JOURNAL OF combinatorial CHEMISTRY

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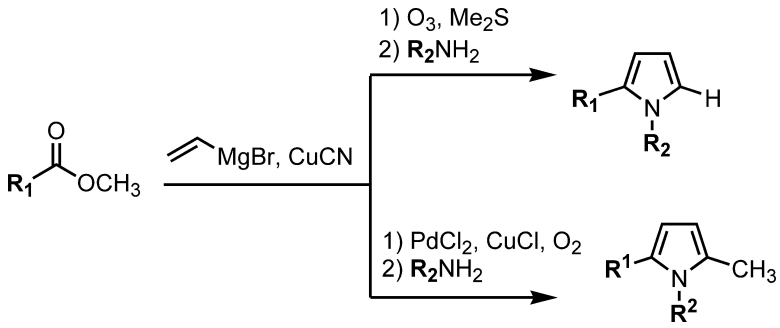
J. Comb. Chem., **2004**, 6 (6), 893-898• DOI: 10.1021/cc049904x • Publication Date (Web): 08 September 2004



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Three-Step Solution-Phase Combinatorial Access to 1,2-Disubstituted and 1,2,5-Trisubstituted Pyrroles from Carboxylic Esters

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Received May 25, 2004

An efficient diversity-oriented strategy has been developed for the solution-phase parallel synthesis of di- and trisubstituted pyrrole libraries. Methyl esters **1** were effectively converted to 1,2-di- and 1,2,5-trisubstituted pyrroles **5** and **6** in three steps. Treatment of ester **1** with vinylmagnesium bromide in the presence of copper (I) cyanide yielded the corresponding homoallylic ketone **2**, which was subjected to ozonolysis or Tsuji−Wacker oxidation to yield the respective cyclization precursors **3** and **4** after aqueous workup. Compounds **3** and **4** were condensed without further purification with a primary amine to afford the desired 1,2-di- or 1,2,5-trisubstituted pyrroles **5** and **6** in good yield and purity.

Introduction

Pyrroles[1−4] are abundant as constituents of natural products[5−8] and have broad synthetic utility in both materials science and medicine. Pyrrole-containing pharmaceuticals include the cholesterol-lowering drug atorvastatin calcium (Lipitor, Figure 1), notable[9] as the first drug to earn in excess of $1 billion in its first year of sales. Pyrroles exhibiting a 1,2,5-trisubstitution pattern display interesting biological properties, including antipsychotic,[10−12] antiinflammatory,[13,14] radioprotective,[15] and spasmolytic[16,17] activity. Two clinical examples of pyrroles displaying this substitution pattern are the nonsteroidal antiinflammatory agents amtolmetin and tolmetin[18] (Figure 1).

Despite the value of pyrrole-containing compounds as biological agents, few combinatorial strategies exist for their synthesis, relative to the abundant approaches available for the related indole and imidazole counterparts.[19] Multicomponent coupling has been most often used to prepare multisubstituted pyrroles because preassembly of complex precursors for cyclization is not required. Nevertheless, pyrroles prepared from multicomponent pathways typically possess limited diversity and invariably contain at least one aryl substituent, often juxtaposed with one or more electron withdrawing groups. For example, pyrrole libraries have been constructed in solution[20,21] and on solid support[22,23] by the cycloaddition of 1,3-dipoles to activated olefins (nitrostyrenes) or alkynes. Pyrrole assembly by the addition of enaminones or imines to nitrostyrenes has found application using solvent-free,[24] solid-supported,[25] and microwave-assisted[26] conditions. A solid-phase adaptation of the classical Hantzsch[27] cyclocondensation of enaminones with α-bromoketones has also been described.[28] The paucity of commercially available olefins and alkynes and the tendency for unsymmetrical alkynes to give regioisomeric mixtures are general limitations to the above approaches.[29] Recent strategies that may be amenable to improving diversity in pyrrole library synthesis include the rhodium-catalyzed cyclocondensation of isonitriles with 1,3-diones,[30] Lewis acid-activated [3 + 2] dipolar cycloaddition of donor−acceptor cyclopropanes with nitriles,[31] [3 + 2] cycloaddition of *O*-propargylic salicylaldehydes with *N*-alkylglycinates,[32] regiospecific alkylation of lithiated 2-alkynylamines or 2-alkynyl alcohols with alkyl isothiocyanates,[33] and the microwave-assisted cyclization of 1,4-diketoesters.[34]

