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Synthesis of 2,2′-Bipyrroles and 2,2′-Thienylpyrroles from Donor–Acceptor Cyclopropanes and 2-Cyanoheteroles

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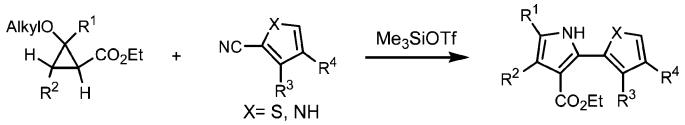
ABSTRACT



Two new series of 2,2′-bipyrroles and 2,2′-thienylpyrroles have been prepared by trimethylsilyl trifluoromethanesulfonate (TMSOTf)-mediated reaction of donor–acceptor cyclopropanes with 2-cyanopyrroles and 2-cyanothiophene, respectively. This method opens the door toward a wide variety of unsymmetrical bipyrroles and thienylpyrroles.

Pyrrole and its derivatives are ubiquitous in nature.[1] Pyrrole-containing compounds are spread throughout the phylogenic tree;[1] leaves (chlorophyll), red-blood cells (heme), and seabird eggs[2] (bipyrrole) are just a few well-known examples. Thienylpyrrole and bipyrroles have been the focus of material science and medicinal chemistry. In material science, they have found applications in indigoid dyes,[3] conducting polymers,[4] anion binding agents,[5] and nuclear waste removal agents,[6] while in medicinal chemistry, they are important building blocks for the synthesis of antitumor agents (prodigiosins,[7] sapphyrins[8]) and therapeutic agents in photodynamic therapy as radiation sensitizers.[8]

Classic bipyrrole syntheses mostly employ oxidative,[9] Ullman-type[10] homocouplings or couplings of pyrrolinones

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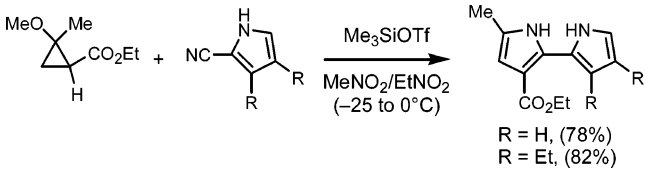
with pyrroles.[11] These methods, although widely employed, are generally limited to the preparation of symmetric bipyrroles (oxidative and Ullman couplings) or to a limited range of unsymmetrical products (pyrrolinone pathway). In recent years, advances in Suzuki[12] and Stille[4] couplings, mostly focused on prodigiosin synthesis, were developed for preparing unsymmetric bypyrroles. A different approach to α,α′-fused heterocycles is to assemble the heterocycles from a single appropriate precursor rather than coupling two preformed assemblies.[13]

Recently, we reported a new strategy for diversity-oriented synthesis of pyrroles[14] that involves the reaction of donor−acceptor (DA) cyclopropanes with aliphatic, aromatic, and α,β-unsaturated nitriles.[15] Advantages to this method include the use of readily accessible starting materials, complete regiochemical control over substituent placement, and ease of product purification. Herein we present a useful application of this methodology to the synthesis of unsymmetrical bipyrroles and thienylpyrroles, which employs the classic synthetic strategy for pyrrole construction of utilizing a functional group extending from a preexisting heterocycle.[13]

For our initial studies, we directed our attention toward the synthesis of α,α′-bipyrroles from two 2-cyanoprroles that are commercially available (1*H*-pyrrole-2-carbonitrile) or accessible by reported procedures (3,4-diethyl-1*H*-pyrrole-2-carbonitrile) (Scheme 1).[16] When a cold (−25 to 0 °C)

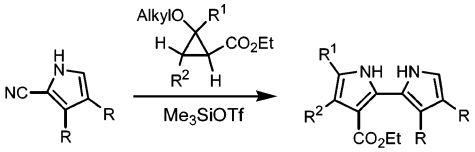
Scheme 1

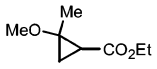
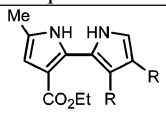
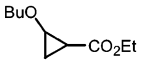
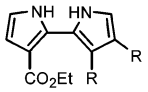
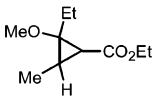
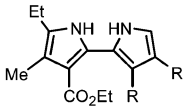
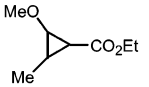
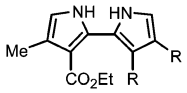
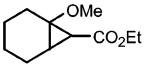
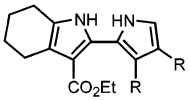
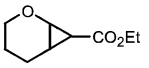
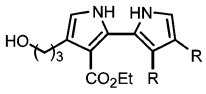
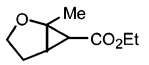
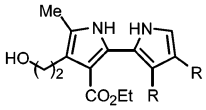
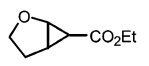
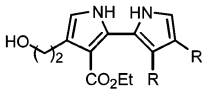


$MeNO_2$ or $EtNO_2$ solution of DA cyclopropane and pyrrole-2-carbonitrile was treated with a stoichiometric amount of trimethylsilyl triflate, a cyclization, tautomerization, and dehydration reaction cascade ensued that gave the targeted byprrole products in good isolated yields (78 and 82%). Protection of the pyrrole nitrogen proved to be unnecessary.

