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A Powerful New Strategy for Diversity-Oriented Synthesis of Pyrroles from Donor–Acceptor Cyclopropanes and Nitriles

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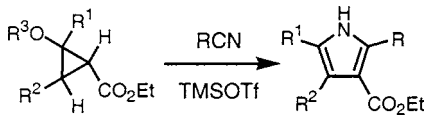
ABSTRACT



Lewis acid activated donor–acceptor cyclopropanes react with aliphatic, aromatic, and α,β-unsaturated nitriles in a novel cascade [3 + 2] dipolar cycloaddition, dehydration, and tautomerization sequence to afford pyrroles in moderate to excellent overall yield. This cost-effective and regiospecific method is ideally suited for the preparation of combinatorial libraries.

Pyrroles, important heterocycles that occur in porphyrins,[1] pigments,[2] and other natural products,[3] have found applications in materials science[4] and are common components in molecular recognition and self-assembly ensembles.[5−7] There are dozens of reported pyrrole syntheses, some of the most reliable of which date from the 19th century, such as the Hantzsch[8] and Paal−Knoor[9] procedures.[10,11] These classic condensation reactions between activated methylenes and amino ketones can be limited by their efficiency, functional group compatibility, regiospecificity, or the variety of substituents that can be introduced around the pyrrole. More recent pyrrole syntheses typically showcase special methodology or excel at accessing one substitution motif, but a universal strategy for efficiently preparing all combinations of substituted pyrroles from easily handled materials is lacking.[12]

Recently, we reported the first formal [3 + 2] cycloaddition between nitriles and donor−acceptor (DA) cyclopropanes to afford 3,4-dihydro-2*H*-pyrroles.[13,14] Cycloaddition reactions between DA-cyclopropanes and other kinds of dipolarophiles are known,[15,16] but the novelty and the clear synthetic potential of the nitrile cycloaddition prompted us to explore extending the strategy to include additional classes of DA-cyclopropanes. However, all attempted nitrile cycloaddition reactions with cyclopropanes other than those prepared by intramolecular cyclopropanation failed to incorporate nitrile,[17] and only the rearrangement products **3** were obtained (Scheme 1).

We speculated that a solvent capable of sufficiently stabilizing the intermediate oxocarbenium ion might funnel the reaction pathway back into the cycloaddition manifold. In this regard, we found that the use of nitromethane or nitroethane as solvent at low temperature (−45 to −30 °C)

(1) For a recent review: Smith, K. M. J. *Porphyrins and Phthalocyanines* **2000**, *4*, 319−324.
(2) Battersby, A. R. *Nat. Prod. Rep*. **2000**, *17*, 507−526.
(3) Christophersen, C. In *The Alkaloids*; Brossei, A., Ed.; Academic Press: Orlando, 1985; Vol. 24, Chapter 2.
(4) For reviews: (a) Baumgarten, M.; Tyutyulkov, N. *Chem. Eur. J*. **1998**, *4*, 987−989. (b) Deronzier, A.; Moutet, J.-C. *Curr. Top. Electrochem*. **1994**, *3*, 159−200.
(5) Gale, P. A.; Anzenbacher, P.; Sessler, J. L. *Coord. Chem. Rev*. **2001**, *222*, 57−102.
(6) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed*. **2001**, *40*, 2383−2426.
(7) Wemmer, D. E. *Biopolymers* **1999**, *52*, 197−211.
(8) Hantzsch, A. *Ber*. **1890**, *23*, 1474−1483.
(9) Paal, C. *Ber*. **1885**, *18*, 367−371. (b) Knorr, L. *Ber*. **1885**, 18, 299−311. (c) Elming, N.; Clauson-Kaas, N. *Acta Chem. Scand*. **1952**, *5*, 867−874.
(10) Piloty, O. *Ber*. **1910**, *43*, 489−498.
(11) For reviews, see: (a) Patterson, J. M. *Synthesis* **1976**, 281−304. (b) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2849−2866. (c) Ketcha, D. M. *Prog. Heterocycl. Chem*. **2002**, *14*, 114−138.

