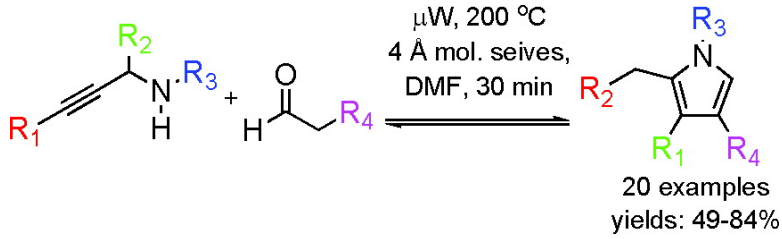
JOURNAL OF combinatorial CHEMISTRY

Article

Formation of Substituted Pyrroles via an Imine Condensation/Aza-Claisen Rearrangement/Imine#Allene Cyclization Process by MAOS

W. Stacy Bremner, and Michael G. Organ

J. Comb. Chem., **2008**, 10 (1), 142-147• DOI: 10.1021/cc700159u • Publication Date (Web): 07 December 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Formation of Substituted Pyrroles via an Imine Condensation/Aza-Claisen Rearrangement/Imine−Allene Cyclization Process by MAOS

W. Stacy Bremner and Michael G. Organ*

Department of Chemistry, York University, 4700 Keele Street, Toronto, Ontario, Canada, M3J 1P3

Received September 24, 2007

A diverse collection of pyrroles has been prepared using a one-pot, domino aldehyde/amine condensation, [3,3]-aza-Claisen rearrangement, imine−allene cyclization strategy. This protocol was accelerated by microwave irradiation and provided very good levels of conversion after reacting for only 30 min.

Introduction

Among nitrogen-containing aromatic heterocycles, the pyrrole ring is the most frequently observed in the structure of natural products[1] and synthetic materials.[2] Importantly, the pyrrole substructure is found in many biologically active compounds,[3] and their synthesis, reactivity, and biological activity continue to be very actively studied.[4] Some of the more traditional methods for their preparation include the Knorr,[5] Pall−Knorr,[6] and Hantzsch[7] condensation reactions, while more recent strategies include multicomponent reactions[8] and the use of transition metal-catalyzed processes.[9] Widespread use of these methods is limited by the harsh nature of some of the reaction conditions, by the production of harmful waste streams, or both.

As part of our ongoing efforts in the development and application of new synthetic methods and techniques for the advancement of microwave-assisted organic chemistry (MAOS), we were interested in the development of a general, simple, and effective method for the preparation of the pyrrole substructure that would lend itself to library preparation. The protocol we settled on involves the reaction of various secondary propargylamines and aldehydes via a tandem condensation/aza-Claisen rearrangement/cyclization sequence that generates substituted pyrroles (Table 1). A similar rearrangement mechanism has been proposed in related systems for the synthesis of annulated[*b*]pyrroles.[10] This reliable procedure can be performed quickly under microwave conditions to generate a library of pyrroles with various functionality and substitution patterns.

Results and Discussion

A solution of *N*-benzylpropargylamine (**1a**) and propionaldehyde (**2a**) in DMF was treated with molecular sieves and heated to 200 °C for 30 min in a Biotage Initiator Microwave Synthesizer reactor (Scheme 1, Table 1, entry 1). Upon formation of the intermediate enynamine (see structure **3**), we propose that a [3,3]-pericyclic rearrangement occurrs giving rise to the imino-allene intermediate (see structure **4**) that undergoes subsequent cylcization to give 1-benzyl-2,4-dimethylpyrrole **5a**.

A variety of propargylamines bearing benzyl or aliphatic substituents have proven to be equally effective in this process with a diverse selection of aldehydes. The reaction tolerates bulky aliphatic groups on nitrogen such as cyclohexyl (entries 7 and 8) and isopropyl (entries 11 and 12), as well as pharmaceutically relevant functionality such as nitrogen and sulfur heterocycles in the acetylenic position (entries 17, 19, and 20). Our substrate survey indicates that the amine in **1** must be secondary; primary propargylamine produces an imine species that would not react further. However, if the N-unsubstituted pyrrole is desired, this can be achieved easily by hydrogenation of the corresponding *N*-benzyl derivative (e.g., **5a**−**5f**).

