Ethynyl Azides

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1-Azido-1-Alkynes: Synthesis and Spectroscopic Characterization of Azidoacetylene**

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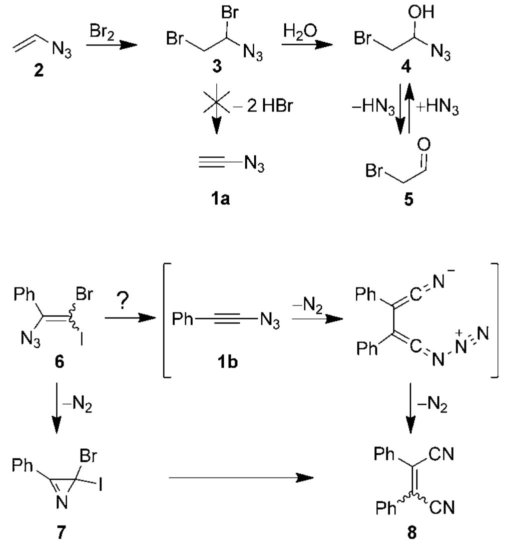
Dedicated to Professor K. Barry Sharpless

In 1910, Forster and Newman had already studied the addition of bromine to vinyl azide (**2**) in an aqueous solution to prepare azidoacetylene (**1a**) by based-induced elimination of two molecules of hydrogen bromide (Scheme 1). However, owing to the explosion-like course of the addition reaction and the high sensitivity of the product **3** to hydrolysis, **3** could not be detected and aldehyde **5** was generated instead.[1] A hundred years later, it was shown that the transformation **2**→**3** can be performed conveniently and quantitatively with bromine in organic solvents at low temperature. Careful hydrolysis of **3** led to an equilibrium mixture of α-azido alcohol **4** and aldehyde **5**,[2] but all efforts to convert **3** into the alkyne **1a** were in vain. Since the 1950s, many groups have tried to generate 1-azido-1-alkynes, but these species have remained elusive even until today.[3] Other attempts at preparing these compounds were also unsuccessful or yielded unwanted products.[4] For example, the reactions of (phenylethynyl)sodium or alkyl-1-ynyl lithiums and aromatic sulfonyl azides exclusively led to 1,2,3-triazole derivatives instead of ethynyl azides.[5] Furthermore, the transformation of azide **6** into the dinitriles **8**, a reaction that can be performed under a variety of conditions and in high yield, was postulated to proceed via the short-lived alkyne **1b** (Scheme 1).[6] However, 2*H*-azirine **7** was also predicted to be an intermediate in the transformation **6**→**8**.[7] Recently, the highly unstable heterocycle **7** was photochemically prepared from **6** in 90% yield, characterized by its NMR data, and thermolyzed to give the nitriles **8**, nearly quantitatively.[8]



Scheme 1. Some of numerous unsuccessful attempts to prepare ethynyl azides **1a** and **1b**.

In 1983, Tanaka and Yamabe reported on the treatment of chloride **9** with sodium azide in dimethyl sulfoxide, a reaction that was claimed to afford in low yield (5–8%) the sulfoximine **17** and some other products but no dinitriles **8** (Scheme 2). The synthesis of **17** was rationalized to proceed through the formation of short-lived azide **1b** followed by loss of dinitrogen and trapping of the nitrene **14** by the solvent.[9] When the experiment starting with **9** was repeated recently, it was shown that the actual product **18**, resulting from the reaction pathway via carbene **15b**, had been erroneously taken for **17**.[8] Furthermore, previous ab initio studies demonstrated that ethynylnitrenes such as **14** do not correspond to a local minimum of energy and that cleavage of dinitrogen from azide **1b** should generate carbene **15b**.[10,11] Not only the carbene-interception product **18** but also the triazole **13b** was obtained when the reaction of **9** with lithium azide in dimethyl sulfoxide was performed in the presence of cyclooctyne.[8] This heterocyclic product is currently the most plausible evidence for short-lived ethynyl azides. To the best of our knowledge, any spectroscopic proof for the existence of these azides is still missing.

