Anal. Calcd for $C_{12}H_{10}N_4OS$: C 55.80, H 3.90, N 21.69. Found: C 56.21, H 4.09, N 21.65.

N-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-3-pyridinecarbothioamide (2c): off-yellow microcrystals, 162−164 °C;^1H NMR δ 6.69 (d, 2H, J = 5.5 Hz), 7.30−7.43 (m, 2H), 7.52−7.57 (m, 1H), 8.01−8.04 (m, 2H), 8.14 (dd, 1H, J = 1.9, 9.8 Hz), 8.63 (d, 1H, J = 4.5 Hz), 8.97 (s, 1H), 11.38 (br s, 1H); ^{13}C NMR δ 55.8, 110.1, 118.5, 121.9, 123.3, 126.8, 131.8, 134.6, 135.2, 144.7, 147.0, 150.8, 197.2. Anal. Calcd for $C_{13}H_{11}N_5S$: C 57.97, H 4.12, N 26.00. Found: C 58.08, H 4.22, N 26.22.

***N*-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-4-pyridinecarbothioamide (2d)**: yellow microcrystals, mp 154.0−156.0 °C; ^1H NMR δ 6.56 (s, 2H), 7.42−7.47 (m, 2H), 7.61 (d, 2H, J = 6.0 Hz), 7.70 (d, 1H, J = 6.0 Hz), 7.91−7.94 (m, 1H), 8.07 (dd, 1H, J = 7.4, 7.9 Hz), 8.66 (d, 2H, J = 6.0 Hz); ^{13}C NMR δ 56.5, 111.1, 119.2, 120.9, 124.2, 127.7, 132.5, 145.0, 146.6, 149.9, 197.9. Anal. Calcd for $C_{13}H_{11}N_5S$: N 26.00. Found: N 25.74.

***N*-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-4-methoxyphenylthioamide (2e)**: yellow needles; mp 178.0−180.0 °C; ^1H NMR δ 3.80 (s, 3H), 6.77−6.84 (m, 4H), 7.32 (t, 1H, J = 7.2 Hz), 7.49 (t, 1H, J = 7.5 Hz), 7.88−7.92 (m, 3H), 8.04 (d, 1H), 9.38 (t, 1H, J = 3.5 Hz); ^{13}C NMR δ 56.0, 57.1, 111.8, 114.1, 119.7, 125.1, 126.6, 128.6, 129.8, 133.1, 146.1, 163.3, 200.4. Anal. Calcd for $C_{15}H_{14}N_4OS$: N 18.79. Found: N 18.39.

***N*-[1*H*-1,2,3-Benzotriazol-1-yl(phenyl)methyl]ethanethioamide (3a)**: yellow oil; ^1H NMR δ 2.62 (s, 3H), 7.22−7.35 (m, 6H), 7.44 (t, 1H, J = 8.3 Hz), 7.73 (d, 1H, J = 8.3 Hz), 7.90 (d, 1H, J = 8.3 Hz), 8.61 (d, 1H, J = 8.3 Hz), 10.31 (br s, 1H); ^{13}C NMR δ 33.3, 69.1, 110.2, 119.4, 124.5, 126.6, 128.0, 128.8, 129.3, 132.9, 134.8, 145.0, 203.7. Anal. Calcd for $C_{15}H_{14}N_4S$: C 63.80, H 5.00. Found: C 63.55, H 4.97.

***N*-[1*H*-1,2,3-Benzotriazol-1-yl(2,4-dichlorophenyl)methyl]benzenecarbothioamide (3b)**: yellow microcrystals, mp

(4) (a) Lahiri, S.; Mahajan, M. P.; Prasad, R.; George, M. V. *Tetrahedron* **1977**, *33*, 3159. (b) McEwen, W. E.; Grossi, A. V.; MacDonald R. J.; Stamegna, A. P. *J. Org. Chem*. **1980**, *45*, 1301. (c) Tsuge, O.; Ueno, K. *Heterocycles* **1982**, *19*, 1411. (d) Padwa, A.; Haffmanns, G.; Tomas, M. *J. Org. Chem*. **1984**, *49*, 3314. (e) Anderson, W. K.; Heider, A. R. *Synth. Commun*. **1986**, *16*, 357. (f) Katritzky, A. R.; Drewniak, M.; Lue, P. *J. Org. Chem*. **1988**, *559*, 5854. (g) Washizuka, K.-I.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1999**, *55*, 12969.