Conclusions

In summary, an efficient reaction sequence for the production of a diverse collection of pyrroles has been developed. A wide variety of starting propargylamines can be prepared readily by a number of different approaches including substitution and reductive alkylation chemistry.[11] For more complex propargylamines, such as the case in entry 18 (**1h**), a three-component reaction process can be envisioned that would give rise to an even wider range of starting materials.[12] Further, Sonogashira-type chemistry could be used to prepare a number of derivatives functionalized at the acetylenic position, such as **1g**, **1h**, and **1i**.[13] We are presently considering the adaptation of this batch MAOS methodology to a flowed format, such as microwave-assisted continuous-flow organic synthesis (MACOS).[14]

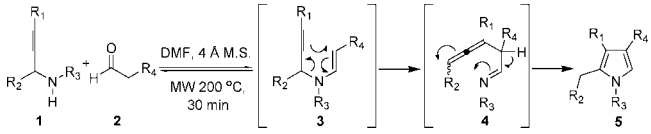
Experimental Section

All microwave reactions were carried out in a sealed microwave vial equipped with a magnetic stir bar and heated in a Biotage Initiator Microwave Synthesizer programmed to heat for the 30 min. All reagents and solvents were purchased from commercial sources and were used without further purification. All NMR spectra were recorded on a

* To whom correspondence should be addressed. E-mail: organ@yorku.ca.

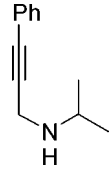
10.1021/cc700159u CCC: $40.75
Published on Web 12/07/2007

Scheme 1



Bruker Avance 400 MHz spectrometer. ^{1}H and ^{13}C NMR signals and were referenced to 7.26 ppm and 77.23 ppm for the residual proton and carbon resonance signals of deuterated chloroform solvent ($CDCl_3$), respectively. Analogously, the ^{1}H and ^{13}C NMR signals were referenced to 2.54 ppm and 40.45 ppm for the residual proton and carbon resonance signal of deuterated dimethyl sulfoxide solvent (DMSO-d_6), respectively. ^{13}C J-MOD NMR spectra were collected exclusively for the carbon data and have positive peaks (+) for quaternary carbons or carbons with two attached protons and negative peaks (−) for carbons with one or three attached protons.

Isopropyl-(3-phenyl-prop-2-ynyl)-amine (1d). To a solution of propargyl alcohol (2 g, 35.68 mmol) and iodobenzene

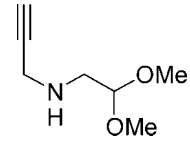


(7.3 g, 35.68 mmol) in triethylamine (45 mL) was added $PdCl_2(PPh_3)_2$ (252 mg, 0.36 mmol) and CuI (135 mg, 0.71 mmol), and the reaction mixture was stirred at room temperature for 16 h. The solution was then diluted with an equal mixture of diethyl ether/water (50 mL), and the layers were partitioned. The aqueous layer was extracted twice with diethyl ether, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated. The resulting crude material was purified by flash chromatography on silica gel (30% diethyl ether in pentane) to afford 4.3 g of pure 3-phenyl-prop-2-ynol.

To a suspension of 3-phenyl-prop-2-ynol (3.6 g, 27.24 mmol) and K_2CO_3 (4.52 g, 32.69 mmol) in dichloromethane (20 mL) at 0 °C was added $Me_3N \cdot HCl$ (260 mg, 2.72 mmol), and stirring was continued for 5 min. *p*-TsCl (6.23 g, 32.69 mmol) was added, along with an additional 20 mL of dichloromethane, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was then quenched with 40 mL of water and was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed successively with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude material was crystallized from hexane with a minimal amount of ethyl acetate to afford 4.3 g of pure toluene-4-sulfonic acid 3-phenyl-prop-2-ynyl ester.

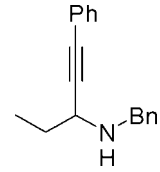
To a solution of the toluene-4-sulfonic acid 3-phenyl-prop-2-ynyl ester (1.24 g, 4.33 mmol) in acetonitile (12 mL) was added isopropylamine (640 mg, 10.83 mmol) at room temperature. After it was heated to 60 °C for 18 h, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was then taken up in diethyl ether and washed twice with a saturated solution of sodium bicarbonate. The combined aqueous layers were then extracted twice with diethyl ether, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated to afford 815 mg of crude product. Flash chromatography on silica gel (40% diethyl ether in pentane) yielded 460 mg of clean isopropyl-(3-phenyl-prop-2-ynyl)-amine (**1d**). ^{1}H NMR (DMSO-d_6): δ 7.37 (m, 5H), 3.55 (s, 2H), 2.95 (m, J = 6 Hz, 1H), 1.96 (s, 1H), 0.99 (d, J = 6 Hz, 6H). ^{13}C NMR (DMSO-d_6): δ 131.7 (−), 129.0 (−), 128.5 (−), 123.4 (+), 89.8 (+), 82.8 (+), 46.9 (−), 36.2 (−), 22.8 (−). HRMS Calcd for $C_{12}H_{15}N$: m/z [M+] 173.1204. Found: 173.1198.

