Organic LETTERS

Letter

pubs.acs.org/OrgLett

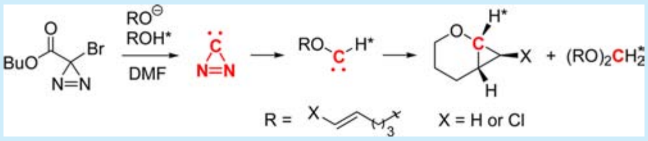
Evidence for the Cyclic CN$_2$ Carbene in Solution

Eva Hanzlová, Rafael Navrátil, Jan Čejka, Stanislav Böhm, and Tomáš Martinů*

Department of Organic Chemistry, Institute of Chemical Technology, Technická 5, 166 28 Prague, Czech Republic

Supporting Information

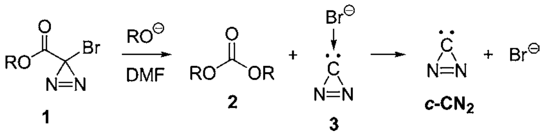
ABSTRACT: Diazirinylidene (c-CN$_2$) is formally the simplest of the N-heterocyclic carbenes. The intermediacy of this elusive species in the fragmentation of butyl 3-bromodiazirine-3-carboxylate (**1a**) with pent-4-en-1-ols and their sodium alkoxides in DMF is supported by the formation of 2-oxabicyclo[4.1.0]heptanes and dipentenoxymethanes. These products result from an intramolecular [2 + 1] cycloaddition and O−H insertion, respectively, of pentenoxymethylenes suggested to originate from the reaction of the electrophilic c-CN$_2$ with an alkoxide ion. The reaction of **1a** with primary or secondary amines in methanol affords the corresponding 3-bromodiazirine-3-carboxamides.



Diazirinylidene (**c-CN$_2$**), formally the simplest of the unsaturated N-heterocyclic carbenes (NHCs), is the last experimentally elusive member of the CN$_2$ family of reactive intermediates remaining. Comparatively, its two valence isomers, ground state triplets diazomethylene (CNN, $E_{\mathrm{rel,calc}}$ = 4 kcal/mol) and cyanonitrene (NCN, $E_{\mathrm{rel,calc}}$ = −25 kcal/mol),[1a] were cryogenically isolated and characterized in the 1960s.[2] Much like other NHCs, ab initio calculations predict **c-CN$_2$** to have a singlet ground state.[1] Typically for NHCs, such singlet states are stabilized by electron delocalization from the neighboring π-symmetry nitrogen lone pairs, providing some extent of aromaticity to the unsaturated NHCs.[3] Although **c-CN$_2$** should also benefit from aromatic stabilization,[1b] it is expected to behave quite differently from typical NHCs, as its σ-symmetry nitrogen lone pairs cannot be delocalized into the carbene center. Thus **c-CN$_2$** is calculated to exhibit nucleophilicity as low as that of CF$_2$ and electrophilicity comparable to that of CFCl.[4] The **c-CN$_2$** still should be capable of binding to some transition metals,[5] although less strongly than the regular nucleophilic NHCs.[6]

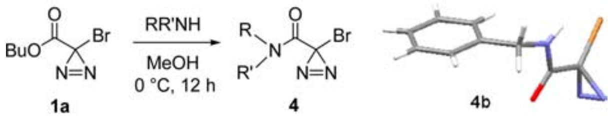
We have recently shown that **c-CN$_2$** is a plausible reactive intermediate in the facile fragmentation of 3-bromodiazirine-3-carboxylic esters **1** with alkoxide ions in DMF, affording, upon liberation of molecular nitrogen, high yields of dialkyl carbonates **2** (Scheme 1).[4] Experimental and computational results indicate that alkoxide ions attack at the ester carbonyl group instead of the diazirine ring nitrogens of **1** (the latter pathway is typical for the halodiazirines and results in the halogen exchange by two consecutive S$_N$2′-like steps[7]). Calculations predict the resulting tetrahedral intermediate eliminates the 3-bromodiazirinyl anion, c-CN$_2$Br$^-$ (**3**),[8] a weakly bound complex of **c-CN$_2$** with the Br$^-$ ion which spontaneously dissociates under the reaction conditions.

Scheme 1. Reaction of Esters 1 with Alkoxide Ions



The preference of diazirine carboxylates **1** for a nucleophilic acyl displacement is further demonstrated by the transformation of butyl ester **1a** to secondary or tertiary amides **4** in good yield upon treatment with 0.95 equiv of the corresponding amines in methanol,[9] with virtually no observed C−C bond cleavage (Table 1).

