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2*H*-Azirines from a Concerted Addition of Alkylcarbenes to Nitrile Groups[†]

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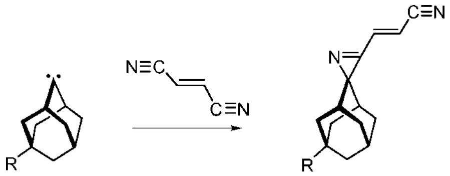
ABSTRACT



Photolysis of aziadamantanes in the presence of fumaronitrile (FN) unexpectedly afforded conjugated 2*H*-azirines resulting from addition of the carbene to the CN triple bond. This represents the first example of a direct azirine formation starting from an alkylcarbene for which a concerted pathway is postulated. The novel outcome of the reaction is favored by the prior formation of a carbene−alkene complex, a type of adduct that only recently has been described.

2*H*-Azirines are important synthetic intermediates in organic chemistry. They occur, foremost, during the well-known Neber rearrangement.[1] And whereas intramolecular routes to azirines dominate, syntheses via intermolecular pathways are rare.[2] Usually, 2*H*-azirines are formed from nitrene intermediates generated by pyrolysis or photolysis of vinyl azides.[3] Other approaches include ring contraction of azete derivatives[4] and isoxazoles at high temperatures,[5] as well as oxidation of aziridines.[6] Intermolecular reactions are far less successful. In particular, the addition of nitrenes to alkynes afforded minimal yields.[7] Correspondingly, in the reaction between carbenes and nitriles, the carbene tends to react as an electrophile and generate nitrile ylides.[8] These transient species can be very efficiently trapped as pyrrolines by using dipolarophiles; this was demonstrated in the case of the addition of 1-naphthylcarbene to acetonitrile.[8,9] In an extreme case, a stable crystalline ylide formed by tetrakis(trifluoromethyl)cyclopentadiene and 1-adamantyl nitrile could even be synthesized.[10] To date, the sole example of a cycloaddition of a carbene to a nitrile to yield an azirine is the direct azirination of benzonitrile by a highly nucleophilic phosphinosilylcarbene.[11]

[†] Carbene Rearrangements 79. For Part 78 see: Wagner, G.; Knoll, W.; Bobek, M. M.; Brecker, L.; van Herwijnen, H.W.G.; Brinker, U. H. *Org. Lett.* **2010**, *12*, 332.

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(1) (a) Neber, P. W.; Burgard, A. *Justus Liebigs Ann. Chem.* **1932**, *493*, 281. (b) Neber, P. W.; v. Friedolsheim, A. *Justus Liebigs Ann. Chem* **1926**, *449*, 109.

(2) For a review, see: (a) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; De los Santos, J. M. *Eur. J. Org. Chem.* **2001**, 2401. (b) Rai, K. M. L.; Hassner, A. In *Advances in Strained and Interesting Organic Molecules*; Halton, B., Ed.; JAI: Stamford, CT, 2000; Vol. 8, pp 187−257. (c) Backes, J. In *Houben-Weyl*; Klamann, D., Ed.; Thieme: Stuttgart, Germany, 1992; Vol. E16c, pp 321−369.

(3) Smolinsky, G. *J. Org. Chem.* **1962**, *27*, 3557.

(4) Vogelbacher, U. J.; Lederman, M.; Schach, T.; Michels, G.; Hess, U.; Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 272.

(5) (a) Sauers, R. R.; Hadel, L. M.; Scimone, A. A.; Stevenson, T. A. *J. Org. Chem.* **1990**, *55*, 4011. (b) Himbert, G.; Kuhn, H.; Barz, M. *Liebigs Ann. Chem.* **1990**, 403.

(6) Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 4665.

(7) Huisgen, R.; Blaschke, H. *Chem. Ber.* **1965**, *98*, 2985.

(8) (a) Escolano, C.; Duque, M. D.; Vazquez, S. *Curr. Org. Chem.* **2007**, *11*, 741. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

(9) Barcus, R. L.; Hadel, L. M.; Johnston, L. J.; Platz, M. S.; Savino, T. G.; Scaiano, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3928.

(10) Janulis, E. P., Jr.; Wilson, S. R.; Arduengo, A. J., III *Tetrahedron Lett.* **1984**, 405.