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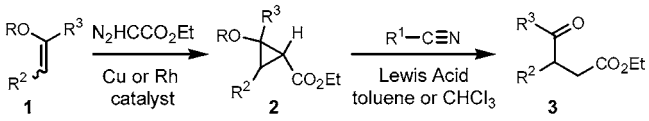
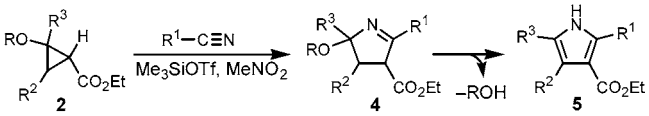
Scheme 1



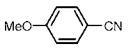
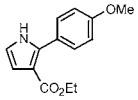
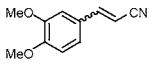
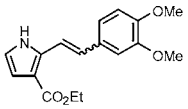
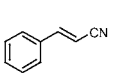
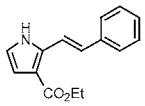
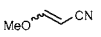
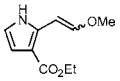
was critical to suppress the elimination pathway. Herein we report a new and efficient synthesis of di-, tri-, and tetrasubstituted pyrroles from DA-cyclopropanes by a domino cycloaddition, dehydration, and tautomerization strategy (Scheme 2).[18]

Scheme 2



For our initial studies on the pyrrole synthesis we chose as a model substrate the unsubstituted donor−acceptor cyclopropane **2a** (Table 1). Trimethylsilyl trifluoromethanesulfonate emerged as an ideal Lewis acid for cyclopropane activation, and addition of Me_3SiOTf to a solution of **2a** in acetonitrile gave the pyrrole in 80% isolated yield (entry 1, yields based on cyclopropane).[19] The inclusion of other solvents generally gave lower yields (e.g., 73% in nitromethane), but practical considerations required the use of solvent when most other nitriles were employed. The standard reaction conditions[20] for other nitriles were to add 1 equiv of Me_3SiOTf to a solution of cyclopropane and 10 equiv of nitrile in either nitromethane or nitroethane solvent. Butyronitrile gave a yield similar to that obtained with acetonitrile (entry 2, 77%), and both aromatic (entries 3 and 4) and α,β-unsaturated nitriles (entries 5−7) participate in the reaction. No products from reaction across the double bond of the unsaturated nitriles were detected.

Table 1. Pyrroles from DA Cyclopropane Nitrile Cycloadditions

entry	Nitrile, RCN	pyrrole	isolated yield
1	MeCN	R = Me	80%
2	PrCN	R = Pr	77%
3	PhCN	R = Ph	35%
4			55%
5			85%
6			39%
7			91%

The next examples in Table 2 illustrate the power of the method to install alkyl groups selectively at either or both of the C(4) and C(5) positions without formation of constitutional isomers, which can plague traditional condensation

(12) For some contemporary examples, see: (a) Martinez, G. R.; Grieco, P. A.; Srivivasan, C. V. *J. Org. Chem.* **1981**, *46*, 3760−3761. (b) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, *22*, 4647−4650. (c) Baldwin, J. E.; Bottaro, J. C. *J. Chem. Soc., Chem. Commun.* **1982**, 624−625. (d) Barton, D. H. R.; Zard, S. Z. *Chem. Commun.* **1985**, 1098−100. (e) Hegedus, L. S.; Mulhern, T. A.; Mori, A. *J. Org. Chem.* **1985**, *50*, 4282−4288. (f) Katrizky, A. R.; Hitchings, G. J.; Zhao, X. *Synthesis* **1991**, 863−7. (g) Van Leusen, D.; Van Echten, E.; Van Leusen, A. M. *J. Org. Chem.* **1992**, *57*, 2245−9. (h) Winkler, J. D.; Siegel, M. G. *Tetrahedron Lett.* **1993**, *34*, 7697−700. (i) Trofimov, B. A.; Mikhaleva, A. I. *Heterocycles* **1994**, *37*, 1193−232. (j) Chan, W. H.; Lee, A. W. M.; Lee, K. M.; Lee, T. Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2355−2356. (k) QuicletSire, B.; Thevenot, I.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 9469−9470. (l) Curran, T. P.; Keaney, M. T. *J. Org. Chem.* **1996**, *61*, 9068−9069. (m) Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999−5003. (n) Meyers, A. I.; Warmus, J. S.; Dilley, G. *Org. Synth.* **1996**, *73*, 246−252. (o) Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 873−874. (p) Katritzky, A. R.; Huang, T.-B.; Voronkov, M. V.; Wang, M.; Kolb, H. *J. Org. Chem.* **2000**, *65*, 8819−8821. (q) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075. (r) Takaya, H.; Kojima, S.; Murahashi, S. I. *Org. Lett.* **2001**, *3*, 421−424. (s) Braun, R. U.; Zeitler, K.; Müller, T. J. *J. Org. Lett.* **2001**, *3*, 3297−3300. (t) Quiclet-Sire, B.; Wendeborn, F.; Zard, S. Z. *Chem. Commun.* **2002**, 2214−2215. (u) Hover, J. A.; Bock, C. W.; Bhat, K. L. *Heterocycles* **2003**, *60*, 791−798.