Table 1. Transformation of Ester 1a to Amides 4, X-ray Structure of 4b

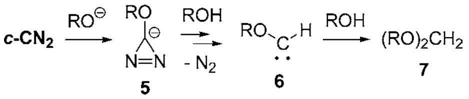


compound		isolated yield (%)
4a	R = Et, R′ = H	52
4b	R = Bn, R′ = H	60
4c	R, R′ = (CH$_2$)$_5$	56

The only suitable conditions available thus far for the fragmentation of esters **1**, the strongly nucleophilic environment of an alkoxide solution in DMF,[10] have hindered our attempts at the direct trapping of **c-CN$_2$** by cycloaddition to a C═C bond of alkenes, expected to form the unprecedented and highly strained 1,2-diazaspiro[2.2]pent-1-enes.[4] The electrophilic **c-CN$_2$** may rather prefer to react with the excess alkoxide ions, likely resulting in a 3-alkoxydiazirinyl anion **5**, and this alternative reactivity is supported by experimental results (Scheme 2). In the presence of an alcohol, acetals **7** are obtained in moderate yields (ca. 35%) along with unchanged yields of carbonates **2** (ca. 80%). The formation of **7** can be

Received: December 16, 2013
Published: January 17, 2014

Scheme 2. Proposed Mechanism of the Formation of Acetals 7 in the Presence of Alcohols



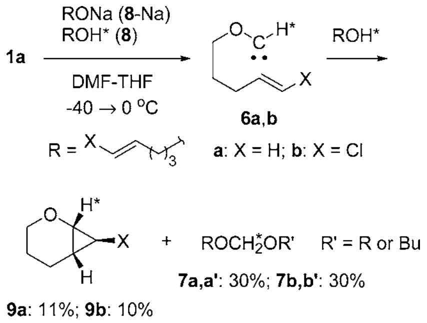
rationalized by a transformation of **5** to an alkoxymethylene **6** followed by its insertion into the O−H bond of the alcohol.

Singlet carbene O−H insertions are very facile processes; however, it would be the [2 + 1] cycloaddition of **6** to a C=C bond, the signature reaction of carbenes, the observation of which would lend much credence to the mechanistic picture shown in Schemes 1 and 2.[11] Our attempts to trap **6** by cycloaddition to the electron-deficient C=C bonds of an acrylic ester or acrylonitrile only resulted in the conjugate addition of alkoxide/alcohol to these bonds, demonstrating again the limits imposed by the reaction environment on the observation of carbenic reactivity.

Thus we optimized the structure of the trapping agent to limit its undesired reaction with alkoxide ions while improving the carbene's ability to undergo cycloaddition readily enough to compete with the fast O−H insertion. The latter requirement could be met by enabling the cycloaddition to proceed in an intramolecular fashion, and therefore, we set out to generate alkenoxymethylenes bearing a suitably situated C=C bond to form a cyclopropane-fused 2-oxa[*n*.1.0]bicyclic system. Since the corresponding bicyclohexanes ($n = 3$) are known to be rather labile,[12] we targeted the more stable 2-oxa[4.1.0]bicycloheptanes.[13]

A mixture of pent-4-en-1-ol (**8a**) and its sodium alcoholate (2 + 4 equivs) was allowed to react with butyl ester **1a** in DMF−THF (10:1)[14] at −40 to 0 °C (Scheme 3). Upon the evolution of nitrogen, the expected intramolecular cycloadduct **9a**[13] was obtained in 11% yield (by NMR and GC/MS) along with a 30% yield of a 2.3:1 mixture of bis(pentenyl) and butyl(pentenyl) acetals **7a** and **7a′**. When *O*-deuterated pentenol **8a**-*d* was used, deuterium was incorporated selectively as expected at the C1 atom of **9a** and the methylene C atom of acetals **7a**,**a′** (by ^{1}H, ^{2}H, ^{13}C NMR and MS). The reaction of **1a** with *E*-5-chloropent-4-en-1-ol (**8b**)[15] and its sodium alcoholate afforded the *exo*-chloro cycloadduct **9b**[13] as the only expected diastereoisomer in 10% yield along with a 30% yield of a 4.5:1 mixture of bis(chloropentenyl) and butyl(chloropentenyl) acetals **7b** and **7b′**. Interestingly, the increased electron deficiency of the chloro-substituted C=C bond did not result in a higher yield of cycloadduct **9b** at the expense of acetals **7b**,**b′**. Further experiments with *E*-4,5-dichloro- (**8c**), 5,5-dichloro- (**8d**),[15] and *E*-5-(4-nitrophenyl)-pent-4-en-1-ol (**8e**),[16] bearing ever more electron deficient C=C bonds, did not afford quantifiable amounts of acetals **7** or cycloadducts **9** due to the fast degradation of the corresponding sodium alcoholates.

