ORGANIC
LETTERS

2007
Vol. 9, No. 4
695−698

Zwitterion from a Cyclopropane with Geminal Donor and Acceptor Groups

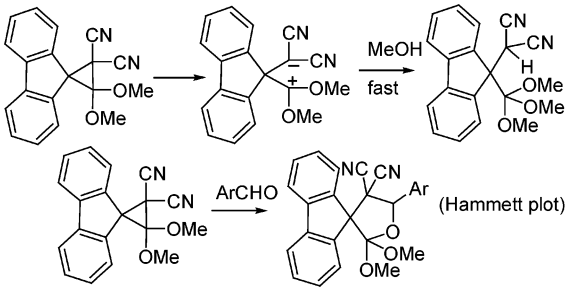
Anna Sliwinska, Wojciech Czardybon, and John Warkentin*

Department of Chemistry, McMaster University, Hamilton, Ontario L8S 4M1, Canada

warkent@mcmaster.ca

Received December 14, 2006

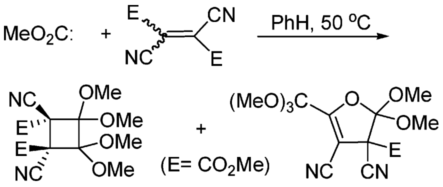
ABSTRACT



2,2-Dimethoxy-3,3-dicyanospiro[cyclopropane-1,9′-[9*H*]fluorene] reacted fast with methanol to afford 9-trimethoxymethyl-9-dicyanomethyl-9*H*-fluorene. Reaction with benzaldehydes also gave products of cyclopropane ring opening. Strong electron-donor *p*-substituents or a strong attractor enhanced the rate. Ring opening of the cyclopropane to a zwitterion that recloses or reacts with an aryl aldehyde, to form either a CO or a CC bond first, can explain the result. The former mode of closure is sensitive to *p*-substituents because they are directly conjugated to the positive charge at the benzylic carbon of the former aldehyde. The latter mode is sensitive to the ground-state electrophilicity of the carbonyl carbon of the former aldehyde. Thus, reaction of the cyclopropane with *p*-substituted aldehydes is accelerated by either electron-donor or -acceptor substituents.

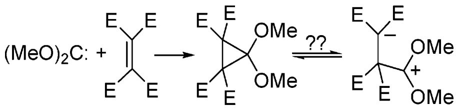
Dimethoxycarbene (DMC) is nucleophilic,[1,2] and it reacts with electrophilic alkenes bearing four electron-withdrawing groups[3] by an unknown mechanism (Scheme 1). A stepwise cycloaddition mechanism has been proposed,[3] but electron transfer followed by bond formation are among other possibilities.

Scheme 1



In any case, the cyclopropane expected from such a cycloaddition has never been isolated, raising the question as to whether such cyclopropanes are inherently unstable, possibly because they undergo reversible ring opening to a zwitterion, even in relatively nonpolar solvents (Scheme 2).

Scheme 2



(E= electron withdrawing group)

Zwitterions are postulated intermediates in some of the well-known synthetic applications of donor−acceptor cyclopropanes.[4,5] We now report the isolation and properties of two cyclopropanes that might be disposed toward such ring openings.

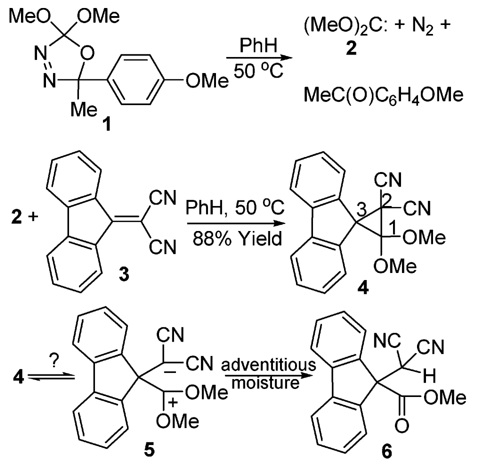
---

(1) Hoffmann, R. W. *Angew. Chem.* **1971**, *83*, 595; *Angew. Chem., Int. Ed.* **1971**, *10*, 529.
(2) Moss, R. A.; Wlostowski, M.; Shen, S.; Krogh-Jespersen, K.; Matro, A. *J. Am. Chem. Soc.* **1988**, *110*, 4443.