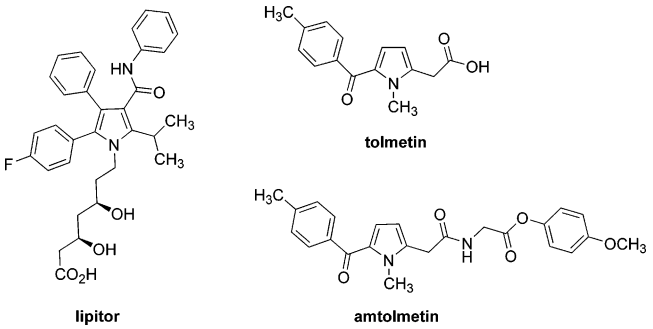


Figure 1. Representative pyrrole-containing drugs.

The commonly utilized Paal−Knorr[35,36] approach, in which a 1,4-diketone is condensed with an amine, is particularly well suited for the synthesis of pyrroles bearing a 1,2,5-trisubstitution pattern. The requisite 1,4-diketone[37,38] component is often obtained by the Stetter[39,40] reaction, which typically combines an aldehyde with an α,β-unsaturated ketone under cyanide or thiazolium salt catalysis. The usefulness of a combined Stetter−Paal−Knorr sequence for the diversity oriented generation of pyrroles has been exemplified by several recent solid-[41,42] and solution-phase[14,43] examples. Although of wide scope, the Stetter reaction usually only gives best yields[39] with straight-chain aliphatic, aryl, and heteroaryl aldehydes, and chromatography is usually required to obtain suitably pure 1,4-dicarbonyl compounds. In the context of pyrrole generation, alternative strategies for 1,4-dione synthesis have generally been less tolerant of structural diversity.[44−49]

Recently, we described[50] a protocol for synthesizing homoallylic ketones **2** by a copper-catalyzed cascade addition