(11) (a) Alcaraz, G.; Wecker, U.; Baceiredo, A.; Dahan, F.; Bertrand, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1246. (b) Piquet, V.; Baceiredo, A.; Gornitzka, H.; Dahan, F.; Bertrand, G. *Chem.−Eur. J.* **1997**, *3*, 1757.

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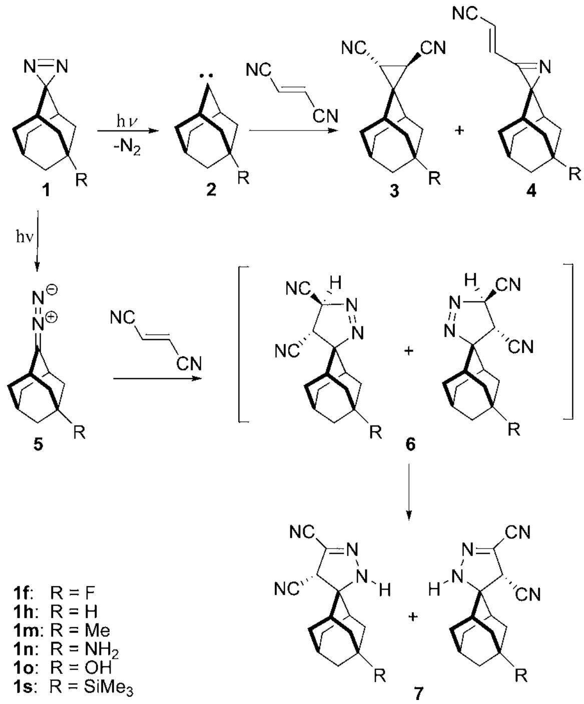
Our discovery that a dialkylcarbene is able to form a 2*H*-azirine was quite serendipitous. During the investigation of the products resulting from substituted adamantanylidenes **2** generated by photolysis of the corresponding 3*H*-diazirines **1**,[12,13] it was necessary to add fumaronitrile (**FN**) to scavenge the intermediate diazo compounds **5** (Scheme 1).[14,15] It has already been demonstrated that diazo protonation has a falsifying effect on the ratios observed from intermolecular carbene insertions into the O−H bond of CH_3OH.[12−14] In these reactions, the scavenging product is not the initially formed Δ^1-pyrazoline **6** but the rearranged Δ^2-pyrazoline **7**, which is more stable and not prone to eliminate nitrogen.

Scheme 1. Diazo vs Carbene Chemistry and Tautomerization of **6** to **7**



To investigate the reactive behavior of aziadamantanes **1** (λ_{max} ca. 330 nm) with **FN** in aprotic solvents, photolyses were performed in both benzene and ether with excess **FN**. Unexpectedly, this dipolarophile not only scavenges diazoadamantanes **5** effectively but also adamantanylidenes **2**! Under these conditions, formation of pyrazolines **7** and cyclopropanes **3** was anticipated. Due to its singlet ground state with a small S−T (singlet−triplet) gap of 2.8 kcal/mol, the relatively long-lived adamantanylidene should react by a singlet pathway.[16]

Thus, exclusive formation of trans-substituted **3** was expected. Indeed, *trans*-cyclopropanes **3h** and **3f** were obtained in 22% and 6% yield, respectively (Table 1); no *cis*-cyclopropanes were observed. The cis-isomer could have been formed by the decomposition of the corresponding intermediate Δ^1-pyrazoline **6**.

The main products remaining are pyrazolines **7** (50% for **7h** and 51% for **7f**). This agrees well with previous results obtained from the photolyses of aziadamantane **1h**, wherein 60% of the diazirine reacts through the intermediacy of diazo compound **5** and only 40% decomposes directly to adamantanylidene **2**.[15] Since carbene **2f** is diastereotopic, two diastereomers of pyrazoline **7f** are formed in a ratio of about 1:1, which is characteristic for a product evolving from diazoadamantane **5f**. The formation of pyrazoline **7** can be prevented if adamantanylidene **2** is generated thermally. Then diazirine **1** decomposes preferably to the carbene.[17] Almost no diazo compound **5** is formed and hence no trapping products **7** are observed.