Scheme 3. Proposed Mechanism of the Formation of Acetals 7 and Bicycles 9 in the Presence of Pentenols 8



The results of diazirine **1a** cleavage in the presence of pentenols **8a**,**b** are consistent with the intermediacy of pentenoxymethylenes **6a**,**b** formed in at least 40% yield by denitrogenation of a corresponding precursor, diazirine **10** or diazomethane **11** (Figure 1). Both species can be expected to originate from diazirinyl anion **5** by a proton transfer from alcohol **8**, either directly or preceded by a ring opening to diazo anion **12**. The formation of **12** is, however, calculated to proceed through a significant barrier (E_A = 23 kcal/mol).[17]

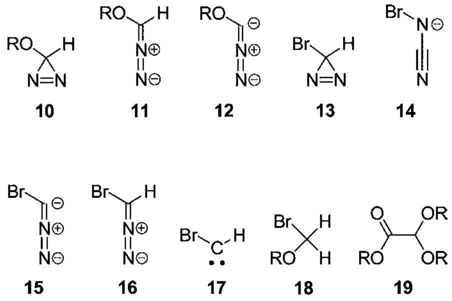


Figure 1. Species potentially involved in the reaction of **1** with alkoxide ions in the presence of alcohol.

Diazirine **10** can also be formed by the halogen exchange of 3-bromodiazirine (**13**), potentially resulting from a protonation of anion **3** competing with its dissociation to ***c*-CN$_2$**. However, such a proton transfer would have to occur from the weakly acidic alcohol **8** to the loose complex **3**, calculated to carry most of the negative charge on the Br atom.[18] Importantly, the basicity of **3** is comparable to that of CF_2Br^- and CCl_3^- ions (Table 2), the former dissociating[19] to CF_2 and Br^- faster than it is protonated in aqueous solution,[20] and the latter being protonated only very slowly in DMF, even by trichloroacetic acid.[21] On the other hand, diazirinyl anion **5**, with an increased cyclic 4π-electron character imposed by the majority of negative charge on the CN_2 ring,[18] is a significantly stronger base than **3**, rendering the **3** → **5** → **10** pathway more plausible (the lower basicity of the acyclic diazo anion **12**, together with the relatively high barrier to its formation, makes this species a less likely intermediate).

Table 2. Calculated Relative Proton Affinities

process	ΔG^a
HCF_2Br + **3** → CF_2Br^- + **13**	−1.7[b]
$HCCl_3$ + **3** → CCl_3^- + **13**	−0.6
H*c*-$CN_2(OCH_3)$ (**10′**) + **3** → *c*-$CN_2(OCH_3)^-$ (**5′**) + **13**	15.7[b]
$HCNN(OCH_3)$ (**11′**) + **3** → $CNN(OCH_3)^-$ (**12′**) + **13**	3.4

[a] Values in kcal/mol at 298 K calculated at the PBE/6-311+g(d,p) level in DMF (CPCM solvation model). [b] Values from ref 4.

The formation of ***c*-CN$_2$** can also potentially be avoided by the isomerizations of **3** to cyanamide anion **14** or diazo anion **15**, but these processes are unlikely to occur due to their high activation energies (E_A = 33 and 52 kcal/mol, respectively).[17] Even if formed, **14** or **15** cannot be the precursor of carbenes **6**, as there is no such conceivable pathway for **14** and species **15** would not spontaneously dissociate the Br$^-$ ion analogously to **3** (ΔG = 33 kcal/mol vs −3 kcal/mol)[22] as this would lead to the high energy singlet ^{1}CNN (estimated to be ca. 24 kcal/mol above ^{1}***c*-CN$_2$**).[23] Ion **15** would then more likely be protonated to afford bromodiazomethane (**16**), readily denitrogenating to bromomethylene (**17**),[24] rather than exchanging its halogen to form **11**. It should be, however, pointed out that carbene **17** can give rise to acetals **7** by an O−H insertion resulting in bromoether **18** followed by a nucleophilic halogen displacement.