10.1021/ol063021s CCC: $37.00

Dicyanomethylene compounds **3** and **7** were synthesized by means of the reaction of fluorenone and adamantanone, respectively, with malononitrile,[6] and dimethoxycarbene (**2**) was generated by thermolysis of the 5-methyl-5-[*p*-methoxyphenyl] oxadiazoline precursor **1**.[3] Compound **3** reacted with DMC (**2**) in benzene at 50 °C to afford cyclopropane **4** (Scheme 3) as indicated by means of NMR spectroscopy and X-ray crystallography.

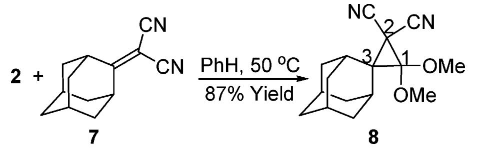
Scheme 3



It was difficult to obtain good crystals of **4**. Attempts to purify it by chromatography on silica or by crystallization of crude **4** from hot toluene led to its conversion to **6** (Scheme 3). Nearly pure **4** was obtained by washing the crude material with hexane, thereby removing most of the *p*-methoxyacetophenone that comes from the oxadiazoline. Crystallization of **4** from hot, dry hexane was ultimately achieved.

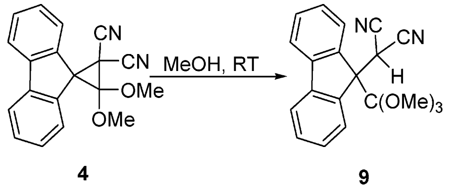
Dicyanomethylenadamantane (**7**) added **2** to form the more hindered **8** that could be purified by chromatography on silica and recrystallized from hexane without any appreciable reaction (Scheme 4).

Scheme 4



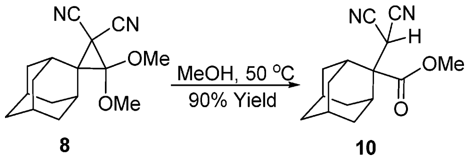
The high reactivity of **4** could mean that it is equilibrated in solution with the corresponding zwitterion **5**. In fact, **4** reacted very rapidly with anhydrous methanol, at room temperature, to afford **9**, and the reaction was over before an NMR scan could be made (Scheme 5).

Scheme 5



Cyclopropane **8** also reacted with methanol but at a much slower rate. After 72 h at 50 °C, there was 90% conversion of the substrate to ester **10** (Scheme 6).

Scheme 6



Reaction of **4** with CD_3OH and CD_3OD (1:1) did not afford a meaningful kinetic isotope effect because the dicyanomethine proton of **9** exchanged in the medium. Dicyanomethane also exchanged its protons for deuterons under the same conditions.

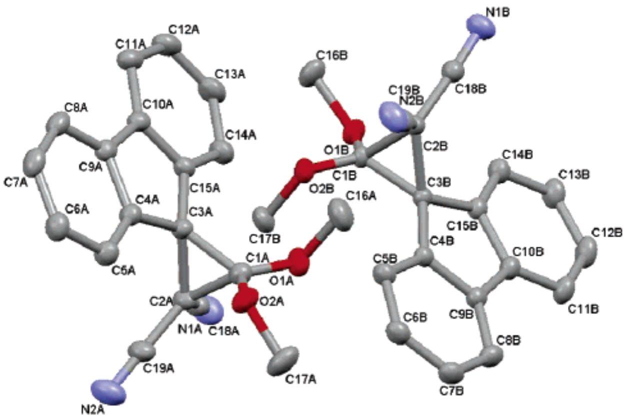


Figure 1. X-ray structure of the unit cell of **4**.

An X-ray crystal structure of **4** (Figure 1) showed that the unit cell contains two molecules. In molecule A, the C1–C2, C1–C3, and C2–C3 bond lengths are 1.544(3), 1.494(3), and 1.600(2) Å, and in molecule B, they are 1.542(3), 1.492(2), and 1.608(2) Å (Scheme 3).