Surprisingly, however, a third compound was isolated. It shows an intense UV band at 263 nm, which fits well within the range of substituted azirines. Although the analytical data, HRMS, IR, and NMR were in accordance with this interpretation, the NMR analysis was insufficient, because the anticipated azirine ring bears no proton. Thus, X-ray data are essential and crystallization was successful in the case of 1-fluoro-4-aziadamantane (**1f**) with **FN** (Figure 1). In summary, azirines **4h** and **4f** were synthesized in 17% and 16% yield, respectively. In stark contrast to pyrazolines **7f** (1:1), azirine **4f** was nearly exclusively present in its *anti* form (*anti*:*syn* ratio = 9:1). Such high selectivity results from the intermediacy of carbene **2f**, in which the reacting carbon atom is unequally stabilized by its neighboring bonds depending on the electronic properties of the substituent.[13] This is one of the major arguments against formation of the azirine via cyclization of a nitrile ylide intermediate.[18]

A second argument stems from the experimental conditions. Nitrile ylides are known to be very reactive toward 1,3-dipolar cycloadditions[8a] and an excess of the electron-deficient fumaronitrile dipolarophile was present in the reaction mixture. So, formation of pyrrolines should be

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(12) Bobek, M. M.; Brinker, U. H. *J. Am. Chem. Soc.* **2000**, *122*, 7430.

(13) (a) Knoll, W.; Bobek, M. M.; Giester, G.; Brinker, U. H. *Tetrahedron Lett.* **2001**, *42*, 9161. (b) Knoll, W.; Bobek, M. M.; Kalchhauser, H.; Rosenberg, M. G.; Brinker, U. H. *Org. Lett.* **2003**, *5*, 2943. (c) Tomoda, S.; Kaneno, D. *Org. Lett.* **2003**, *5*, 2947.

(14) (a) Holm, K. H.; Skattebøl, L. *J. Am. Chem. Soc.* **1977**, *99*, 5480. (b) Warner, P. W.; Chu, I.-S. *J. Am. Chem. Soc.* **1984**, *106*, 5366. (c) Kirmse, W.; Meinert, T.; Modarelli, D. A.; Platz, M. *J. Am. Chem. Soc.* **1993**, *115*, 8918. (d) Kirmse, W. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; JAI: Greenwich, CT, 1994; Vol. 1, pp 1−57. (e) Kirmse, W. In *Advances in Carbene Chemistry*; Brinker, U. H., Ed.; Elsevier: Amsterdam, The Netherlands, 2001; Vol. 3, pp 1−52.

(15) (a) Niino, Y.; Wakahara, T.; Akasaka, T.; Liu, M. T. H. *ITE Lett. Batteries, New Technol. Med.* **2002**, *3*, 82. (b) Bonneau, R.; Liu, M. T. H. *J. Am. Chem. Soc.* **1996**, *118*, 7229. (c) Akasaka, T.; Liu, M. T. H.; Niino, Y.; Maeda, Y.; Wakahara, T.; Okamura, M.; Kobayashi, K.; Nagase, S. *J. Am. Chem. Soc.* **2000**, *122*, 7134. (d) Pezacki, J. P.; Shukla, D.; Lusztyk, J.; Warkentin, J. *J. Am. Chem. Soc.* **1999**, *121*, 6589.

(16) (a) Shustov, G. V.; Liu, M. T. H.; Houk, K. N. *Can. J. Chem.* **1999**, *77*, 540. (b) Bonneau, R.; Liu, M. T. H. *J. Phys. Chem. A* **2000**, *104*, 4115. (c) Liu, M. T. H.; Ramakrishnan, K. *Tetrahedron Lett.* **1977**, *36*, 3139.

(17) Liu, M. T. H.; Choe, Y.-K.; Kimura, M.; Kobayashi, K.; Nagase, S.; Wakahara, T.; Niino, Y.; Ishitsuka, M. O.; Maeda, Y.; Akasaka, T. *J. Org. Chem.* **2003**, *68*, 7471.