(13) Yu, M.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8122−8123.

(14) Meyers, A. I.; Sircar, J. C. In *The Chemistry of the Cyano Group*; Rapporport, Z., Ed.; John Wiley: Belfast, 1970; Chapter 8.

(15) Donor−acceptor cyclopropane reviews: (a) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66−72. (b) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27−31. (c) Paquette, L. A. *Chem. Rev.* **1986**, *86*, 733−750. (d) Reissig, H.-U. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, 1987; Chapter 8, pp 375−443. (e) Reissig, H. U. *Top. Curr. Chem.* **1988**, *144*, 73−135. (f) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198. (g) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20−32. (h) Kulinkovich, O. G. *Russ. Chem. Rev.* **1993**, *62*, 839−850. (i) Carbocyclic Three- and Four-Membered Ring Compounds. In *Houben-Weyl, Methods of Organic Chemistry*, 4th ed.; de Meijere, A., Ed.; Thieme Verlag: Stuttgart, 1997; Vol. E17a, E17b, E17c, E17d. (j) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1−67. (k) de Meijere, A.; Kozhushkov, S. I.; Khlebnikow, A. F. *Top. Curr. Chem.* **2000**, *207*, 89−147. (l) de Meijere, A.; Kozhushkov, S. I.; Hadjiarapoglou, L. P. *Top. Curr. Chem.* **2000**, *207*, 149−227. (m) Reissig, H. Y.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151−1196. (n) Gnad, F.; Reiser O. *Chem. Rev.* **2003**, *103*, 1603−1624.

(16) Dipolar cycloaddition reviews: (a) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984. (b) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1111. (c) A. Padwa, In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1069. (d) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002.

(17) Yu. M.; Lynch, V.; Pagenkopf, B. L. *Org. Lett.* **2001**, *3*, 2563−2566.

(18) The vinyl ethers were readily prepared by the method of Gassman: (a) Gassman, P. G.; Burns, S. J. *J. Org. Chem.* **1988**, *53*, 5574−5576. (b) Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58*, 1449−1457.

(19) For activation with Lewis acids, see: (a) Yu, M.; Lynch, V.; Pagenkopf, B. L. *Tetrahedron* **2003**, *59*, 2765−2771. (b) Reference 17.

(20) A solution of cyclopropane (1 mmol) and nitrile (10 equiv) in nitromethane (2 mL) cooled to ca. −35 °C, depending on reaction partners, was treated with Me_3SiOTf (1 mmol). After 2−12 h, the reaction was poured into vigorously stirred saturated aqueous $NaHCO_3$, extracted and purified by chromatography.