Bond lengths in the cyclopropyl group of **8** were very similar to those of the corresponding bonds in **4**. The structures suggest that, in the solid state, the species are not at all zwitterionic and that unhindered cyclopropanes such as **4** may form zwitterions only if the polar groups can be

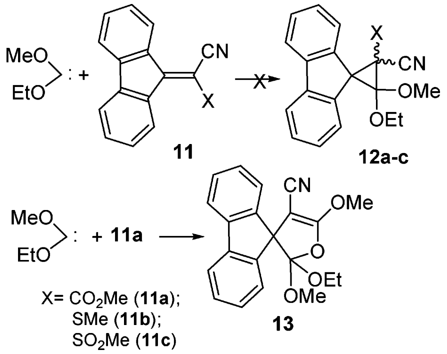
---

[3] Zhou, H.; Mloston, G.; Warkentin, J. *Org. Lett.* **2005**, *7*, 487.
[4] Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.
[5] Graziano, M. L.; Cimminiello, G. *J. Chem. Res. (S)* **1989**, 42.
[6] Mirek, J.; Adamczyk, M.; Mokrosz, M. *Synthesis* **1980**, 296.

adequately solvated. The lower reactivity of **8** toward methanol might be attributed to steric hindrance to rotation and solvation in the corresponding zwitterion, which would affect heterolytic bond scission of **8**.

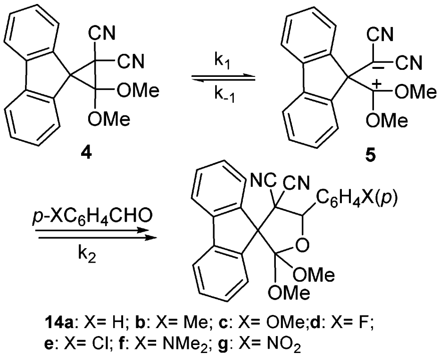
Attempts to *cis*/*trans* equilibrate unsymmetrically substituted cyclopropanes **12a−c** in solution in the manner of Chmurny and Cram[7] failed. Treatment of **11a** with ethoxy(methoxy)carbene at 50 °C did not afford **12a** but only the five-membered ring **13** (Scheme 7). Equilibration of **12b−c** could not be attempted because ethoxy(methoxy)carbene failed to add to **11b** or **11c**.

Scheme 7



Advantage was then taken of the reaction of **4** with benzaldehydes to afford **14** (Scheme 8). We thought that there might be a substantial *p*-substituent effect that could betray the mechanism by which **4** reacts with an aryl aldehyde. The *p*-substituents chosen were H, F, Cl, Me, MeO, Me_2N, and NO_2.

Scheme 8



Stringent purification of the aldehydes was required because any hydroxylic impurities, such as acids or H_2O, were known to react fast with the cyclopropane. Washing of the aldehydes with dilute aqueous sodium carbonate was not effective, presumably because of the Cannizzaro reaction. In the end, vacuum distillation of the liquids under N_2, and handling by means of glove bag techniques, was effective. Excellent pseudo first-order plots, with aldehyde in 20-fold excess over the cyclopropane, were obtained with benzaldehyde **14a** as well as with *p*-F, *p*-Cl, *p*-Me, and *p*-OMe benzaldehydes in benzene-d_6 at room temperature, by means of ^1H NMR spectroscopy at 600 MHz. *p*-$Me_2NC_6H_4CHO$ reacted much too quickly, and *p*-$O_2NC_6H_4CHO$ was too insoluble in benzene at 20-fold excess. The second-order rate constants were determined (equal concentrations of **4** and aldehyde), and the pseudo first-order rate constants at a 20-fold excess of aldehyde were estimated by multiplying the experimental second-order rate constants by 20. Figure 2 is a Hammett plot of log (k/k_0) against the σ^+ constants of the substituents, where k and k_0 are the pseudo first-order rate constants for reaction of a substituted benzaldehyde and benzaldehyde.

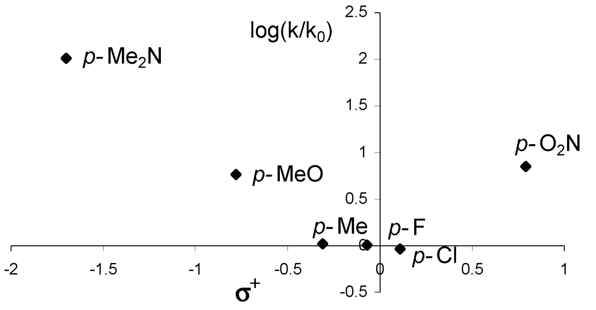


Figure 2. Plot of log (k/k_0) vs σ^+.

It is clear at once, whether σ or σ^+ is chosen, that there is a change of mechanism with substituent. The two electron-donor and the *p*-nitro substituents accelerate the rate of cycloaddition compared to the others. What could it mean?

A simple explanation would have *p*-nitrobenzaldehyde react with the zwitterion to make a CC bond first, and *p*-MeO and *p*-Me_2N aldehydes make a CO bond first. Electron transfer (ET) as the rate-limiting step is excluded because the *p*-nitro compound, one of the faster reactants, should be the poorest at transferring from its HOMO to the LUMO of the cyclopropane.