(18) In fact, only a few publications can be found in which a nitrile ylide cyclization is postulated.[8b,11] For instance, it concerns the formation of an azirine after the generation of fluorenylidene in acetonitrile: (a) Grasse, P. B.; Brauer, B. E.; Zupancic, J. J.; Kaufmann, K. J.; Schuster, G. B. *J. Am. Chem. Soc.* **1983**, *105*, 6833. (b) Griller, D.; Hadel, L.; Nazran, A. S.; Platz, M. S.; Wong, P. C.; Savino, T. G.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2227.

Table 1. Photolysis of Substituted Aziadamantanes **1** in 1,3,5-Trimethoxybenzene/C_6D_6

		aziadamantane **1**						
		1s, $SiMe_3$	**1h**, H	**1m**, Me	**1n**, NH_2	**1o**, OH	**1f**, F	**1h**, H, Δ[a]
carbene products	azirine **4**	13	17	8	16	11	16	17
	cyclopropane **3**	24	22	12	12	5	6	64
diazo product	pyrazoline **7**	61	51	42	45	24	50	
	starting material			23		7		
	obsd yield[b]	98	90	85	73	47	72	81

[a] Thermolysis at 140 °C in molten fumaronitrile. [b] The remaining material consists of insoluble material and of products formed in less than 1% yield.

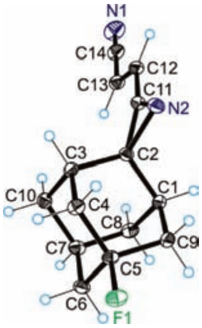

Figure 1. X-ray diffraction structure of **4f**.

expected. However, none was observed and therefore the presence of nitrile ylides during the photolyses of **1** can be excluded, because they would have been trapped by **FN**. The absence of nitrile ylides was further ensured by laser-flash photolysis experiments: no ylidic band arose from the decomposition of **1h** at 351 nm. In contrast, azirine **4h** could be decomposed by excitation at 248 and 308 nm, but not at 351 nm. The generated signal at 400 nm decays rapidly for about 0.5−0.7 ms. Azirines are known to generate nitrile ylides upon irradiation.[8a,19] Although this photoreaction may be reversible,[20] the transient nature of the obtained nitrile ylide probably does not allow a photochemical activation. Moreover, azirine **4h** was also obtained thermally.

Finally, DFT calculations[21] were performed at the B3LYP/6-31G(d) level of theory in order to find the most realistic pathway. For the reaction between adamantanylidene **2f** and **FN**, the formation of azirine **4f** *and* the ylide is strongly exothermic (256 and 235 kJ/mol, respectively). A transition state connecting the ylide and the azirine could be located, but it was highly energetic (+163 kJ/mol from the ylide), and the ground state reaction is forbidden. Considering the fact that usually nitrile ylides are nonisolable reactive species, this high energetic barrier would speak against a thermally driven ring closure reaction. Furthermore, the energies of the two transition states between the nitrile ylide and both azirines **4f** differ by less than 1 kJ/mol. This difference is too small to account for the large excess obtained experimentally for one diastereomer (9:1).

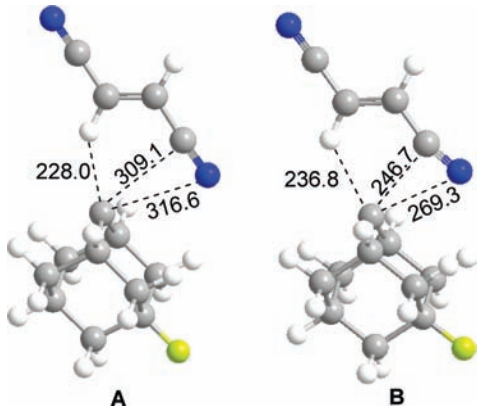

Figure 2. Structure **A**: carbene−alkene complex between **2f** and **FN**. Structure **B**: transition state between adamantanylidene **2f** and fumaronitrile. Distances in pm.