Inspired by these results, the generality of the bipyrrole synthesis was examined with variously substituted DA cyclopropanes, and the results are summarized in Table 1.

Table 1. Synthesis of Bipyrroles from DA Cyclopropanes and Pyrrole-2-carbonitriles



entry	cyclopropane	product	R	yield
1			H	78%
2			Et	82%
3			H	41%
4			Et	45%
5			H	82%
6			Et	85%
7			H	48%
8			H	62%
9			Et	82%
10			H	46%
11			Et	54%
12			Et	84%
13			Et	42%

The first examples studied gave bipyrroles with a methyl group installed at the α-position (Scheme 1, Table 1, entries 1 and 2), and the reactions in entries 3 and 4 show that the α-position need not be substituted. The experiments in entries 5 and 6 provided bipyrroles with alkyl substitution at both the α- and β-positions, and entry 7 completes the series by providing a bipyrrole with only β-substitution. The remaining

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(14) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099−5101.

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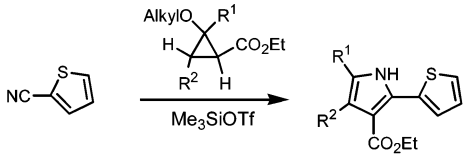
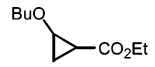
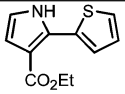
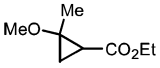
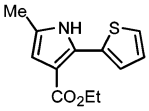
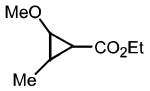
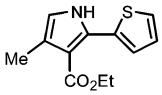
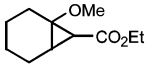
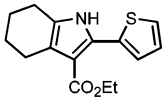
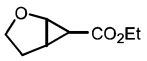
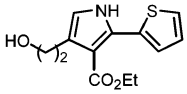
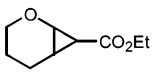
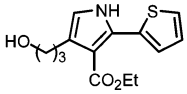
(16) (a) Barnett, G. H.; Anderson, H. J.; Loader, C. E. *Can. J. Chem.* **1980**, *58*, 409−411. (b) Loader, C. H.; Anderson, H. J. *Can. J. Chem.* **1981**, *59*, 2673−2676.

Table 2. Synthesis of Thienylpyrroles from DA Cyclopropanes and Thiophene-2-carbonitriles



entry	cyclopropane	product	yield
1			47%
2			69%
3			63%
4			37%
5			41%
6			73%

entries in Table 1 explore reactivity with 6,3- and 5,3-fused DA cyclopropanes. These substrates afforded bipyrroles with different substitution patterns, and in entries 10−13, a hydroxyl group terminates the chain at the β-position, thereby providing a synthetically useful functional handle.

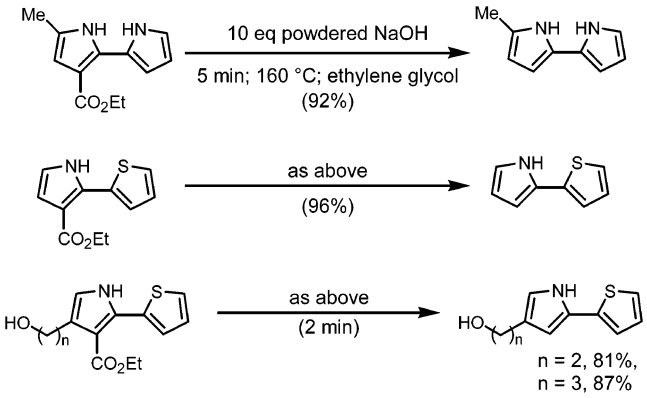
A quick inspection of the results summarized in Table 1 reveals that the yields for the formation of bipyrroles starting from 3,4-diethyl-1*H*-pyrrole-2-carbonitrile were consistently higher than those obtained from the unsubstituted pyrrole. This outcome is consistent with the greater nucleophilicity expected to be endowed to the nitrile by the electron-donating ethyl groups at the pyrrole β-positions.

The identical reaction conditions were then applied to the synthesis of thienylpyrroles by the combination of various DA cyclopropanes and thiophene-2-carbonitrile (Table 2). These results again demonstrate the ability of this synthetic method to control the installation of alkyl groups at the α- and β-positions of the newly formed pyrrole.

Higher yields were obtained from reaction with DA cyclopropanes wherein the alkoxy group is attached to a quaternary carbon (e.g., Table 1, entries 1, 2, 5, 6, 8, 9, and 12; Table 2, entry 2 (but not 4)), results that generally parallel the stability of the intermediate oxocarbenium ion generated from cyclopropane ring opening.

In some prospective applications, electron-rich variants of these bipyrroles and thienylpyrroles will be required. In this regard, the β-ethyl carboxylate can be removed by decarboxylation in hot alkaline ethylene glycol (Scheme 2). High reaction temperatures and short reaction times (e.g., 160 °C oil bath, 5 min) give the best yields.

Scheme 2



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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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