(2,2-Dimethoxy-ethyl)-prop-2-ynyl-amine (1f). Propargyl bromide (80% in toluene, 3.7 g, 25.0 mmol) was added to a reaction flask, followed by the dropwise addition of 2,2-



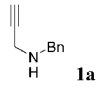
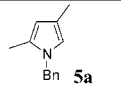
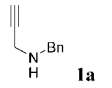
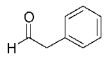
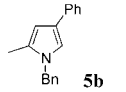
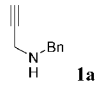
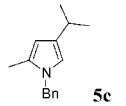
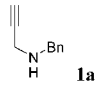
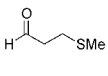
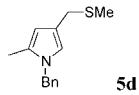
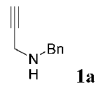
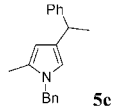
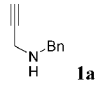
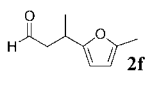
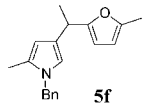
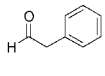
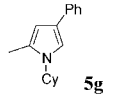
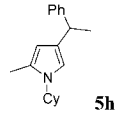
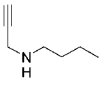
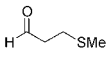
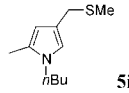
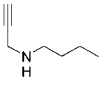
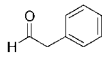
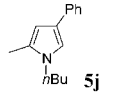
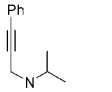
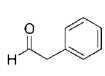
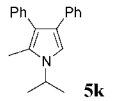
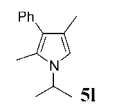
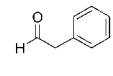
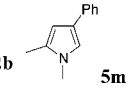
dimethoxy-ethylamine (16 mL, 150.0 mmol). The reaction mixture was allowed to stir at room temperature for 18 h, after which it was diluted with diethyl ether. After they were washed with water and saturated $NaHCO_3$, the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting crude material was loaded directly onto a column and flashed on silica gel (90% ethyl acetate in hexane) to afford 1.7 g (47%) of the title compound as a yellow oil. ^{1}H NMR (DMSO-d_6): δ 4.39 (t, J = 5.6 Hz, 1H), 3.32 (s, 2H), 3.26 (s, 6H), 3.01 (s, 1H), 2.64 (d, J = 5.6 Hz, 2H), 1.74 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 103.8 (−), 83.3 (+), 73.9 (+), 53.4 (−), 49.5 (+), 37.8 (+). HRMS Calcd for $C_7H_{13}NO_2$: m/z [M+] 143.0946. Found: 143.0989.

Benzyl-(1-ethyl-3-phenyl-prop-2-ynyl)-amine (1h). To a microwave reaction vial equipped with a magnetic stir bar



was added benzylamine (557 mg, 5.2 mmol), propionaldehyde (232 mg, 4.0 mmol), phenylacetylene (654 mg, 6.4 mmol), and copper iodide (114 mg, 0.6 mmol). The reaction vessel was then sealed, and the Biotage Initiator Microwave Synthesizer programmed to heat at 110 °C for 10 min. The resulting reaction mixture was loaded directly onto a column and flashed on silica gel (15% ethyl acetate in hexane) to afford 290 mg (29% yield) of the title compound as a yellow oil. ^{1}H NMR (DMSO-d_6): δ 7.43–7.21 (m, 10H), 3.96 (d, J = 13.0 Hz, 1H), 3.79 (d, J = 13.0 Hz, 1H), 3.44 (m, 1H), 2.44 (s, 1H), 1.66 (m, J = 7.0 Hz, 2H), 1.02 (t, J = 7.0 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 141.0 (+), 131.8 (−), 129.0 (−), 128.5 (−), 127.0 (−), 123.5 (+), 92.1 (+), 83.8 (+), 51.3 (−), 51.1 (+), 29.0 (+), 11.0 (−). HRMS Calcd for $C_{18}H_{19}N$: m/z [M+] 249.1517. Found: 249.1511.

Table 1. MAOS Reaction of Various Propargylamines (**1**) and Aldehydes (**2**) to Produce Substituted Pyrroles

Entry	Amine	Aldehyde	Product	Yield (%)[a]
1	 **1a**	 **2a**	 **5a**	73
2	 **1a**	 **2b**	 **5b**	59
3	 **1a**	 **2c**	 **5c**	61
4	 **1a**	 **2d**	 **5d**	65
5	 **1a**	 **2e**	 **5c**	75
6	 **1a**	 **2f**	 **5f**	59
7	 **1b**	 **2b**	 **5g**	54
8	 **1b**	 **2e**	 **5h**	51
9	 **1c**	 **2d**	 **5i**	57
10	 **1c**	 **2b**	 **5j**	61
11	 **1d**	 **2b**	 **5k**	84
12	 **1d**	 **2a**	 **5l**	66
13	 **1e**	 **2b**	 **5m**	61
14	 **1e**	**2f**	**5n**	64
15	**1f**	**2f**	**5o**	51
16	**1f**	**2d**	**5p**	70
17	**1g**	**2a**	**5q**	51
18	**1h**	**2a**	**5r**	52
19	**1i**	**2d**	**5s**	58
20	**1i**	**2g**	**5t**	49

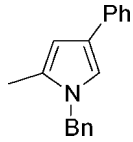
[a] Isolated yield after passing through a short plug of silica gel.