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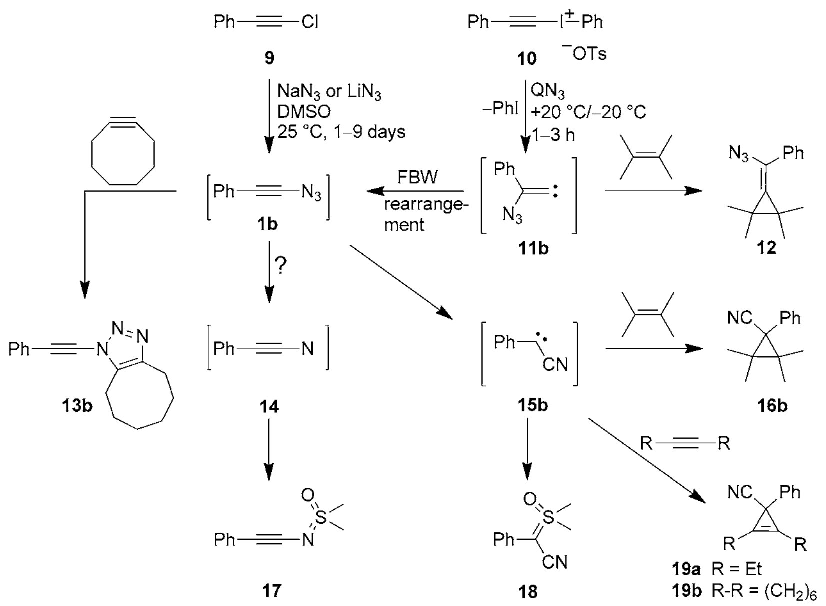


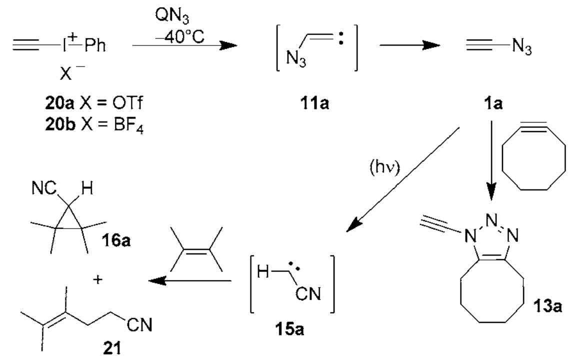
Scheme 2. Generation of phenylethynyl azide (**1b**). QN$_3$ = hexadecyltributylphosphonium azide.

Herein, we show that 1-azidoalkynes can be synthesized more rapidly and under significantly milder reaction conditions when ethynyliodonium salts instead of 1-chloroacetylenes are treated with azide salts. Moreover, better yields of the trapping products are achieved, and it was possible to detect azidoacetylene (**1a**) for the first time by using IR and NMR spectroscopy. These results are strongly supported by quantum chemical calculations.

The conversion of **9** with sodium azide in dimethyl sulfoxide is very slow at ambient temperature and furnished only low yields of **18** (up to 10%) and **13b** (2–12%). Even slower reactions were observed when the polar solvent (DMSO or DMF) was diluted by the less-polar interception-reagent cyclooctyne.[12] We assume that the nucleophilic substitution **9**→**1b** is a two-step addition–elimination process with attack of azide at the carbon atom that is connected to the chlorine atom. On the other hand, phenyliodonium salts, such as **10**,[13] are well-known to react with azide at the other carbon atom to generate azidovinylidene intermediates such as **11b** after cleavage of iodobenzene.[14] Proof for short-lived azidovinylidenes was presented by Stang and Kitamura, who analyzed the subsequent reactions, which led to insertion products.[15]

When we treated the salt **10** with a highly soluble azide source such as QN$_3$[16] (hexadecyltributylphosphonium azide) in the presence of 2,3-dimethyl-2-butene, not only the vinylidene-trapping product **12** (17% yield) but also the known[17] cyanocyclopropane **16b** (29%) were isolated (Scheme 2). We explain the formation of **16b** through a Fritsch–Buttenberg–Wiechell-like rearrangement (FBW) of **11b**, cleavage of dinitrogen from resulting **1b**, and interception of carbene **15b**. After we had repeated the experiment with 3-hexyne instead of 2,3-dimethyl-2-butene, we found exclusively the 3-cyanocyclopropene **19a** (43%). Whereas general trapping of vinylidenes by olefins to produce methylidenecyclopropanes is well-known,[18] the analogous reaction with alkynes has seldom been investigated because the corresponding methylidenecyclopropenes are highly unstable and could only be characterized after interception by Diels–Alder reaction.[19] Thus, it is not surprising that no methylidenecyclopropenes were detected from the reaction mixture of **10**, QN$_3$, and alkynes. On the other hand, treatment of **10** with QN$_3$ in the presence of ring-strained cyclooctyne instead of open-chain acetylenes afforded not only a small yield of **19b** (7%) but also the triazole **13b** (21%), which is the trapping product of azide **1b**.

