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Synthesis of Δ^1-1,2-Diazetines via a Diels−Alder Cycloaddition Approach

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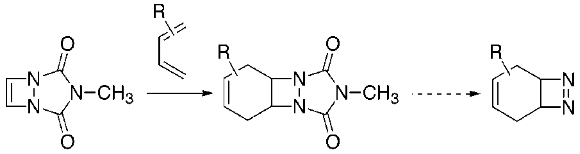
ABSTRACT



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A novel method for the synthesis of Δ^1-1,2-diazetines is presented. Diels−Alder cycloaddition of dienophile 4 with five dienes afforded cycloadducts in good to excellent yields. Four of the obtained cycloadducts were converted to the corresponding diazetines.

Δ^1-1,2-Diazetines (**1**, Figure 1) are a class of strained four-membered ring azo compounds.[1,2] Their properties remain largely unexplored presumably as a result of the difficulty of their synthesis. Even though the first member of this family of compounds was described in 1962, fewer than a dozen diazetines are currently known.[3] Despite the propensity for decomposition of diazetines to ultimately afford nitrogen and the corresponding alkene (Figure 1, $\Delta H \approx -50$ kcal/mol), diazetines are quite thermally robust ($\Delta H^{\ddagger} \approx 35$ kcal/mol).[1,4] This has prompted questions concerning the mechanism of decomposition of these compounds with advocacy of concerted (both [2s + 2s] and [2s + 2a] retrocycloadditions being suggested) and nonconcerted (i.e., via diradical intermediates) processes.[1,5] Detailed studies on the decomposition process have been hampered by the inaccessibility of diazetine substrates.[1a,6] We sought to develop a synthetic method that would be more generally applicable than traditional methods and allow for additional studies on this fascinating class of organic compounds.

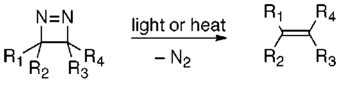

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Figure 1. Products from the decomposition of diazetines.

The Diels−Alder cycloaddition reaction is widely recognized as a powerful synthetic method that is broadly applicable for a given dienophile in its reactions toward diene substrates.[7] We sought to develop a suitable dienophile that would act as a diazetine synthon as illustrated in Figure 2.

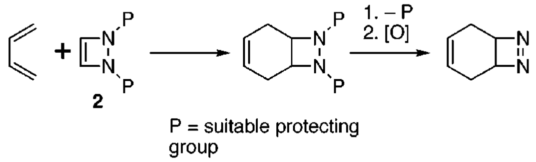

Figure 2. A route for the synthesis of 1,2-diazetines that utilizes a diazetine synthon (**2**) in a Diels−Alder reaction.

A compound with a suitable structure, **3**, was already known (Figure 3),[8] but its limited thermal stability toward electrocyclic ring opening ($t_{1/2}$[20 °C] = 7 h) suggested it would be an ineffective dienophile since Diels−Alder reactions

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[1] (a) Engel, P. S. *Chem. Rev.* **1980**, *80*, 99−150. (b) Hogenkamp, D. J.; Greene, F. D. *J. Org. Chem.* **1993**, *58*, 5393−5399.

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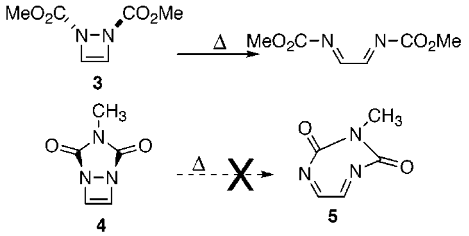
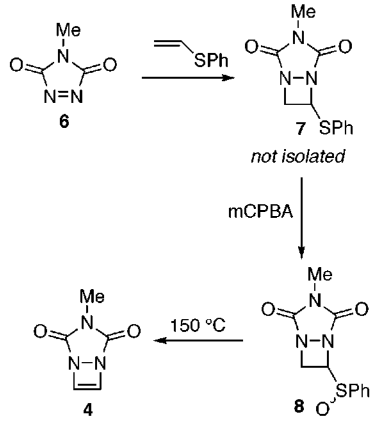