(5) Katritzky, A. R.; Hitchings, G. J.; Zhao, X. *Synthesis* **1991**, 863.

(6) (a) Katritzky, A. R.; Yao, G.; Lan, X.; Zhao, X. *J. Org. Chem*. **1993**, *58*, 2086. (b) Katritzky, A. R.; Denisko, O.; Lang, H. *Tetrahedron* **1995**, *51*, 8703. (c) Katritzky, A. R.; Drewniak, M. *Tetrahedron Lett*. **1988**, *29*, 1755.

173.0−175.0 °C; ^{1}H NMR δ 7.18 (dd, 1H, J = 1.9, 8.4 Hz), 7.25−7.36 (m, 3H), 7.42−7.51 (m, 4H), 7.59 (d, 1H, J = 8.1 Hz), 7.74 (d, 1H, J = 8.1 Hz), 7.87 (d, 2H, J = 7.5 Hz), 8.82 (d, 1H, J = 7.7 Hz), 9.76 (br s, 1H); ^{13}C NMR δ 67.0, 110.0, 119.4, 124.8, 127.4, 127.6, 128.3, 128.4, 129.5, 130.0, 131.2, 131.9, 132.6, 134.6, 136.2, 140.1, 145.0, 200.2. Anal. Calcd for $C_{20}H_{14}Cl_2N_4S$: C 58.12; H 3.41; N 13.56. Found: C 58.38; H 3.26; N 13.75.

***N*-[1*H*-1,2,3-Benzotriazol-1-yl(4-methylphenyl)methyl]-4-chlorobenzenecarbothioamide (3c):** yellowish microcrystals; mp 152.0−154.0 °C; ^{1}H NMR δ 2.37 (s, 3H), 7.19−7.48 (m, 7H), 7.55 (t, 1H, J = 7.2 Hz), 7.73−7.83 (m, 3H), 8.03 (d, 1H, J = 8.4 Hz), 8.64 (d, 1H, J = 8.4 Hz), 9.25 (d, 1H, J = 7.8 Hz); ^{13}C NMR δ 21.1, 69.2, 109.8, 119.9, 124.5, 126.5, 128.1, 128.5, 128.7, 129.9, 132.4, 132.9, 138.2, 138.8, 139.8, 145.4, 198.5 Anal. Calcd for $C_{21}H_{17}ClN_4S$: C 64.20; H 4.36. Found: C 64.22; H 4.44.

The Synthesis of Tri- and Tetrasubstituted Pyrroles 6 and 7. General Procedure. The *t*-BuOK (3.3 mmol) was added to a solution of a *N*-(benzotriazol-1-ylmethyl)thioamide (**2**) (3 mmol) and iodomethane (3.3 mmol) in THF (50 mL) at 0 °C, and the mixture was stirred for 2 h. After an appropriate Michael acceptor (3.3 mmol) was added, the *t*-BuOK (9 mmol) was added in two portions at 0 °C. The mixture was refluxed for 2 h, and the solvent was removed on an evaporator. The solid residue was dissolved in 50 mL of dichloromethane and washed with 5% $NaHCO_3$ (100 mL × 3∼5) and dried over $MgSO_4$. After evaporation of the solvents, the residue was recrystallized from dichloromethane−ethanol to give the expected product.

