J|A|C|S
COMMUNICATIONS

Published on Web 06/13/2003

Formal [3 + 2] Cycloadditions of Donor−Acceptor Cyclopropanes and Nitriles

Ming Yu and Brian L. Pagenkopf*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, Texas 78712

Received December 12, 2002; E-mail: pagenkopf@mail.utexas.edu

Lewis acid promoted [3 + 2] cycloaddition reactions of donor−acceptor cyclopropanes are valuable synthetic processes for the construction of heterocyclic and carbocyclic structures (Scheme 1).[1−3] In an effort to extend the versatility of cyclopropanes to the synthesis and functionalization of carbohydrate derived systems, we have recently reported the facile, stereospecific preparation of **4** and established its utility for the asymmetric synthesis of natural products.[4] Investigations into the unique chemistry of glycal-derived cyclopropanes prepared by intramolecular cyclopropanation revealed novel reactivity, and herein we report the highly stereoselective formal [3 + 2] cycloaddition of these cyclopropanes with a wide variety of nitriles, affording synthetically versatile dihydropyrroles in high yield (see Tables 1 and 2). To the best of our knowledge, dipolar cycloaddition reactions of donor−acceptor cyclopropanes with nitriles are unknown.[5−7] The efficient and stereoselective assembly of densely functionalized amine-containing heterocycles is an active area of investigation due to wide occurrence of these species in natural products and synthetic materials. The 2*H*-3,4-dihydropyrrole products from the cycloaddition contain an aminal, a functional group that has classically served as a latent iminium ion.[8]

We have found that successfully revealing the dipolar nature of glycal-derived cyclopropanes is highly dependent upon the Lewis acid employed.[9,10] Activation with Me_3SiOTf, even in the presence of potential nucleophiles such as allyltrimethylsilane, gave the anhydrosugar **5** (Scheme 2). In stark contrast, when benzonitrile was added to the reaction mixture, activation of **4** by Me_3SiOTf at room temperature gave the imine **6a** in 81% isolated yield.[11,12] The structural assignment of **6a** was unambiguously established by X-ray crystallography (Figure 1).

A wide variety of nitriles were found to participate in the cycloaddition reaction (Table 1).[13] Aliphatic nitriles ranging from MeCN to the much larger *t*-BuCN all gave the expected imine adduct (entries 2−6). The nitrile could be used as solvent, and where this was impractical, the use of $MeNO_2$ or CH_2Cl_2 with 5 to 10 equiv of nitrile also gave excellent yields (compare entries 2 and 3). The cycloaddition of α,β-unsaturated nitriles in nitromethane occurred exclusively at the nitrile functional group (entries 7−9).[7a] Reaction with β-methoxy acrylonitrile proved useful for introducing an aldehyde functional group (entry 9), and the vinylogous amide **6h** was isolated in 78% yield. All the cycloaddition reactions reported herein were highly stereoselective, providing solely one diastereomeric product.

The di-*tert*-butylsilylene protective group is not a necessary structural feature for successful [3 + 2] cycloaddition, and cyclopropanes with distal acetate and benzyl ether protective groups were equally effective substrates (Table 2, entries 1 and 2). In addition to carbohydrate-derived substrates, cyclopropanes prepared from other readily available γ-hydroxy dihydropyrans participate in the cycloaddition reaction (entries 3 and 4).[14] This and related processes offer a new approach to the functionalization and utilization of the growing number of enantiomerically pure dihydropyrans available from hetero-Diels−Alder cycloadditions.[15] Ring expansion of the pyran to the seven-membered oxacycle was not observed from any of these cycloaddition reactions.[16,17] Reaction with the furanose substrate in entry 5 gave the imine addition product in 43% yield. Intramolecular cyclopropanation of dihydrofuran substrates was not possible due to facile furan formation.[4,18]

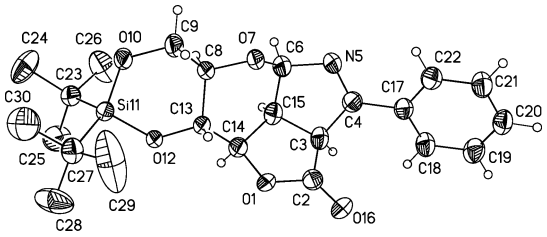
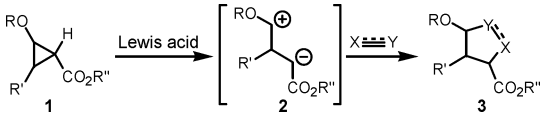


Figure 1. X-ray structure of **6a**.