The most probable pathway for the azirination of fumaronitrile is a concerted addition of the reactive-nucleophilic[22] carbene **2f** to the triple bond of the nitrile group (Figure 2, structure **B**; this transition state is only 4.5 kJ/mol higher in energy than complex **A**). In the special case of fumaronitrile, this reaction is highly favored by the prior formation of a carbene−alkene complex (CAC, structure **A**). This CAC is strongly stabilized by 37 kJ/mol. As revealed by the NBO analysis, the stabilization of this structure results from electron donation from the carbenic lone pair to the C−H antibond of **FN** assisted by electrostatic dipole−dipole interactions.[23] For a C−H bond-based interaction this is an impressively high value. Its strength is correlated with the presence of electron-withdrawing groups at the double bond.[23] Because of this hydrogen bridge, the two reactants

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(19) The UV spectra of several nitrile ylides have been recorded with λ_{max} ranging from 280 to 410 nm. See ref 8a.

(20) Photolyses of azirines are widely used to generate nitrile ylides, since the reaction pathways are barrierless. However, little is known about the feasibility of the reverse reaction, which involves a barrier of ca. 45 kJ/mol: Bornemann, C.; Klessinger, M. *Chem. Phys.* **2000**, *259*, 263.

(21) The energetic values given represent E+ZPVE.

(22) Mieusset, J.-L.; Brinker, U. H. *J. Org. Chem.* **2008**, *73*, 1553.

(23) (a) Mieusset, J.-L.; Abraham, M.; Brinker, U. H. *J. Am. Chem. Soc.* **2008**, *130*, 14634. This type of complex resulting from interactions with the vinylic proton should be differentiated from the proposed carbene−olefin complexes (COC) based on interactions with the olefinic π orbitals which have been discussed in the past: (b) Nigam, M.; Platz, M. S.; Showalter, B. M.; Toscano, J. P.; Johnson, R.; Abbot, S. C.; Kirchhoff, M. M. *J. Am. Chem. Soc.* **1998**, *120*, 8055.

are oriented in such a way that the nitrile moiety is placed in immediate proximity to the carbenic center, thus favoring the azirine formation. For the ylide formation and for the cyclopropanation reaction, no transition structures could be located, in accordance with the fact that no energetic barrier exists during these reactions as long as the reactants and their orbitals are properly oriented.[23] The only barrier to be overcome is of entropic nature.

Analysis of the data obtained with other substituents ($SiMe_3$, Me, NH_2, OH) revealed a strong dependence of the azirine:cyclopropane ratio upon the substituent, which can be correlated with their electronegativity. The electron-withdrawing −F, −OH, and $-NH_2$ groups favor azirine formation whereas the electron-releasing $SiMe_3$ even more strongly favors cyclopropanation. Indeed, azirination of fumaronitrile by adamantanylidenes depends on a delicate balance of the ambiphilicity of the carbene. As mentioned,[8b,9] many carbenes are too electrophilic and preferably form nitrile ylides whereas the more nucleophilic[22] carbenes can very efficiently cyclopropanate the electron-deficient double bond of fumaronitrile.[23] Moreover, azirine formation could be obtained with maleonitrile.

A second observation can be made from this series of experiments: the azirine:cyclopropane ratio is strongly dependent on the solvent. Undoubtedly, ether strongly favors azirine formation. Indeed, major solvent effects on the reactivity of alkylcarbenes have been observed previously,[24] which can be explained in terms of carbene complexation by the solvent.[25,26]

In conclusion, azirines have been synthesized which comprise a double bond in conjugation with the azirine C═N bond, a rather rare feature.[27] We provide strong evidence that during the synthesis of azirines generated by the reaction of reactive-nucleophilic carbenes with nitriles, a concerted addition of the carbene to the triple bond is preferred over the two-step pathway (formation of a nitrile ylide and its subsequent cyclization) previously postulated. With this background knowledge, the carbene route to azirines will become more practicable and will expand the repertoire of methods available to prepare 2*H*-azirines.

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Supporting Information Available: Experimental procedures, spectral and crystallographic data (CIFs) for **1f** and **4f**, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) (a) Ruck, R. T.; Jones, M., Jr. *Tetrahedron Lett.* **1998**, *39*, 2277. (b) Tomioka, H.; Ozaki, Y.; Izawa, Y. *Tetrahedron* **1985**, *41*, 4987.

(25) For a review about carbene complexes, see: Kirmse, W. *Eur. J. Org. Chem.* **2005**, 237.

(26) Mieusset, J.-L.; Brinker, U. H. *Eur. J. Org. Chem.* **2008**, 3363.

(27) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103.