1,3-Diphenyl-2-cyano-1*H*-pyrrole (6a): gray plates, mp 255.0 °C; ^{1}H NMR δ 7.06 (d, 1H, J = 2.7 Hz), 7.25−7.30 (m, 1H), 7.35−7.50 (m, 5H), 7.66 (d, 2H, J = 6.9 Hz), 7.83 (d, 2H, J = 6.9 Hz), 11.94 (br s, 1H); ^{13}C NMR δ 86.3, 116.2, 117.1, 125.0, 125.3, 125.7, 126.6, 127.2, 127.5, 127.7, 129.1, 132.1, 138.9. Anal. Calcd for $C_{17}H_{12}N_2$: C 83.58; H 4.95; N 11.47. Found: C 83.20; H 4.96; N 11.49.

2,3-Diphenyl-4-(phenylsulfonyl)-1*H*-pyrrole (6b): red microcrystals; mp 156.0−159.0 °C; ^{1}H NMR δ 6.65 (d, 1H, J = 2.5 Hz), 7.12 (q, 3H, J = 8.2 Hz), 7.23−7.31 (m, 7H), 7.34−7.37 (m, 3H), 7.49−7.53 (m, 2H), 8.78 (br s, 1H); ^{13}C NMR δ 118.0, 126.8, 127.1, 127.5, 127.9, 128.0, 128.9, 130.2, 130.5, 131.0, 131.8, 133.4, 137.0, 143.1. Anal. Calcd for $C_{22}H_{17}NO_2S$: N 3.90. Found N 4.05.

Dimethyl 2-(3-pyridinyl)-1*H*-pyrrole-3,4-dicarboxylate (6c): white solid; mp 165−166 °C; ^{1}H NMR δ 3.60 (s, 6H), 7.11−7.21 (m, 2H), 7.69 (d, 1H, J = 7.8 Hz), 8.33 (d, 1H, J = 4.6 Hz), 8.55 (s, 1H), 11.61 (br s, 1H); ^{13}C NMR δ 50.8, 51.5, 113.9, 115.6, 122.7, 124.7, 127.0, 130.4, 134.7, 147.9, 148.1, 163.6, 165.9. Anal. Calcd for $C_{13}H_{12}N_2O_4$: C 60.00, H 4.65, N 10.76. Found: C 59.85, H 4.79, N 10.72.

2-Phenyl-3-(4-methylbenzoyl)-3-(2-thienyl)-1*H*-pyrrole (6d): yellow prisms; mp 199.0−200.0 °C; ^{1}H NMR δ 2.26 (s, 3H), 6.79−6.84 (m, 3H), 6.99−7.03 (m, 3H), 7.08−7.11 (m, 3H), 7.17−7.21 (m, 2 H), 7.70 (d, 2H, J = 7.2 Hz), 9.25 (br s, 1H); ^{13}C NMR δ 21.6, 117.5, 118.9, 119.7, 123.1, 124.5, 127.2, 127.3, 128.5, 128.7, 130.2, 131.4, 134.2, 135.9, 136.6, 143.5, 195.4. Anal. Calcd for $C_{22}H_{17}NOS$: N 4.08. Found: N 4.02.

Ethyl 2,4-diphenyl-1*H*-pyrrole-3-carboxylate (6e): oil; ^{1}H NMR δ 0.92 (t, 3H, J = 7.1 Hz), 3.95 (q, 2H, J = 7.1 Hz), 6.48 (d, 1H, J = 1.5 Hz), 7.30−7.40 (m, 10H), 8.94 (s, 1H); ^{13}C NMR δ 13.6, 59.9, 110.4, 117.5, 126.2, 127.2, 127.7, 127.8, 127.9, 128.6, 128.8, 132.2, 135.3, 136.8, 166.1. Anal. Calcd for $C_{19}H_{17}NO_2$: C 78.33, H 5.88, N 4.81. Found: C 77.97, H 6.06, N 4.90.