10.1021/cc049904x CCC: $27.50
Published on Web 09/08/2004

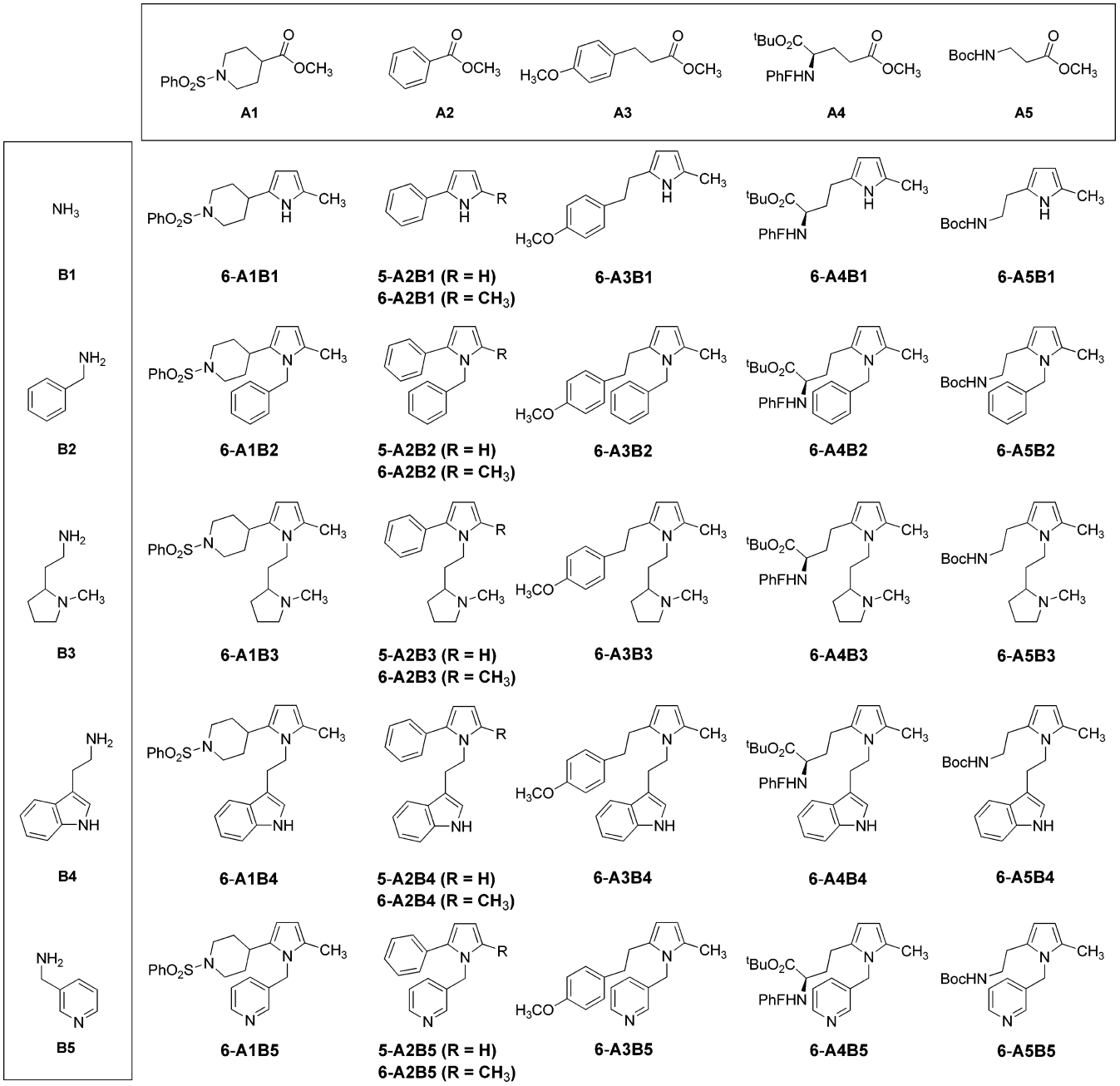


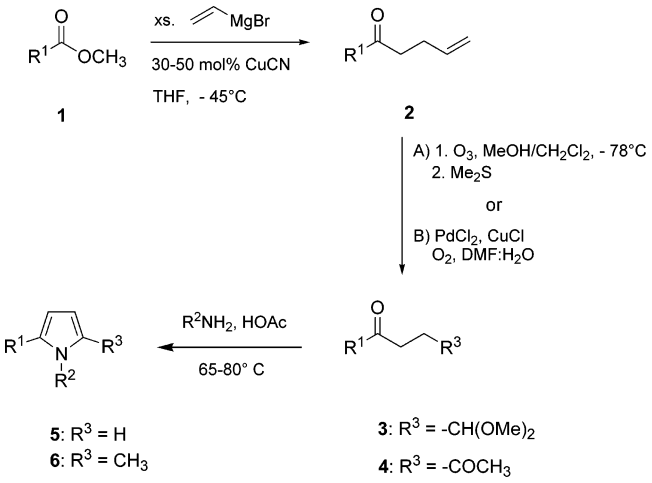
Figure 2. Diversity elements **A1**-**A5**, **B1**-**B5**, and 1,2-di- and 1,2,5-trisubstituted pyrroles **5** and **6**.

of vinyl Grignard reagent to carboxylic esters[51−56] **1** (Scheme 1). Homoallylic ketones **2** possessing a wide variety of functional groups, such as amines, sulfonamides, alcohols, and carbamates, have been effectively prepared by this reaction. Oxidation of the olefin terminus of **2** has now been explored to afford the Paal−Knorr cyclization precursors **3** and **4** for use in the generation of 1,2-di- and 1,2,5-trisubstituted pyrroles **5** and **6**, respectively (Scheme 1 and Figure 2). The utility and general scope of this convenient method for combinatorial solution-phase synthesis has now been demonstrated.