Figure 3. The result of thermal orbital-symmetry allowed conrotatory ring openings for compounds **3** and **4**.

often require elevated temperatures. We reasoned, on the basis of the behavior of hydrocarbon analogues,[9] that by "tying back" the free ends of the carbamate groups of compound **3** into a urazole ring (i.e., compound **4**) that the thermal stability of the dienophile would be enhanced. Ring opening of **4** is expected to be hindered since a thermally allowed conrotatory electrocyclic process would ultimately lead to the hopelessly strained (1*Z*,3*E*)-heterocyle **5** (Figure 3).

Synthesis of dienophile **4** was accomplished via the route illustrated in Scheme 1. Reaction of *N*-methyltriazolinedione **6** with phenyl vinyl sulfide yielded a labile [2 + 2] adduct **7** that was oxidized (without isolation) to a diastereomeric mixture of the more stable sulfoxides **8**.[10] The poor overall yield of this two-step reaction (~15%) can be traced to the [2 + 2] reaction where formation of a polymer competes with the cycloaddition.[11] Attempts to increase the yield by varying the reaction solvent, altering the sequence of reagent mixing, and changing the reaction temperature have not yet been successful. Furthermore, attempts to effect the direct [2 + 2] cycloaddition of **6** with phenyl vinyl sulfoxide to yield **8** directly either thermally (80 °C, CHCl$_3$), via Lewis acid catalysis (BF$_3$·Et$_2$O, CH$_2$Cl$_2$), or photochemically met with failure.

Scheme 1



Solution-phase pyrolysis of sulfoxide **8** (C$_6$H$_5$Cl, 150 °C, 4 h) yielded the desired diazetine **4** in good yield (~70%). The ^{1}H NMR spectrum of **4** displays two singlets (δ 3.1 [N-Me] and 6.71) consistent with the proposed structure. Similarly, the three signals observed in the ^{13}C NMR (δ 156.4, 130.9, and 26.8) were consistent with the symmetry of the compound's structure. The overall yield of **4** from **6** was only 8–10%, but the ability to synthesize **4** with only a single rigorous purification step (see Supporting Information) still makes it a feasible route. We are currently seeking higher-yielding alternative routes, however. The ability of **4** to withstand the temperatures required for its synthesis (150 °C), as well as those required for subsequent Diels–Alder reactions (see below), demonstrate that it is indeed resistant to electrocyclic ring opening as predicted.

Diels–Alder cycloadditions of **4** with various dienes took place readily in benzene or chlorobenzene at temperatures of 100–150 °C (Table 1). Cyclopentadiene afforded a mixture of both *endo* and *exo* stereoisomers in a 15:1 ratio, respectively. The *exo* isomer was readily identified by comparison of its ^{1}H and ^{13}C NMR spectrum with that of authentic material formed via the [2 + 2 + 2] cycloaddition of **6** with quadricyclane.[12]

In contrast, 1,3-cyclohexadiene afforded a single stereoisomer, which is assumed to have the *endo* stereochemistry (Table 1). Reaction with anthracene afforded the expected cycloadduct in very good yield. The acyclic diene 2,3-dimethyl-1,3-butadiene afforded the expected cycloadduct in 67% yield. Reaction with 2,4-hexadiene yielded a mixture of two stereoisomers **14** and **15** in a 2.9:1 ratio, respectively. These isomers were differentiated primarily on the basis of their ^{1}H NMR spectra. The vinyl protons of the minor isomer were split into a doublet ($J = 7.2$ Hz) by coupling with the neighboring methine protons, which was more consistent with the geometry of the lowest energy conformation of isomer **15** (predicted $J = 5.4$ Hz) than that of **14** (predicted $J = 1.4$ Hz).[13] Furthermore, the vinyl protons of the major

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(2) Preliminary results on this work: Breton, G. W. Ph.D. Dissertation, Massachusetts Institute of Technology, Cambridge, MA, 1991. We thank Prof. F. D. Greene for encouragement in the investigation and publication of these findings.