These results encouraged us to also investigate the reaction of iodonium salts **20**[20] with QN$_3$ (Scheme 3). We assume that the attack of azide at the terminal carbon atom of **20** will be more rapid than the analogous reaction of **10**. Furthermore, quantum chemical calculations,[10] in which energy barriers for the cleavage of dinitrogen were studied for different ethynyl azides, predicted an even greater stability of **1a** than that of **1b**, whereas azidoacetylenes with donor groups, such as amino or ethylsulfanyl, should cleave dinitrogen very easily.[21–23]



Scheme 3. Synthesis and reactions of azidoacetylene (**1a**). QN$_3$ = hexadecyltributylphosphonium azide.

After treatment of the iodonium salt **20b** with QN$_3$ at −40 °C in the presence of 2,3-dimethyl-2-butene, we isolated the known[24] cyclopropane **16a** (15% yield) and the insertion product **21** (7%), which obviously result from carbene **15a** (Scheme 3). We could not detect the corresponding azidomethylidenecyclopropane, which may form by the trapping of vinylidene **11a**. Thus, we assume that the isomerization **11a**→**1a** is more rapid than the FBW-like rearrangement **11b**→**1b**. When the reaction of **20a** with QN$_3$ was performed at −40 to −30 °C with cyclooctyne instead of 2,3-dimethyl-2-butene, we exclusively isolated the triazole **13a** (91%), which is a consequence of the 1,3-dipolar cycloaddition of azide **1a** to the cycloalkyne. Treatment of **20a** or **20b** with QN$_3$ in acetone, dichloromethane, or chloroform (−40 °C/30–120 min) in the

Table 1: Selected experimental and calculated spectroscopic data of azidoacetylene (**1a**) and [$^{15}N_3$]-**1a**.[a,b,c]

1a	IR ($CHCl_3$, −20 °C):[c]	$\tilde{\nu} = 3312$ (m, C−H), 2188 (s, C≡C), 2148 (w), 2086 (s, N_3), 1251 cm^{-1} (w, N_3)
	^1H NMR ([D_6]acetone):	$\delta = 3.38$ (s) [$\delta = 3.7$]
	^{13}C NMR ([D_6]acetone):	$\delta = 55.81$ (d, $^1J = 265.5$ Hz, CH), 72.25 (d, $^2J = 58.3$ Hz, CN_3) [$\delta = 55.5$ ($^1J = 259$ Hz), 76.5 ($^2J = 59$ Hz)]
	^1H NMR (CD_2Cl_2):	$\delta = 2.55$ (s) [$\delta = 3.0$]
	^{13}C NMR (CD_2Cl_2):	$\delta = 54.52$ (d, $^1J = 262.8$ Hz, CH) 71.94 (d, $^2J = 57.5$ Hz, CN_3) [$\delta = 54.0$ ($^1J = 259$ Hz), 75.0 ($^2J = 59$ Hz)]
[$^{15}N_3$]-**1a**	^1H NMR (CD_2Cl_2):	$\delta = 2.57$ (dd, $^4J_{HN} = 1.7$ Hz, $^3J_{HN} = 0.9$ Hz)
	^{13}C NMR (CD_2Cl_2):	$\delta = 54.31$ (ddd, $^1J_{CH} = 264.9$ Hz, $^2J_{CN} = 5.7$ Hz, $^3J_{CN} = 2.9$ Hz, CH), 71.69 (dd, $^2J_{CH} = 58.8$ Hz, $^1J_{CN} = 15.4$ Hz, CN_3) [$^1J_{CN} = -17$ Hz, $^2J_{CN\alpha} = 5.6$ Hz, $^2J_{CN\beta} = 2.6$ Hz]
	^{15}N NMR (CD_2Cl_2):	$\delta = -314.6$ (br d, $^1J_{NN} = 15.5$ Hz, N_α), −151.8 (d, $^1J_{NN} = 7.4$ Hz, N_γ), −139.9 (ddd, $^1J_{N\alpha N\beta} = 15.5$ Hz, $^1J_{N\beta N\gamma} = 7.4$ Hz, $^4J_{NH} = 1.7$ Hz, N_β) [$\delta = 317.8$ ($^1J_{NN} = -15.5$ Hz, $^3J_{NH} = -0.8$ Hz, N_α), −151.8 reference value ($^1J_{NN} = -6$ Hz, N_γ), −133.8 ($^1J_{N\alpha N\beta} = -15.5$ Hz, $^1J_{N\beta N\gamma} = -6$ Hz, $^4J_{NH} = 1.9$ Hz, N_β)]