Results and Discussion

A library of 30 diverse pyrroles has been synthesized by judicious choice of a primary amine **B**, the requisite starting ester **1**, and oxidation conditions for the respective introduction of diversity at the 1-, 2-, and 5-positions of the pyrrole core (Figure 2). Pyrrole construction began with the preparation[50] of homoallylic ketones **2**, obtained by treatment of a series of esters **1** with excess vinylmagnesium bromide in the presence of catalytic amounts of CuCN in THF at −45 °C (Scheme 1). Ketones **2** usually required purification by flash chromatography, except in the case of ketone **2-A5**, which was sufficiently pure after aqueous workup to be used in subsequent chemistry. Oxidation of the olefin terminus was performed in two ways. Ozonolysis of ketone **2-A2** in $MeOH/CH_2Cl_2$ (5:1) at −78 °C followed by treatment with excess Me_2S afforded the masked 1,4-ketoaldehyde **3-A2**.[57] Alternatively, ketone **2** was oxidized[58] with 20 mol % of $PdCl_2$ and 100 mol % of CuCl in the presence of oxygen to generate the 1,4-dione **4** (Scheme 1). The crude products obtained after aqueous work up and lyophilization of the residual DMF were typically of sufficient purity for subsequent steps. Pyrrole formation was completed by condensa-

Scheme 1. Grignard/Ozonolysis/Paal−Knorr and Grignard/Tsuji−Wacker/Paal−Knorr Sequences for the Synthesis of Pyrroles **5** and **6**



tion of five primary amine **B** diversity elements with compounds **3** and **4** under Paal−Knorr conditions to generate the pyrroles **5** and **6**, respectively (Scheme 1). Two sets of cyclization conditions were utilized. Masked ketoaldehyde **3-A2** was successfully cyclized onto amine **B** (300−500 mol %) in a biphasic mixture of 1,2-dichloroethane and HOAc/H_2O (1:1) at 80 °C. Alternatively, dione **4** was condensed with amine **B** (300−500 mol %) in the presence of a 1:1 mixture of NaOAc/HOAc (1 equiv w/w) in anhydrous toluene or acetonitrile at 65 °C. Under both sets of conditions, pyrrole formation was generally rapid (∼1−5 h) and uneventful, as monitored by TLC analysis. Typical workup involved removal of excess amine by partitioning of the reaction mixture between Et_2O/CH_2Cl_2 (2:1) and phosphate buffer (pH 6.8), followed by drying over $MgSO_4$ and removal of volatiles by rotary evaporation and lyophilization. In this manner, pyrroles **5** and **6** were isolated in 54−87% and 42−99% yields, respectively, with purities ranging from 56−99% to 68−97%, as determined by reversed-phase HPLC at 214 nM (Table 1). In several instances, chromatography was performed to provide spectrally pure material (Table 1).

Pyrroles rich in functionality were thus efficiently delivered by the three-step Grignard/Tsuji−Wacker/Paal−Knorr sequence from aliphatic and aromatic esters **1**. Although the Tsuji−Wacker process limits diversity at the 5-position to a methyl substituent, the potential may exist to oxidize this position for further modifications.[59−61] Moreover, the sequential ozonolysis/Paal−Knorr reaction sequence on homoallylic ketone **2-A2** furnished pyrroles **5-A2B1**−**B5**, which may be suitable for derivatization at the 5-position by various chemical modifications, such as Vilsmeier−Haack[62] formylation (Figure 2). Furthermore, pyrroles such as **6-A4B1**−**B5** and **6-A5B1**−**B5** that possess amine and carboxylate handles offer potential for the attachment of additional diversity elements. In comparison to the related Stetter/Paal−Knorr approaches, this route exhibits certain advantages, such as the ability to employ relatively stable, functionally diverse esters instead of aldehydes in the synthesis of the penultimate cyclization intermediates **3** and **4** (Scheme 1). Furthermore, although chromatography of the homoallylic ketone **2** is usually necessary, the subsequent oxidation and cyclization steps provide pyrrole products **5** and **6** that are sufficiently pure for biological assays. This is usually not the case in solution-phase approaches[14,43,63] involving the Stetter[39,40] reaction because chromatography is typically required in the later part of the sequence to remove the thiazolium catalyst used in the 1,4-dione synthesis.