Table 2. Nitrile Cycloadditions with DA Cyclopropanes

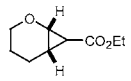
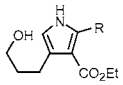
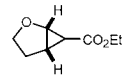
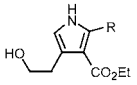
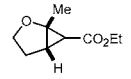
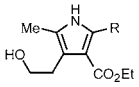
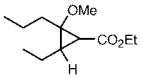
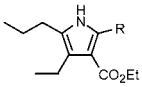
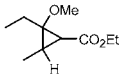
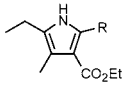
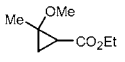
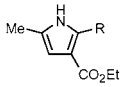
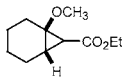
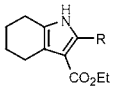
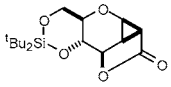
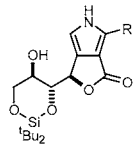
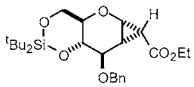
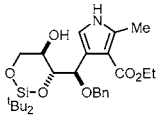
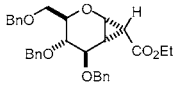
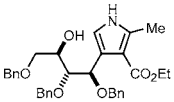
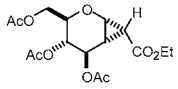
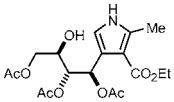
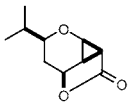
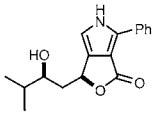
entry	substrate	nitrile	pyrrole	isolated yield
1		MeCN		72%
2		PrCN		78%
3		PhCN		58%
4		$Cl(CH_2)_3CN$		61%
5		MeCN		52%
6		PrCN		58%
7		$MeOC_2H_2CN$		81%
8		MeCN		31%
9		PrCN		25%
10		MeCN		93%
11		PrCN		82%
12		PhCN		76%
13		MeCN		98%
14		PrCN		85%
15		MeCN		62%
16		PrCN		55%
17		MeCN		72%
18		PrCN		75%

Table 3. Nitrile Cycloadditions with DA Cyclopropanes

entry	substrate	nitrile	pyrrole	isolated yield
1[a]		^{t}BuCN		87%
2[a]		PhCN		85%
3[a]		ArCN		93%
4		MeCN		87%
5		MeCN		77%
6		MeCN		58%
7[a]		PhCN		82%

[a] Acidic workup (1 M HCl). [b] ArCN = *p*-$MeOC_6H_4CN$.

methods. In entries 1−9, various nitriles are shown to react with pyran and furan derived cyclopropanes, affording pyrroles with functionalized side chains at C(4). Introduction of an alkyl group at C(5) resulted in lower yields for entries 8 and 9, but fortunately reaction efficiency was restored when unnecessary ring strain in the starting materials was avoided (entries 10−14). In entries 15 and 16, C(5) methyl pyrroles were obtained in 55−62% isolated yield without substitution at C(4). Placing the alkoxy leaving group at the bridgehead of the [3.1.0] bicyclic system permitted the synthesis of 4,5,6,7-tetrahydroindoles (entries 17 and 18). These are useful synthetic intermediates in natural product and pharmaceutical chemistry and can be readily oxidized to the indole.[21,22] The results in Table 2 reveal the diverse substitution permutations that are possible with this methodology. Another advantage is that the stereochemistry of the cyclopropane appears to have no effect on reaction efficiency. For example, in entries 3, 10, and 13, identical yields were obtained whether mixtures or single stereoisomers of cyclopropanes were used.

Table 3 summarizes the results from cycloaddition reactions with more densely functionalized cyclopropanes that were prepared from glycals or related structures. These reactions illustrate that the pyrrole synthesis is compatible with a variety of protective groups, including di-*tert*-butyl silylenes (entries 1−4), benzyl ethers (entries 4 and 5), and acetates (entry 6).[23] The considerable substrate and functional group compatibility will be an important asset when preparing pyrroles of increased complexity.

In conclusion, the domino donor−acceptor cyclopropane nitrile [3 + 2] cycloaddition, dehydration, and tautomerization strategy is a powerful and efficient new method for pyrrole synthesis that allows precise control over the installation of substituents at three positions around the pyrrole. The method is characterized by operational simplicity, substrate generality, and mild reaction conditions. The material costs associated with this procedure are generally less than other modern strategies, and the ease of product purification simplifies large-scale reactions. Given the compatibility of this method with various nitrile classes and the great number of nitriles that are commercially available (over 4000), it is likely that this work will find useful application in diversity-oriented synthesis.

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

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(21) For a review: Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 615−628.

(22) For a recent example: Hodges, L. M.; Spera, M. L.; Moody, M. W.; Harman, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 7117−7127.

(23) A notable difference in reactivity with those substrates prepared by intramolecular cyclopropanation is that under the standard reaction conditions the 3,4-dihydro-2*H*-pyrroles **4** can be isolated, but treating them during workup or in a separate step with aqueous acid affords the pyrrole in high yield.