Benzyl-(3-thiophen-2-yl-prop-2-ynyl)-amine (1i). To a solution of benzyl-prop-2-ynyl-amine (500 mg, 3.44 mmol)

and 2-iodothiophene (796 mg, 3.79 mmol) in THF (15 mL) was added $Pd(PPH_3)_4$ (21 mg, 0.03 mmol) and CuI (19 mg, 0.1 mmol). After the mixture was stirred for 5 min at room temperature, triethylamine (0.6 mL, 4.3 mmol) was added, and the reaction mixture heated to 70 °C for 5 h. After it was cooled, the solution was diluted with diethyl ether; the organic layer was washed successively with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting crude material was flashed on silica gel (50% diethyl ether in pentane) to afford 480 mg (61%) of the title compound as a dark yellow oil. ^{1}H NMR (DMSO-d_6): δ 7.56 (d, J = 5.2 Hz, 1H), 7.36–7.22 (m, 6H), 7.07 (t, J = 4.4 Hz, 1H), 3.79 (s, 2H), 3.55 (s, 2H), 2.65 (br s, 1H). ^{13}C NMR (DMSO-d_6): δ 140.5 (+), 132.3 (−), 128.6 (−), 128.5 (−), 128.2 (−), 127.9 (−), 127.1 (−), 122.9 (+), 93.4 (+), 76.6 (+), 52.0 (+), 38.1 (+). HRMS Calcd for $C_{14}H_{13}NS$: m/z [M+] 226.0689. Found: 226.069.

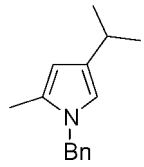
General Procedure for the Synthesis of Substituted Pyrroles. To a microwave vial equipped with a magnetic stir bar was added the amine (**1**, 1 mmol), the aldehyde (**2**, 2 mmol), 4 Å molecular sieves (approximately 0.5 g), and DMF (4 mL). The vial was sealed, and the Initiator Synthesizer programmed to heat for 30 min at 200 °C. The resulting reaction mixture was diluted with diethyl ether; the organic layer was washed twice with water, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated. The crude residue was purified by flash chromatography on silica gel (1 to 2% diethyl ether in pentane) to afford the desired pyrrole.

1-Benzyl-2-methyl-4-phenyl-1H-pyrrole (5b). ^{1}H NMR (DMSO-d_6): δ 7.47 (d, J = 7.6 Hz, 2H), 7.36–7.24 (m, 6H), 7.09 (m, 3H), 6.24 (s, 1H), 5.10 (s, 2H), 2.11 (s, 3H). ^{13}C



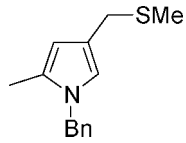
NMR ($CDCl_3$): δ 139.1 (+), 136.3 (+), 129.8 (+), 129.0 (−), 128.9 (−), 127.6 (−), 127.0 (−), 125.2 (−), 124.5 (−), 122.6 (+), 118.5 (−), 105.4 (−), 50.1 (+), 12.2 (−). HRMS Calcd for $C_{18}H_{17}N$: m/z [M+] 247.1361. Found: 247.1370.

1-Benzyl-4-isopropyl-2-methyl-1H-pyrrole (5c). ^{1}H NMR ($CDCl_3$): δ 7.38 (t, J = 7.2 Hz, 2H), 7.32 (d, J = 7.2 Hz,



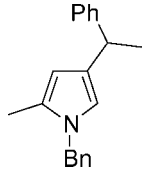
1H), 7.08 (d, J = 7.2 Hz, 2H), 6.48 (s, 1H), 5.93 (s, 1H), 5.03 (s, 2H), 2.88 (qd, J = 6.8 Hz, 1H), 2.20 (s, 3H), 1.28 (d, J = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 138.7 (+), 130.8 (+), 128.7 (−), 128.5 (+), 127.2 (−), 126.5 (−), 116.4 (−), 105.9 (−), 50.3 (+), 26.4 (−), 24.1 (−), 12.1 (−). HRMS Calcd for $C_{15}H_{19}N$: m/z [M+] 213.1517. Found: 213.1514.