4-(2-Furyl)-2-phenyl-1*H*-pyrrole-3-carboxylic acid (6h): oil; ^{1}H NMR δ 6.41 (dd, 1H, J = 1.9, 3.4 Hz), 6.85 (d, 1H, J = 3.2 Hz), 7.09 (d, 1H, J = 2.6 Hz), 7.33−7.37 (m, 4H), 7.41−7.49 (m, 3H), 9.02 (br s, 1H); ^{13}C NMR δ 107.7, 111.2, 117.7, 118.0, 128.1, 128.4, 129.1, 132.1, 139.3, 140.6, 148.7, 170.2, 171.4, 177.4; HRMS calcd for $C_{15}H_{11}NO_3$ (M): 253.0739, found: 253.0737.

Ethyl 2-(2-furyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (6i): 65% pale brown oil; ^{1}H NMR δ 1.04 (t, 3H, J = 7.1 Hz), 4.14 (q, 2H, J = 7.1 Hz), 6.42 (dd, 1H, J = 2.1, 2.0 Hz), 6.62 (d, 1H, J = 2.7 Hz), 7.23−7.36 (m, 7H), 9.25 (s, 1H); ^{13}C NMR δ 14.0, 60.1, 109.6, 109.7, 112.1, 117.8, 126.5, 127.8, 127.9, 128.0, 129.3, 135.6, 141.6, 146.1, 165.6. Anal. Calcd for $C_{17}H_{15}NO_3$:N 4.98. Found: N 5.32.

Ethyl 2-phenyl-4-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (6j): red microcrystals; mp 120−121 °C, ^{1}H NMR δ 1.15 (t, 3H, J = 7.0 Hz), 4.08 (q, 2H, J = 7.0 Hz), 6.96 (d, 1H, J = 2.6 Hz), 7.33−7.42 (m, 5H), 9.17 (br s, 1H); ^{13}C NMR δ 13.7, 60.4, 109.4, 119.8, 121.2, 124.7, 128.1, 128.8, 129.0, 131.1, 139.3, 157.7, 163.8, 186.4. Anal. Calcd for $C_{14}H_{12}F_3NO_2$: C 59.37, H 4.27, N 4.95. Found: C 59.25, H 4.34, N 4.94.

Ethyl 2-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (6k): white crystals; mp 136.0−138.0 °C, ^{1}H NMR δ 0.99 (t, 3H, J = 7.2 Hz), 3.82 (s, 3H), 4.06 (q, 2H, J = 7.2 Hz), 6.71 (d, 1H, J = 2.5 Hz), 6.93 (d, 2H, J = 8.7 Hz), 7.25−7.47 (m, 7H), 8.47 (br s, 1H); ^{13}C NMR δ 13.8, 55.3, 59.8, 110.5, 113.6, 116.8, 124.8, 126.3, 127.7, 129.0, 130.1, 135.5, 137.1, 159.5, 165.7. Anal. Calcd for $C_{20}H_{19}NO_3$: C74.75, H 5.96, N 4.36. Found: C 74.60, H 6.33, N 4.31.

1-[2,3-Diphenyl-4-(phenylsulfonyl)-1*H*-pyrrol-1-yl]-1-ethanone (6l): white microcrystals; mp 136.0−138.0 °C, ^{1}H NMR δ 2.00 (s, 3H), 7.15−7.20 (m, 4H), 7.32−7.49 (m, 12H); ^{13}C NMR δ 25.3, 120.0, 126.5, 127.1, 127.6, 127.7, 128.0, 128.1, 129.5, 130.3, 130.5, 130.8, 132.1, 132.3, 136.6, 142.0, 168.8. Anal. Calcd for $C_{24}H_{19}NO_3S$: N 3.49. Found: N 3.55.