Scheme 1



Scheme 2

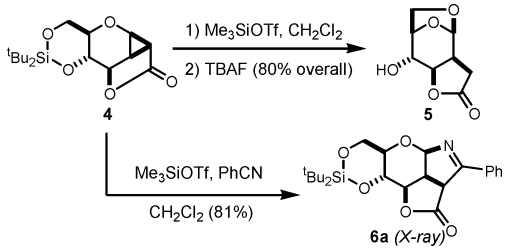
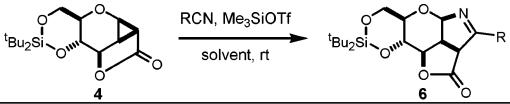
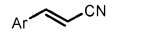
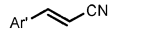
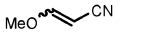
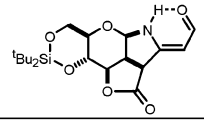
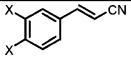


Table 1. Nitrile Additions to Cyclopropane 4

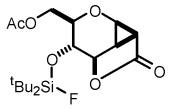
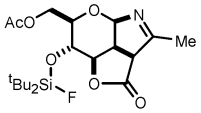
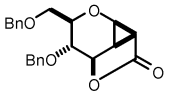
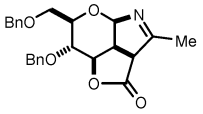
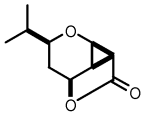
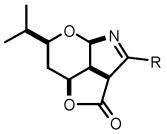
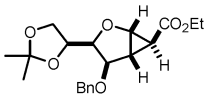
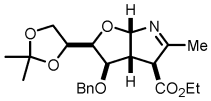


Entry	Nitrile	Solvent	Cycloaddition Product	Yield[a]
1	PhCN	CH_2Cl_2	**6a**, R = Ph	81%
2	MeCN	MeCN	**6b**, R = Me	96%
3	MeCN	CH_2Cl_2	**6b**, R = Me	84%
4	PrCN	CH_2Cl_2	**6c**, R = Pr	95%
5	^{t}BuCN	CH_2Cl_2	**6d**, R = ^{t}Bu	79%
6	$Cl(CH_2)_3CN$	CH_2Cl_2	**6e**, R = $(CH_2)_3Cl$	87%
7[b]		$MeNO_2$	**6f**, R = CHCHAr, X = H	60%
8[b]		$MeNO_2$	**6g**, R = CHCHAr, X = OMe	75%
9		CH_2Cl_2	**6h**, 	78%

[a] Isolated yields. [b] Nitrile = 

10.1021/ja029716f CCC: $25.00

Table 2. Nitrile [3 + 2] Cycloadditions Acetonitrile

Entry	Substrate	Nitrile	Cycloaddition Product	Yield[a]
1[b]		MeCN		92%
2		MeCN		90%
				
3	**7**	MeCN	**8a**, R = Me	96%
4[b]	"	PhCN	**8b**, R = Ph	92%
5		MeCN		43%

[a] Isolated yields. [b] Reaction solvent = CH_2Cl_2.

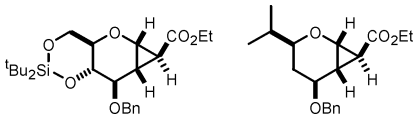


Figure 2.

The intramolecular glycal cyclopropanation strategy[4] appears to have been an important advance necessary for accessing the 3,4-dihydro-2*H*-pyrrole cycloaddition products. The substrates in Figure 2 were prepared by intermolecular cyclopropanation,[19] but attempted nitrile [3 + 2] cycloaddition reactions with these cyclopropanes gave multiple products. The ^{1}H NMR spectra of the crude reaction mixtures suggested imine formation, but decomposition occurred before purification was possible.