1-Benzyl-2-methyl-4-methylsulfanylmethyl-1*H*-pyrrole (5d). ^{1}H NMR (DMSO-d_6): δ 7.32 (t, J = 7.2 Hz, 2H),



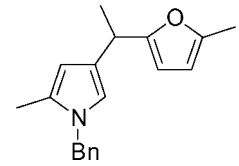
7.24 (t, J = 7.2 Hz, 1H), 7.01 (d, J = 7.2 Hz, 2H), 6.65 (s, 1H), 5.76 (s, 1H), 5.01 (s, 2H), 3.47 (s, 2H), 2.04 (s, 3H), 1.96 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 139.4 (+), 129.0 (−), 128.7 (+), 127.5 (−), 126.9 (−), 120.2 (−), 118.2 (+), 108.1 (−), 49.7 (+), 30.5 (+), 14.9 (−), 12.1 (−). HRMS Calcd for $C_{14}H_{17}NS$: m/z [M+] 231.1082. Found: 231.1082.

1-Benzyl-2-methyl-4-(1-phenyl-ethyl)-1*H*-pyrrole (5e). ^{1}H NMR (DMSO-d_6): δ 7.32 (t, J = 7.2 Hz, 2H), 7.28−7.24



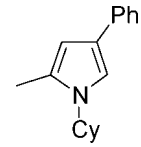
(m,5H), 7.14 (t, J = 6.4 Hz, 1H), 7.02 (d, J = 7.2 Hz, 2H), 6.51 (s, 1H), 5.64 (s, 1H), 4.98 (s, 2H), 3.89 (q, J = 6.8 Hz, 1H), 2.01 (s, 3H), 1.45 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 148.5 (+), 139.6 (+), 128.9 (−), 128.5 (−), 128.2 (+), 127.6 (−), 127.4 (−), 127.2 (+), 126.9 (−), 125.9 (−), 118.0 (−), 107.1 (−), 49.8 (+), 37.9 (−), 23.1 (−), 12.2 (−). Anal. Calcd for $C_{20}H_{21}N$: C, 87.23; H, 7.69; N, 5.09. Found: C, 86.92; H, 8.04; N, 5.36.

1-Benzyl-2-methyl-4-[1-(5-methyl-furan-2-yl)-ethyl]-1*H*-pyrrole (5f). ^{1}H NMR (DMSO-d_6): δ 7.32 (t, J = 7.6



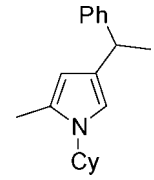
Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H), 7.02 (d, J = 7.6 Hz, 2H), 6.53 (s, 1H), 5.89 (s, 1H), 5.85 (s, 1H), 5.68 (s, 1H), 4.99 (s, 2H), 3.85 (q, J = 7.2 Hz, 1H), 2.19 (s, 3H), 2.03 (s, 3H), 1.40 (d, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 158.8 (+), 149.6 (+), 139.5 (+), 128.9 (−), 128.0 (+), 127.5 (−), 127.0 (−), 125.0 (+), 118.0 (−), 106.7 (−), 106.4 (−), 104.7 (−), 49.8 (+), 31.5 (−), 21.0 (−), 13.8 (−), 12.2 (−). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.48; H, 7.82; N, 5.27.

1-Cyclohexyl-2-methyl-4-phenyl-1H-pyrrole (5g). ^{1}H NMR (DMSO-d_6): δ 7.46 (d, J = 7.6 Hz, 2H), 7.26 (t, J =



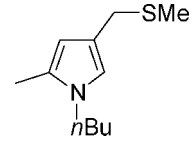
7.6 Hz, 2H), 7.19 (s, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.12 (s, 1H), 3.81 (m, 1H), 2.20 (s, 3H), 1.89–1.20 (m, 10H). ^{13}C NMR (DMSO-d_6): δ 136.6 (+), 128.9 (−), 128.8 (+), 124.9 (−), 124.4 (−), 122.3 (+), 113.9 (−), 104.3 (−), 54.7 (−), 34.2 (+), 25.9 (+), 25.5 (+), 12.3 (−). HRMS Calcd for $C_{17}H_{21}N$: m/z [M+] 239.1674. Found: 239.1673.

1-Cyclohexyl-2-methyl-4-(1-phenyl-ethyl)-1*H*-pyrrole (5h). ^{1}H NMR (DMSO-d_6): δ 7.22 (m, 4H), 7.12 (t, J = 7.0



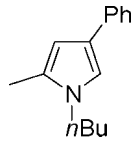
Hz, 1H), 6.46 (s, 1H), 5.24 (s, 1H), 3.84 (q, J = 7.2 Hz, 1H), 3.69 (t, J = 7.8 Hz, 1H), 2.10 (s, 3H), 1.80–1.16 (m, 13H). ^{13}C NMR (DMSO-d_6): δ 148.6 (+), 128.5 (−), 127.5 (−), 127.3 (+), 127.1 (+), 125.9 (−), 112.8 (−), 106.0 (−), 54.4 (−), 38.0 (−), 34.3 (+), 25.9 (+), 25.4 (+), 23.1 (−), 12.3 (−). HRMS Calcd for $C_{19}H_{25}N$: m/z [M+] 267.1980. Found: 267.1987.