Table 1. Yields and Purities of 1,2-Di- and 1,2,5-Trisubstituted Pyrroles **5** and **6**

entry	pyrrole	isolated yield (%)[a]	crude purity (%)[b]
1	**5-A2B1**	94	56
2	**5-A2B2**	84	≥98
3	**5-A2B3**	54	≥98
4	**5-A2B4**	89	79
5	**5-A2B5**	87	≥98
6	**6-A1B1**	93	95
7	**6-A1B2**	96	85
8	**6-A1B3**	83	96
9	**6-A1B4**	42[c]	95[d]
10	**6-A1B5**	99	93
11	**6-A2B1**	89	98
12	**6-A2B2**	69	95
13	**6-A2B3**	67	78
14	**6-A2B4**	77	95
15	**6-A2B5**	77	97
16	**6-A3B1**	95	96
17	**6-A3B2**	93	79
18	**6-A3B3**	78	96
19	**6-A3B4**	86	76
20	**6-A3B5**	98	97
21	**6-A4B1**	86	85
22	**6-A4B2**	83	98
23	**6-A4B3**	77	97
24	**6-A4B4**	90	95
25	**6-A4B5**	90	92
26	**6-A5B1**	70[e]	83
27	**6-A5B2**	72[e]	84
28	**6-A5B3**	72	94
29	**6-A5B4**	55[e]	68
30	**6-A5B5**	49[e]	88

[a] From **3** or **4**. [b] As determined by reversed-phase HPLC with monitoring at 214 nM. [c] Isolated yield after trituration from EtOAc/hexane (1:1). [d] Purity of product after trituration. [e] Yield after chromatography.

Conclusions

A total of 30 pyrroles was synthesized in good yield and purity from a series of structurally diverse methyl esters by utilizing sequential Grignard/ozonolysis/Paal−Knorr and Grignard/Tsuji−Wacker/Paal−Knorr reaction sequences. Of the 30 examples, 5 were 1,2-disubstituted, and 25 displayed a 1,2,5-trisubstitution pattern. The improved product diversity and ease of product isolation distinguishes this new protocol as an effective method for synthesizing pyrrole libraries.

Experimental Section

General. For reactions performed under anhydrous conditions, glassware was either oven- or flame-dried, and the reaction was performed under a positive pressure of argon. Anhydrous solvents (THF, CH_3CN, toluene) were obtained by passage through solvent filtration systems (GlassContour, Irvine, CA). NMR spectra were recorded on either a Bruker AV 400-MHz or AV 300-MHz spectrometer. Chemical shifts for ^1H and ^{13}C NMR spectra were recorded in parts per

million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.24 ppm, 77.00 ppm). High-resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. HPLC analysis was performed on a Higgins Analytical C18 reversed-phase analytical column (5μm Targa 250 × 4.6 mm; Part No. TS-2546-C185). Analytical elutions were performed using a flow rate of 1 mL/min, and gradients of 96%/4% to 0%/100% A/B over 20 min (method A), 80%/20% to 0%/100% A/B over 20 min (method B), 70%/30% to 0%/100% A/B over 20 min (method C), 60%/40% to 0%/100% A/B over 20 min (method D), and 40%/60% to 0%/100% A/B over 15 min (method E), or under isocratic conditions with 10%/90% A/B (method F), where A = H_2O−0.1% TFA and B = CH_3CN/H_2O(90:10)−0.1% TFA. Retention times (R_t) are reported as follows: R_t (min) and elution conditions. Homoallylic ketones **2A1**−**A3** were prepared as previously reported.[50] Ester **1-A5** was prepared from β-alanine by esterification (MeOH/MeCOCl), followed by Boc-protection (di-*tert*-butyl dicarbonate/Na_2CO_3 in dioxane/H_2O). Palladium (II) chloride (99.9%) and copper (I) chloride (99+ %) were purchased from Aldrich.