In summary, a novel Me_3SiOTf-activated [3 + 2] cycloaddition reaction between donor−acceptor cyclopropanes and nitriles has been described. Excellent yields of 3,4-dihydro-2*H*-pyrrole cycloaddition products are generally observed with aliphatic, aromatic, and α,β-unsaturated nitriles.

Acknowledgment. We thank the Robert A. Welch Foundation, the Texas Advanced Research Program 003658-0455-2001, and the DOD Prostate Cancer Research Program DAMD17-01-1-0109 for partial financial support. M.Y. thanks the Dorothy B. Banks Charitable Trust Fund for a graduate scholarship.

Supporting Information Available: X-ray structure data, CIF file for **6a**, and detailed experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

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

(2) 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., Flemming I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1111. (c) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B M., Flemming, 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.; New York: Wiley: 2002.

(3) (a) Komatsu, M.; Suehiro, I.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1991**, 771−773. (b) Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett.* **1990**, 1093−1096. (c) Shimada, S.; Hashimoto, Y.; Sudo, A.; Hasegawa, M.; Saigo, K. *J. Org. Chem.* **1992**, *57*, 7126−7133.

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

(5) For a conceptually similar nitrile [4 + 2] cycloaddition, see: Stevens, R. V.; Kenny, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 384−385.

(6) For similar products from diazoester methodology, see: Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 4692−4693.

(7) Cycloaddition reactions with the cyano group have been reviewed, see: (a) Myers, A. I.; Sircar, J. C. In *The Chemistry of the Cyano Group*; Rapporport, Z., Ed.; John Wiley: Belfast, 1970, Chapter 8. For a recent example, (b) see: Broggini, G.; Garanti, L.; Molteni, G.; Zecchi, G. *Heterocycles* **1999**, *51*, 1295−1302.

(8) (a) Hepworth, J. D.; Gabbutt, C. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Kirby, G. W., Volume Ed.; Pergamon: Oxford, 1995; Vol. 4. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856. For recent examples, see: (a) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510−12517. (b) Fleming, J. J.; Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028−2029.

(9) Reactions with $BF_3{\cdot}OEt_2$: Yu, M.; Pagenkopf, B. L. *J. Org. Chem.* **2002**, *67*, 4553−4558.

(10) Reactions with $TiCl_4$: Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2003**, *59*, 2765−2771.

(11) Traditional dipolarophiles are compatible, including aldehydes, imines, and silyl enol ethers. These results will be described elsewhere.

(12) For examples of nitriles as glycosyl acceptors, see: (a) Ratcliffe, A. J.; Mootoo, D. R.; Andrews, C. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 7661−7662. (b) Nair, L. G.; Fraser-Reid, B.; Szardenings, A. K. *Org. Lett.* **2001**, *3*, 317−319.

(13) Standard procedure: To a solution of cyclopropane (1 mmol) in CH_2Cl_2 (4 mL) at room temperature were added the nitrile (5.0 equiv) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1.0 equiv) sequentially. After 5 min the reaction mixture was poured into vigorously stirred saturated aqueous $NaHCO_3$ (10 mL). Pure product is obtained by standard purification and silica gel chromatography (See Supporting Information).

(14) Huang, Y.; Rawal, V. H. *Org. Lett.* **2000**, *2*, 3321−3323.

(15) (a) Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon: New York, 1991; Vol. 2, pp 661−706. (b) Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250−259. (c) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *15*, 5−23. (d) Kametani, T.; Hibino, S. *Adv. Heterocycl. Chem.* **1987**, *42*, 245−333.

(16) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694−7703.

(17) Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165−174.

(18) Timmers, C. M.; Verheijen, J. C.; van der Marel, G.; van Boom, J. H. *Synlett* **1997**, 851−853.

(19) (a) Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893−4894. (b) Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533−2536. (c) Henry, K. J.; Fraser-Reid, B. *Tetrahedron Lett.* **1995**, *36*, 8901−8904.

JA029716F