Ethyl 1-methyl-2,4-diphenyl-1*H*-pyrrole-3-carboxylate (6m): oil; ^{1}H NMR δ 0.85 (t, 3H, J = 7.1 Hz), 3.41 (s, 3H), 3.93 (q, 2H, J = 8.0 Hz), 6.66 (s, 1H), 7.33−7.43 (m, 10H); ^{13}C NMR δ 13.5, 34.5, 59.2, 111.8, 121.5, 126.1, 126.2, 127.6, 127.8, 128.1, 129.0, 130.4, 132.0, 135.2, 138.9, 165.0. Anal. Calcd for $C_{20}H_{19}NO_2$: C 78.66, H 6.27, N 4.59. Found: C 78.54, H 6.63, N 4.45.

4-(2-Furyl)-1-methyl-2-phenyl-1*H*-pyrrole-3-carboxylic acid (6n): brown oil; ^{1}H NMR δ 3.34 (s, 3H), 6.38 (dd, 1H, J = 1.7, 3.2 Hz), 6.85 (d, 1H, J = 3.3 Hz), 6.99 (s, 1H), 7.27−7.33 (m, 3H), 7.36−7.38 (m, 4H); ^{13}C NMR δ 35.0 107.9, 109.3, 111.4, 116.6, 121.9, 128.2, 128.6, 130.6, 131.8, 140.6, 140.6, 149.0, 169.8; HRMS calcd for $C_{16}H_{13}NO_3$ (M): 267.0895, found 267.0907.

Ethyl 2-(2-furyl)-4-phenyl-1-*N*-methyl-pyrrole-3-carboxylate (6o): 85% colorless oil; ^{1}H NMR δ 1.00 (t, 3H, J = 7.2 Hz), 3.51 (s, 3H), 4.05 (q, 2H, J = 7.2 Hz), 6.47 (dd, 1H, J = 1.5, 3.6 Hz), 6.63 (s, 1H), 6.64 (d, 1H, J = 3.6 Hz), 7.22−7.25 (m, 1H), 7.28−7.33 (m, 2H), 7.37−7.40 (m, 2H), 7.50 (d, 1H, J = 1.8 Hz); ^{13}C NMR δ_13.9, 35.3, 59.8, 110.9, 112.1, 114.1, 122.9, 126.2, 126.4, 127.5, 127.8, 128.5, 128.9, 135.0, 142.7, 144.4, 164.9. Anal. Calcd for $C_{18}H_{17}NO_3$: C 73.20, H 5.80, N 4.74. Found: C 73.28, H 5.96, N 4.73.

Ethyl 1-methyl-2-phenyl-4-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (6p): pale yellow needles; mp 51−52 °C; ^{1}H NMR δ 1.05 (t, 3H, J = 7.2 Hz), 3.39 (s, 3H), 4.07 (q, 2H, J = 7.1 Hz), 7.03 (s, 1H), 7.27−7.31 (m, 2H), 7.40−7.44 (m, 3H); ^{13}C NMR δ 13.7, 35.0, 59.9, 114.1 (C, J_{C-F} = 36.7 Hz), 123.2 (C, J_{C-F} = 264 Hz), 123.6 (CH, J_{C-F} = 6.3 Hz), 128.2, 128.4 (C, J_{C-F} = 11.4 Hz), 129.0, 130.5, 130.9, 140.7, 163.0. Anal. Calcd for $C_{15}H_{14}F_3NO_2$: N 4.71. Found: N 5.01.

5-(2,4-Dichlorophenyl)-2,4-diphenyl-1*H*-pyrrole-3-carbonitrile (7b): white microcrystalls; mp 193.0−196.0 °C; ^{1}H NMR δ 7.07−7.15 (m, 2H), 7.32 (br s, 5H), 7.43−7.53 (m, 4H), 7.78 (d, 2H, J = 7.3 Hz), 8.96 (br s, 1H); ^{13}C NMR δ 91.7, 117.2, 125.6, 126.2, 127.7, 127.8, 128.3, 128.5, 128.9, 129.2, 129.4, 129.5, 129.6, 130.5, 132.3, 133.7, 134.1, 135.3, 139.7. Anal. Calcd for $C_{23}H_{14}Cl_2N_2$: N 7.20. Found: N 7.15.

JO001160W