(3) See references within ref 1b for leading articles to all known diazetines.

(4) (a) White, D. K.; Greene, F. D. *J. Am. Chem. Soc.* **1978**, *100*, 6760–6761.

(5) Olsen, H. *J. Am. Chem. Soc.* **1982**, *104*, 6836–6838.

(6) Pincock, J. A.; Druet, L. M. *Tetrahedron Lett.* **1980**, *21*, 3251–3252.

(7) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, Part B; Kluwer Academic: New York, 2001; pp 332–359.

(8) Nunn, E. E.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1972**, 818–819.

(9) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, Part A; Kluwer Academic: New York, 2000; p 607.

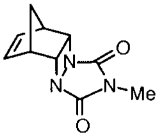
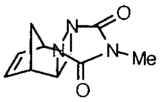
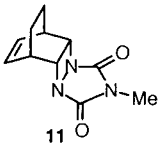
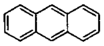
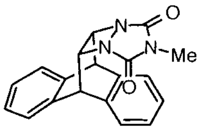
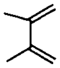
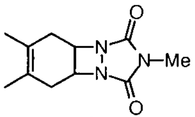
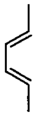
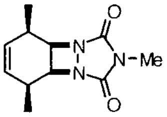
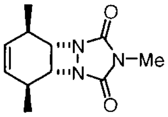
(10) The spectroscopic data for **7** is similar to that reported for the corresponding DMAD adduct; see: Firl, J.; Sommer, S. *Tetrahedron Lett.* **1972**, 4713–4716.

(11) Polymer formation is a common side reaction in the reactions of triazolinediones with electron-rich alkenes; see: Hall, H. J.; Jones, M. L. *J. Org. Chem.* **1983**, *48*, 822–826.

(12) Adam, W.; De Lucchi, O. *Tetrahedron Lett.* **1981**, *22*, 929–932.

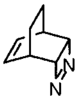
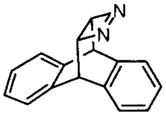
(13) The geometries of stereoisomers **14** and **15** were minimized utilizing the MMFF94 force-field as implemented within PC Spartan Pro software (Wavefunction, Inc.). Coupling constants were estimated from the dihedral angles formed from the vinyl protons and the neighboring methine protons as predicted by the minimized structures.

Table 1. Cycloadduct Products Resulting from Reaction of Dienophile **4** with Various Dienes[a]

diene	cycloaddition product(s)		yield (%)[b] [ratio]
	 **9**	 **10**	82 [9.4:1]
	 **11**		66
	 **12**		94
	 **13**		67
	 **14**	 **15**	98 [2.9:1]

[a] Detailed procedures are available in Supporting Information. [b] Isolated yields.

Table 2. Diazetine Products Synthesized from Some of the Diels−Alder Cycloadducts[a]

cycloadduct	diazetine product	yield (%)[b]
9		60
10		53
11		70
12		46

[a] Detailed procedures are available in Supporting Information. [b] Isolated yields.

isomer revealed themselves as a broadened singlet consistent with the geometry of **14** according to the above analysis.

To demonstrate the utility of this novel synthetic route, four of the cycloadducts were converted to the corresponding diazetines via a standard hydrolysis/oxidation reaction sequence (Table 2).[14] Thus, the urazole rings of the adducts were hydrolyzed with KOH in refluxing 2-propanol to afford the corresponding hydrazines, followed by in situ oxidation with $CuCl_2$. The expected diazetines were obtained in yields typical of this process. The thermal and photochemical reactivities of these new diazetines will be presented in a future publication.

In summary, the Diels−Alder cycloaddition approach for the synthesis of novel diazetines appears to be general and quite useful. We intend to utilize this new method for the synthesis of a series of structurally related diazetines that might ultimately yield new insights into the mechanism of decomposition of these compounds.

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Supporting Information Available: Experimental procedures and full characterization data for all new compounds and ^1H NMR spectra for all of the new diazetines and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Adam, W.; De Lucchi, O.; Erden, I. *J. Am. Chem. Soc.* **1980**, *102*, 4806−4809.