1-Butyl-2-methyl-4-methylsulfanylmethyl-1*H*-pyrrole (5i). ^{1}H NMR (DMSO-d_6): δ 6.52 (s, 1H), 5.67 (s, 1H), 3.71 (t,



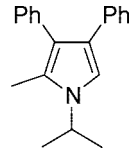
J = 7.2 Hz, 2H), 3.44 (s, 2H), 2.12 (s, 3H), 1.94 (s, 3H), 1.57 (qd, J = 7.2 Hz, 2H), 1.25 (m, J = 7.2 Hz, 2H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 128.1 (+), 119.2 (−), 117.7 (+), 107.4 (−), 45.8 (+), 33.3 (+), 30.6 (+), 19.7 (+), 15.0 (−), 14.0 (−), 12.1 (−). HRMS Calcd for $C_{11}H_{19}NS$: m/z [M+] 197.1234. Found: 197.1238.

1-Butyl-2-methyl-4-phenyl-1*H*-pyrrole (5j). ^{1}H NMR (DMSO-d_6): δ 7.44 (d, J = 7.2 Hz, 2H), 7.26 (t, J = 7.2



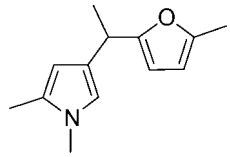
Hz, 2H), 7.09 (s, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.14 (s, 1H), 3.80 (t, J = 7.2 Hz, 2H), 2.19 (s, 3H), 1.64 (m, J = 7.2 Hz, 2H), 1.30 (m, J = 7.2 Hz, 2H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 136.5 (+), 129.2 (+), 128.9 (−), 124.9 (−), 124.4 (−), 122.2 (+), 117.6 (−), 104.7 (−), 46.2 (+), 33.3 (+), 19.8 (+), 14.0 (−), 12.1 (−). HRMS: Calcd for $C_{15}H_{19}N$: m/z [M+] 213.1517. Found: 213.1523.

1-Isopropyl-2-methyl-3,4-diphenyl-1*H*-pyrrole (5k). ^{1}H NMR (DMSO-d_6): 7.29 (t, J = 7.6 Hz, 2H), 7.25–7.02 (m,



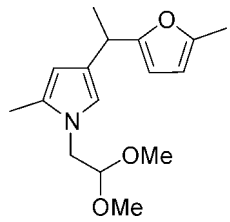
9H), 4.36 (m, J = 6.4 Hz, 1H), 2.17 (s, 3H), 1.42 (d, J = 6.4 Hz, 6H). ^{13}C NMR (DMSO-d_6): δ 137.0 (+), 136.7 (+), 130.7 (−), 128.4 (−), 128.3 (−), 127.6 (−), 126.2 (+), 125.7 (−), 125.1 (−), 122.1 (+), 119.4 (+), 114.7 (−), 47.2 (−), 23.7 (−), 10.5 (−). HRMS Calcd for $C_{20}H_{21}N$: m/z [M+] 275.1674. Found: 275.1672.

4-(1-Furan-2-yl-ethyl)-1,2-dimethyl-1*H*-pyrrole (5n). ^{1}H NMR (DMSO-d_6): δ 6.37 (s, 1H), 5.88 (s, 1H), 5.84 (s, 1H),



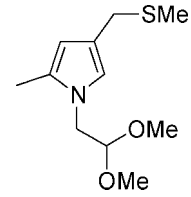
5.61 (s, 1H), 3.81 (q, J = 7.2 Hz, 1H), 3.44 (s, 3H), 2.19 (s, 3H), 2.09 (s, 3H), 1.38 (d, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 158.9 (+), 149.6 (+), 128.1 (+), 124.5 (+), 118.0 (−), 106.3 (−), 105.9 (−), 104.5 (−), 33.4 (−), 31.5 (−), 21.1 (−), 13.8 (−), 12.1 (−). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.80; H, 8.77; N, 6.46.

1-(2,2-Dimethoxy-ethyl)-2-methyl-4-[1-(5-methyl-furan-2-yl)-ethyl]-1*H*-pyrrole (5o). ^{1}H NMR (DMSO-d_6): δ 6.43



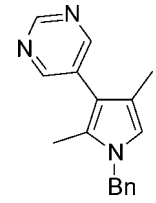
(s, 1H), 5.88 (s, 1H), 5.83 (s, 1H), 5.60 (s, 1H), 4.43 (t, J = 5.2 Hz, 1H), 3.83 (m, J = 7.2 Hz, 1H), 3.79 (d, J = 5.2 Hz, 2H), 3.24 (s, 6H), 2.18 (s, 3H), 2.12 (s, 3H), 1.37 (d, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 158.8 (+), 149.5 (+), 128.3 (+), 124.7 (+), 118.0 (−), 106.2 (−), 104.6 (−), 104.2 (−), 54.6 (−), 48.5 (+), 40.6 (−), 31.4 (−), 21.0 (−), 13.7 (−), 12.2 (−). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.61; H, 8.66; N, 5.35.