Consistently with the substantial endothermicity of the ring opening of ^{1}***c*-CN$_2$** to ^{1}CNN, the calculated activation energy for this process is high (E_A = 67 kcal/mol).[17] The opening of ^{1}***c*-CN$_2$** to ^{1}NCN is energetically almost neutral (ΔE = −2 kcal/mol),[25] with a high estimated barrier ($E_A \approx$ 66 kcal/mol).[26] All the above calculations thus show that ***c*-CN$_2$** and its anionic derivatives **3** and **5** are kinetically stable to the ring-opening reactions on the singlet potential energy surface.

Other possible precursors of products **2** and **7** (but not **9**) obtained upon fragmentation of **1** are DMF itself (the solvent used) and dialkoxyesters **19** potentially formed from **1** by a halogen exchange/denitrogenation/O−H insertion sequence. Both alternatives can be excluded, as the cleavage of **1** also proceeds in DMSO, no deuterium incorporates to **7** when the reaction is performed in DMF-d_7, and an authentic sample of **19** (R = Bu) does not afford any **2** or **7** when subjected to the cleavage reaction conditions.[4]

In conclusion, experimental and computational results indicate that bromodiazirine esters **1** undergo a nucleophilic displacement at the ester group. While the reaction of butyl ester **1a** with amines in methanol affords amides, the reaction with alkoxide ions in DMF leads to the expulsion of the *c*-CN$_2$Br$^-$ ion, likely dissociating to the ***c*-CN$_2$** carbene. In the presence of a pent-4-en-1-ol, this elusive species gives rise to pentenoxymethylenes undergoing O−H insertion and intramolecular [2 + 1] cycloaddition reactions. Alternative pathways have been shown to be inconsistent with experimental observations, and the *c*-CN$_2$ ring of the parent carbene and its anionic derivatives has been calculated to be kinetically stable to opening.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectroscopic data for all new compounds, computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: martinut@vscht.cz.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Specific University Research Grant MSMT 21/2013 from the Ministry of Education, Youth and Sports of the Czech Republic. We thank Dr. Christopher J. Shaffer for helpful discussions and Ms. Květa Bártová for technical assistance.

■ REFERENCES

(1) (a) Moskaleva, L. V.; Lin, M. C. *J. Phys. Chem. A* **2001**, *105*, 4156. (b) Jursic, B. S. *THEOCHEM* **1999**, *491*, 33. (c) Martin, J. M. L.; Taylor, P. R.; François, J. P.; Gijbels, R. *Chem. Phys. Lett.* **1994**, *226*, 475. (d) Kassaee, M. Z.; Ghambarian, M.; Musavi, S. M.; Shakib, F. A.; Momeni, M. R. *J. Phys. Org. Chem.* **2009**, *22*, 919. (e) Gronert, S.; Keeffe, J. R.; More O'Ferrall, R. A. *J. Am. Chem. Soc.* **2011**, *133*, 3381.

(2) (a) Milligan, D. E.; Jacox, M. E.; Bass, A. M. *J. Chem. Phys.* **1965**, *43*, 3149. (b) Milligan, D. E.; Jacox, M. E. *J. Chem. Phys.* **1966**, *44*, 2850.

(3) (a) Heinemann, C.; Müller, T.; Apeloig, Y.; Schwarz, H. *J. Am. Chem. Soc.* **1996**, *118*, 2023. (b) Boehme, C.; Frenking, G. *J. Am. Chem. Soc.* **1996**, *118*, 2039. (c) Tafipolsky, M.; Scherer, W.; Öfele, K.; Artus, G.; Pedersen, B.; Herrmann, W. A.; McGrady, G. S. *J. Am. Chem. Soc.* **2002**, *124*, 5865.

(4) Martinů, T.; Böhm, S.; Hanzlová, E. *Eur. J. Org. Chem.* **2011**, 6254.

(5) Pyykkö, P.; Runeberg, N. *Chem.—Asian J.* **2006**, *1*, 623.

(6) *N-Heterocyclic Carbenes*; Díez-Gonzáles, S., Ed.; The Royal Society of Chemistry: Cambridge, 2011.

(7) Moss, R. A. *Acc. Chem. Res.* **2006**, *39*, 267.