In view of the earlier postulates of zwitterionic intermediates from cyclopropanes with fewer than two donor groups at one carbon and electron-withdrawing groups at another and in view of the literature on zwitterionic intermediates,[4,5,8−16] not neccessarily from cyclopropanes, we calculated the barrier to bond heterolysis in **4**. At the b3pw91/6-31g* level

---

(7) Chmurny, A. B.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 4327.

(8) Nair, V.; Deepthi, A.; Poonoth, M.; Santhamma, B.; Vellalath, S.; Babu, B. P.; Mohan, R.; Suresh, E. *J. Org. Chem.* **2006**, *71*, 2313.

(9) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Bijou, A. T. *Acc. Chem. Res.* **2006**, *39*, 520.

(10) Nair, V.; Deepthi, A. *Tetrahedron Lett.* **2006**, *47*, 2037.

(11) Itoh, K.; Iwata, S.; Kishimoto, S. *Heterocycles* **2006**, *68*, 395.

(12) Cermola, F.; Di Gioia, L.; Graziano, M. L.; Iesce, M. R. *J. Chem. Res.* **2005**, 677.

(13) Esmaeili, A. A.; Zendegani, H. *Tetrahedron* **2005**, *61*, 4031.

(14) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023.

(15) Saigo, K.; Shimada, S.; Hashimoto, Y.; Hasegawa, M. *Chem. Lett.* **1989**, 1293.

(16) Abdallah, H.; Gree, R.; Carrie, R. *Tetrahedron* **1985**, *41*, 4339.

of theory, the barrier to formation of a zwitterion in benzene, with the charge-bearing groups substantially turned, is about 24.4 kcal mol^{-1} (Figure 3). Onsager's method, in which the dielectric constant of the solvent is entered into the calculation, was used.[17] Moreover, the calculation (gas phase) in the restricted mode (electrons paired in the same orbital) gave the same energy and geometry as that in the unrestricted mode. The latter would have permitted a singlet diradical species, if that were of lower energy. We were unable to find a transition state for direct reaction of **4** with benzaldehyde.

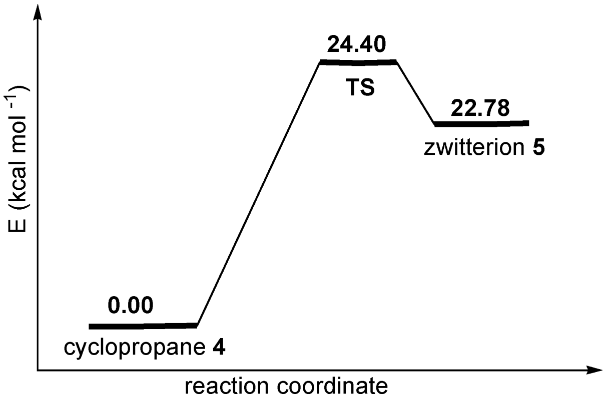


Figure 3. Potential energy vs reaction coordinate for zwitterion formation from **4**.

In summary, the fast reaction of **4** with *p*-MeO, *p*-Me_2N, and *p*-O_2N benzaldehydes in benzene seems to fit with reversible heterolysis of **4** to a zwitterion. There is a considerable body of literature in which the existence of zwitterions from less favorably substituted cyclopropanes has been postulated, but there is no previous proof that such zwitterions can exist in a solvent of relatively low ionizing power. Computation indicated that the barrier to CC heterolysis of **4** in benzene is about 24.4 kcal mol^{-1}. For benzaldehydes to compete with reclosure of the zwitterion, the activation energy for the aldehyde reaction has to be low also.

Acknowledgment. We are grateful to Professor Jim Britten, Dr. Laura Harrington, Erika Bellhouse, and Craig Robertson (all at McMaster) for the X-ray work. SHARCNET graciously provided computation facilities to W.C. (University of Madeira). This work was supported by NSERC of Canada.

Supporting Information Available: Experimental data for the reported reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

OL063021S

---

[17] (a) Onsager, L. J. *J. Am. Chem. Soc.* **1936**, *58*, 1486. (b) Kirkwood, J. G. *J. Chem. Phys.* **1939**, *7*, 911. (c) Tapia, O.; Goscinski, O. *Mol. Phys.* **1975**, *29*, 1653. (d) Wong, M. W.; Wiberg, K. B.; Frisch, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1645.