1-(2,2-Dimethoxy-ethyl)-2-methyl-4-methylsulfanylmethyl-1*H*-pyrrole (5p). ^{1}H NMR (DMSO-d_6): δ 6.55 (s, 1H),



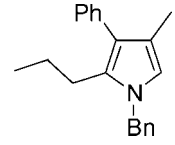
5.68 (s, 1H), 4.44 (t, J = 5.2 Hz, 1H), 3.81 (d, J = 5.2 Hz, 2H), 3.44 (s, 2H), 3.25 (s, 6H), 2.14 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 128.9 (+), 120.2 (−), 118.0 (+), 107.5 (−), 104.2 (−), 54.7 (−), 48.5 (+), 30.5 (+), 14.9 (−), 12.2 (−). Anal. Calcd for $C_{11}H_{19}NO_2S$: C, 57.61; H, 8.35; N, 6.11. Found: C, 57.49; H, 8.67; N, 6.23.

5-(1-Benzyl-2,4-dimethyl-1*H*-pyrrol-3-yl)-pyrimidine (5q). ^{1}H NMR (DMSO-d_6): δ 9.04 (s, 1H), 8.70 (s, 2H), 7.36 (t,



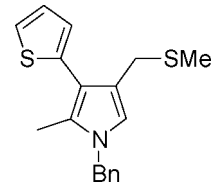
J = 7.4 Hz, 2H) 7.27 (t, J = 7.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 2H), 6.74 (s, 1H), 5.10 (s, 2H), 2.12 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 156.8 (−), 138.9 (+), 130.9 (+), 129.1 (−), 127.7 (−), 127.3 (−), 127.0 (+), 120.3 (−), 115.6 (+), 114.6 (+), 65.4 (+), 50.0 (+), 11.2 (−), 10.7 (−). HRMS Calcd for $C_{17}H_{17}N_3$: m/z [M+] 263.1416. Found: 263.1422. Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51; N, 15.96. Found: C, 77.31; H, 6.30; N, 15.60.

1-Benzyl-4-methyl-3-phenyl-2-propyl-1*H*-pyrrole (5r). ^{1}H NMR (DMSO-d_6): δ 7.38–7.10 (m, 10H), 6.56 (s, 1H),



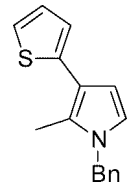
5.06 (s, 2H), 2.42 (t, J = 7.6 Hz, 2H), 1.94 (s, 3H), 1.30 (m, J = 7.6 Hz, 2H), 0.71 (t, J = 7.6 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 139.6 (+), 137.3 (+), 129.9 (+), 129.8 (−), 129.0 (−), 128.7 (−), 128.5 (−), 128.4 (−), 127.5 (−), 127.0 (−), 126.7 (−), 125.7 (−), 122.2 (+), 119.4 (−), 115.4 (+), 49.8 (+), 26.7 (+), 24.0 (+), 14.3 (−), 11.4 (−). HRMS Calcd for $C_{21}H_{23}N$: m/z [M+] 289.1830. Found: 289.1835.

1-Benzyl-2-methyl-4-methylsulfanylmethyl-3-thiophen-2-yl-1*H*-pyrrole (5s). ^{1}H NMR (DMSO-d_6): δ 7.43–6.97 (m,



8H), 6.84 (s, 1H), 5.12 (s, 2H), 3.57 (s, 2H), 2.15 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 138.8 (+), 137.6 (+), 129.1 (−), 127.7 (−), 127.1 (−), 127.0 (+), 125.6 (−), 124.6 (−), 120.9 (−), 117.1 (+), 114.0 (+), 65.4 (+), 50.2 (+), 29.2 (+), 15.2 (−), 11.0 (−). Anal. Calcd for $C_{18}H_{19}NS_2$: C, 68.96; H, 6.11; N, 4.47. Found: C, 68.54; H, 6.17; N, 4.48.

1-Benzyl-2-methyl-3-thiophen-2-yl-1*H*-pyrrole (5t). ^{1}H NMR (DMSO-d_6): δ 7.36–7.26 (m, 4H), 7.09 (d, J = 7.6



Hz, 2H), 7.03 (t, J = 4.4 Hz, 1H), 6.98 (d, J = 3.2 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.24 (d, J = 2.8 Hz, 1H), 5.14 (s, 2H), 2.24 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 140.2 (+), 138.9 (+), 129.1 (−), 127.9 (−), 127.7 (−), 127.0 (−), 125.1 (+), 122.6 (−), 122.1 (−), 121.8 (−), 115.4 (+), 107.3 (−), 50.2 (+), 11.2 (−). HRMS Calcd for $C_{16}H_{15}NS$: *m*/*z* [M+] 253.0916. Found: 253.0925.