(8) Diazirinyl anions (*c*-CN$_2$R$^-$), cyclic 4π-electron systems, are in fact nonaromatic. They have been observed in the gas phase or implicated as reactive intermediates in solution: (a) Kroeker, R. L.; Bachrach, S. M.; Kass, S. R. *J. Org. Chem.* **1991**, *56*, 4062. (b) Kroeker, R. L.; Kass, S. R. *J. Am. Chem. Soc.* **1990**, *112*, 9024. (c) Seburg, R. A.; Hill, B. T.; Jesinger, R. A.; Squires, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 6310. (d) Creary, X.; Sky, A. F.; Phillips, G.; Alonso, D. E. *J. Am. Chem. Soc.* **1993**, *115*, 7584. (e) Moss, R. A.; Xue, S.; Liu, W. G. *J. Am. Chem. Soc.* **1994**, *116*, 10821.

(9) Excess amine was avoided to prevent the halogen exchange reaction leading to aminodiazirines: Moss, R. A.; Cox, D. P.; Tomioka, H. *Tetrahedron Lett.* **1984**, *25*, 1023.

(10) The reaction also readily proceeds in DMSO (with lower isolated yields of **2**), it is very slow in methanol or butan-1-ol, and it does not proceed in THF or hexane.

(11) Jones, M.; Moss, R. A. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jones, M., Eds.; Wiley: Hoboken, NJ, 2004; p 273.

(12) (a) Inoue, Y.; Matsumoto, N.; Hakushi, T.; Srinivasan, R. *J. Org. Chem.* **1981**, *46*, 2267. (b) Anderson, J. C.; Lindsay, D. G.; Reese, C. B. *Tetrahedron* **1964**, *20*, 2091.

(13) Taylor, K. G.; Hobbs, W. E.; Saquet, M. *J. Org. Chem.* **1971**, *36*, 369.

(14) The formation of sodium alkoxide using NaH was performed first in THF in order to prevent concomitant alcoholysis of DMF known to complicate the diazirine cleavage reaction (ref 4).

(15) See the Supporting Information for the syntheses of alcohols **8b−d**.

(16) Bélanger, G.; Lévesque, M.; Pâquet, J.; Barbe, G. *J. Org. Chem.* **2005**, *70*, 291.

(17) Calculated at the MP4(SDTQ)/aug-cc-pVTZ//MP2/aug-cc-pVTZ level in DMF (CPCM solvation model).

(18) According to the NPA at the MP2/6-311+G(d) level in DMF (CPCM solvation model), the *c*-CN$_2$ ring carries 2% of the total negative charge in bromo anion **3** and 55% in alkoxy anion **5** (methoxy-substituted model **5′**).

(19) Moss, R. A.; Zhang, M.; Krogh-Jespersen, K. *Org. Lett.* **2009**, *11*, 5702.

(20) Hine, J.; Langford, P. B. *J. Am. Chem. Soc.* **1957**, *79*, 5497.

(21) This phenomenon has been explained by strong proton solvation in DMF through hydrogen bonding: Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435.

(22) Calculated at the MP2/6-311+g(d) level in DMF (CPCM solvation model).

(23) Based on the calculated relative energies of ^{1}***c*-CN$_2$** and ^{3}CNN (ref 1a) and the measured ΔE_{S-T} = 19.5 kcal/mol of CNN (Clifford, E. P.; Wenthold, P. G.; Lineberger, W. C.; Petterson, G. A.; Broadus, K. M.; Kass, S. R.; Kato, S.; DePuy, C. H.; Bierbaum, V. M.; Ellison, G. B. *J. Phys. Chem. A* **1998**, *102*, 7100).

(24) Closs, G. L.; Coyle, J. J. *J. Am. Chem. Soc.* **1965**, *87*, 4270.

(25) Based on the calculated relative energies of ^{1}***c*-CN$_2$** and ^{3}NCN (ref 1a) and the measured ΔE_{S-T} = 23.3 kcal/mol of NCN (Taylor, T. R.; Bise, R. T.; Asmis, K. R.; Neumark, D. M. *Chem. Phys. Lett.* **1999**, *301*, 41).

(26) Based on a transtition structure with one imaginary frequency corresponding to the N=N bond-breaking vibration (ref 17), the IRC analysis of which, however, led to the acyclic NCN in both the forward and reverse directions. This is likely caused by the use of a single-configuration SCF method not accounting for the two known low-lying singlet states of NCN (ref 25).