4,4-Dimethoxy-1-phenylbutan-1-one (3-A2). A solution of **2-A2** (257 mg, 1.6 mmol) in MeOH/CH_2Cl_2 (5:1, 10 mL) was treated with ozone at −78 °C until a blue color persisted. The −78 °C reaction mixture was purged with a stream of argon to remove excess ozone, treated with dimethyl sulfide (0.6 mL, 8 mmol), and stirred overnight, after which time the bath temperature had warmed to room temperature. Removal of the volatiles by rotary evaporation followed by lyophilization gave crude product (260 mg, 78%) which was sufficiently pure for the next step. NMR data was consistent with the literature.[64]

General Procedure for the Synthesis of 1,4-Diones (4). A two-necked flask fitted with a septum and connected to an oxygen-filled balloon via a three-way tap was charged with $PdCl_2$ (∼0.2 equiv) and CuCl (∼1.0 equiv), treated with a solution of DMF/H_2O (7:1, ∼3 mL/mmol CuCl), evacuated, and flushed with oxygen three times. After stirring at room temperature for 1 h, the mixture was treated via syringe with a solution of homoallylic ketone **2** (1.0 equiv) in DMF/H_2O (7:1, ∼1 mL/mmol homoallylic ketone) and stirred overnight. On occasion, if TLC analysis revealed unreacted starting material, an additional quantity of $PdCl_2$ (∼0.2 equiv) was added to the mixture, and stirring was continued until the starting material was completely consumed (TLC). The reaction mixture was partitioned between EtOAc and HCl solution (1 M aqueous), and the layers were separated. The aqueous layer was extracted with several portions of EtOAc, and the combined organic layers were washed with water and brine. The aqueous washings were extracted with EtOAc, and the combined organic phase was dried with $MgSO_4$ and evaporated. Lyophilization of residual DMF from the crude product afforded 1,4-dione **4** of sufficient purity for the next step.

Example: 1-(1-Benzenesulfonylpiperidin-4-yl)-pentane-1,4-dione (4-A1). Prepared as a pale brown oil (294 mg, 95% yield) from **2-A1** (295 mg, 0.96 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63−1.76 (dq, J = 11.3, ∼3 Hz, 2H), 1.86−1.95 (m, 2H), 2.12 (s, 3H), 2.31 (tt, J = 11.6, 3.8 Hz, 1H), 2.39 (dt, J = 11.6, ∼3 Hz, 2H), 2.56−2.62 (m, 2H), 2.64−2.70 (m, 2H), 3.66−3.74 (m, 2H), 7.47−7.61 (m, 3H), 7.70−7.75 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 29.8, 33.9, 36.8, 45.5, 47.3, 127.6, 129.0, 132.8, 136.2, 207.0, 210.0. HRMS (FAB) m/z 324.1258 [M + H$^+$; calcd for $C_{16}H_{22}NO_4S$: 324.1264].