Acknowledgment. The authors are grateful to the Ontario Research and Development Challenge Fund for financial support of this research and to Biotage Inc. for the donation of an Initiator microwave synthesizer.

Supporting Information Available. Proton and carbon NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Fuerstner, A. *Angew. Chem, Int. Ed.* **2003**, *42*, 3582–3603. (b) Trost, B. M.; Dong, G. *Org. Lett.* **2007**, *9*, 2357–2359. (c) Grube, A.; Kock, M. *J. Nat. Prod.* **2006**, *69*, 1212–1214.

(2) (a) Pu, S.; Liu, G.; Shen, L.; Xu, J. *Org. Lett.* **2007**, *9*, 2139–2142. (b) Gabriel, S.; Cecius, M.; Fleury-Frenette, K.; Cossement, D.; Hecq, M.; Ruth, N.; Jerome, R.; Jerome, C. *Chem. Mater.* **2007**, *19*, 2364–2371. (c) Curran, D.; Grimshaw, J.; Perera, S. D. *Chem. Soc. Rev.* **1991**, *20*, 391–404.

(3) (a) Rossi, R.; Bellina, F. *Tetrahedron* **2006**, *62*, 7213–7256. (b) La Regina, G.; Silvestri, R.; Artico, M.; Lavecchia, A.; Novellino, E.; Befani, O.; Turini, P.; Agostinelli, E. *J. Med. Chem.* **2007**, *50*, 922–931. (c) Tsukamoto, S.; Tane, K.; Ohta, T.; Matsunaga, S.; Fusetani, N.; van Soest, R. *J. Nat. Prod.* **2001**, *64*, 1576–1578.

(4) Jones, R. A. *Pyrroles, Part II, The Synthesis, Reactivity and Physical Properties of Substituted Pyrroles*; Wiley: New York, 1992.

(5) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635–1642.

(6) Paal, C. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367–371.

(7) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474–1476.

(8) (a) Scheidt, K. A.; Galliford, C. V. *J. Org. Chem.* **2007**, *72*, 1811–1813. (b) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238–6241. (c) Scheidt, K. A.; Bharadwaj, A. R. *Org. Lett.* **2004**, *14*, 2465–2468. (d) Arndtsen, B. A.; Dhawan, R. *J. Am. Chem. Soc.* **2004**, *126*, 468–469. (e) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427–4429.

(9) (a) Buchwald, S. L.; Martin, R.; Larsen, C. H.; Cuenca, A. *Org. Lett.* **2007**, *9*, 3379–3382. (b) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181–3184. (c) Liu, R. S.; Li, C. W.; Shen, H. C. *Tetrahedron Lett.* **2004**, *45*, 9245–9247. (d) Odom, A. L.; Armstrong, D.; Keith, A. J.; Ramanathan, B. *Org. Lett.* **2004**, *17*, 2957–2960. (e) Braun, R. U.; Zeitler, K.; Muller, T. J. J. *Org. Lett.* **2001**, *3*, 3297–3300. (f) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. R. *Tetrahedron. Lett* **2001**, *42*, 1399–1341. (g) Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 873–874.

(10) Cossy, J.; Poitevin, C.; Salle, L.; Gomez Pardo, D. *Tetrahedron Lett.* **1996**, *37*, 6709–6710.

(11) (a) Kopka, I.; Fataftah, Z.; Rathke, M. *J. Org. Chem.* **1980**, *45*, 4616–4622. (b) Imada, Y.; Yuassa, M.; Nakamura, I.; Murahashi, S. *J. Org. Chem.* **1994**, *59*, 2282–2284.

(12) (a) Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A. *Org. Lett.* **2004**, *6*, 1001–1003. (b) Bieber, L. W.; da Silva, M. F. *Tetrahedron Lett.* **2004**, *45*, 8281–8283.

(13) (a) Zhang, W.; Cheng, J.; Ding, L.; Zhong, P.; Zhao, L.; Wu, H. *Synth. Commun* **2006**, *14*, 2001–2007. (b) Nakamura, H.; Kamakura, T.; Ishikuma, M.; Biellmann, J. *J. Am. Chem. Soc.* **2004**, *126*, 5958–5959. (c) Dyatkin, Alexey, B.; Rivero, Ralph, A. *Tetrahedron Lett.* **1998**, *22*, 3647–3650.

(14) (a) Comer, E.; Organ, M. G. *J. Am. Chem. Soc.* **2005**, *127*, 8160–8167. (b) Organ, M. G.; Comer, E. *Chem.—Eur. J.* **2005**, *11*, 7223–7227. (c) Bremner, W. S.; Organ, M. G. *J. Comb. Chem.* **2007**, *9*, 14–16.

CC700159U