General Procedure for the Synthesis of Pyrroles (5). For the preparation of pyrroles **5-A2B1**, **5-A2B2**, **5-A2B4**, and **5-A2B5**, a biphasic mixture of **3-A2** (1 equiv) and amine **B** (300−500 mol %) in HOAc/H_2O (1:1, 1 mL) and 1,2-dichloroethane (1 mL) was heated to 80 °C with rapid stirring until complete consumption of the starting material was observed by TLC. Slightly modified conditions were employed for the preparation of pyrrole **5-A2B3** due to the water-soluble nature of amine **B3** and the increased propensity of **5-A2B3** to degrade under the reaction conditions; hence, a mixture of **3-A2** (1 equiv), amine **B3** (500 mol %) was buffered with KOAc (0.86 g) in HOAc/H_2O/CH_3CN (1:1:1, 1.5 mL) and heated at 80 °C for 12 h. After cooling to RT, the reaction mixture was partitioned between Et_2O/CH_2Cl_2 (2:1) and Na_2CO_3 solution (5% aqueous). The layers were separated, and the aqueous phase was extracted with Et_2O/CH_2Cl_2 (2:1). The combined organic phases were washed with pH 6.8 sodium phosphate buffer, dried with $MgSO_4$, and evaporated.

Example: 2-Phenyl-1*H*-pyrrole (5-A2B2). Prepared from **3-A2** (32.5 mg, 0.156 mmol) to yield crude product (21 mg), which was chromatographed (90:10 hexanes/EtOAc) to give the title compound (12.5 mg, 56%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (dd, J = 2.7 Hz, 1H), 6.50−6.56 (m, 1H), 6.83−6.88 (m, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.7 Hz, 2H), 7.44−7.50 (m, 2H), 8.30−8.55 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.9, 110.1, 118.8, 123.8, 126.2, 128.9, 132.1, 132.7. ESMS m/z 144 (M + H)$^+$. R_t: 15.5 (method C).

General Procedure for the Synthesis of Pyrroles (6). A mixture of 1,4-dione **4** (1 equiv), amine **B** (300−500 mol %) and NaOAc/HOAc (prepared by mixing equimolar quantities of NaOAc and HOAc; 1 equiv w/w) in toluene (with amines **B2**−**B5**) or MeCN (with amine **B1**) (∼10 mL solvent per 1 mmol **4**) was heated at 65 °C until complete consumption of starting material (TLC). After cooling to room temperature, the reaction mixture was partitioned between Et_2O/CH_2Cl_2 (2:1) and pH 6.8 sodium phosphate buffer (with amines **B1**, **B3**−**B5**) or 1 M HCl solution (with amine **B2**). The layers were separated, and the organic phase was washed with pH 6.8 sodium phosphate buffer (with amines **B1**, **B3**−**B5**) or 1 M HCl solution (with amine **B2**). The aqueous phase was extracted with Et_2O/CH_2Cl_2 (2:1), and the combined organic phases were dried with $MgSO_4$. Volatiles were removed by successive rotary evaporation/lyophilization.

Example: 1-Benzenesulfonyl-4-(1-benzyl-5-methyl-1*H*-pyrrol-2-yl)-piperidine (6-A1B2). Prepared from **4-A1** (22.2 mg, 0.068 mmol) and **B2** to yield the title compound (25.8 mg, 96%) as an orange/brown powder after lyophilization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68−1.83 (m, 4H), 2.09 (s,

3H), 2.18−2.34 (m, 3H), 3.78−3.88 (m, 2H), 4.97 (s, 2H), 5.89 (d, $J = 3.5$ Hz, 1H), 5.91 (d, $J = 3.5$ Hz, 1H), 6.77 (d, $J = 6.9$ Hz, 2H), 7.18−7.29 (m, 3H), 7.49−7.64 (m, 3H), 7.73−7.78 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 136.1, 135.5, 132.6, 128.9, 128.7, 128.4, 127.6, 127.1, 125.3, 106.0, 103.4, 46.6, 46.4, 33.3, 32.3, 12.2. HRMS (EI) *m*/*z* 394.1725 [M^+; calcd for $C_{23}H_{26}N_2O_2S$: 394.1715]. R_t: 23.7 (method A).

Acknowledgment. This work was supported by grants from Fonds Québécois de la recherche sur la nature et les technologies (FQRNT), Valorisation-Recherche Québéc (VRQ), and the Natural Sciences and Engineering Research Council of Canada (NSERC). We thank Mr. Dalbir Sekhon for mass spectral analysis.

Supporting Information Available. Detailed experimental procedures, characterization and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC049904X