[a] ^1H and ^{13}C NMR spectra were recorded at −40 °C and 400 and 100.6 MHz, respectively. ^{15}N NMR spectra were recorded at −60 °C and 40.5 MHz, and referenced to nitromethane ($\delta = 0$). The sign of experimental J values was not determined. [b] All NMR data based on quantum chemical calculations are given in square brackets. In the case of the ^1H NMR and ^{13}C NMR spectra, the reference of δ values is determined with the help of experimental and calculated chemical shifts of acetylene (see the Supporting Information). Calculated ^{15}N NMR δ values were referenced to the experimental chemical shift of N_γ. All results have been obtained from all-electron calculations and are based on geometries that have been obtained at the CCSD(T)/cc-pVTZ level of theory. NMR chemical shifts have been calculated at the CCSD(T)/pz3d2f level of theory including zero-point vibrational effects calculated at the MP2/cc-pVTZ (geometry and anharmonic force field) CCSD(T)/qz2p (chemical shifts) level of theory. Spin-spin coupling constants have been calculated at the CCSD/unc-cc-pVTZ-J level of theory including FC, SD, PSO and DSO contributions (FC and SD terms have been calculated using an unrelaxed UHF reference). [c] For IR data based on analytical CCSD(T)/cc-pVTZ normal mode calculations, see the Supporting Information.

absence of any trapping reagent led to solutions of **1a** after careful[25] recondensation of the reaction mixtures under reduced pressure (yield approximately 40%, as determined by ^1H NMR spectroscopy). ^{15}N-labeled azidoacetylene ([$^{15}N_3$]-**1a**) was also synthesized using $Q^{15}N_3$[16,26] and **20a**.

We characterized **1a** using IR, ^1H NMR, ^{13}C NMR, and ^{15}N NMR spectroscopy, which provided conclusive proof of the structure (Table 1). These data, especially the δ and J values from the NMR spectra were compared with the corresponding values resulting from quantum chemical calculations at the coupled-cluster level of theory. Experimental and calculated data for acetylene were included for the referencing of the chemical shifts in the case of calculated ^1H NMR and ^{13}C NMR spectra. Generally, good agreement between the measured and the theoretical data was found. The upfield shift for the signal corresponding to the C−H carbon (δ ca. 55) indicates that the azido group acts as a π donor, through which **1a** becomes an electron-rich alkyne. The coupling constants $^1J(^{13}C,^1H)$ and $^2J(^{13}C,^1H)$ of **1a** are significantly larger than those of acetylene. This is typical for terminal alkynes with oxygen or nitrogen donor substituents.[27] The IR spectrum of **1a** shows expected bands corresponding to C−H, C≡C, asymmetric N_3, and symmetric N_3 stretching modes. However, the high extinction of the C≡C stretching vibration is as strong as the azide band; this finding is remarkable and possibly results from coupling of vibration modes.

Azidoacetylene (**1a**) decomposed with a half-life period of approximately 17 hours in dichloromethane at −30 °C. Nevertheless, it can be reacted intermolecularly, for example, with cyclooctyne to furnish **13a** (35% yield based on precursor **20a**). When a cold solution of **1a** in dichloromethane was warmed to ambient temperature in the presence of 2,3-dimethyl-2-butene, the expected compounds **16a** (44%) and **21** (27%) were formed. The same products were also found with 35% and 15% yield, respectively, after irradiation of a solution of **1a** in dichloromethane for 3 hours at −60 °C.

In summary, we have characterized the first ethynyl azide by IR, ^1H NMR, ^{13}C NMR, and ^{15}N NMR spectroscopy. After 102 years of unsuccessful attempts, not only have the azide adducts, for example, the cycloadducts **13** and the cyanocarbene-trapping products **16**, **18**, **19**, and **21**, been observed but also the parent azide itself has been characterized. Currently, we are investigating whether the properties of azidoacetylene (**1a**) as an electron-rich alkyne can be utilized for electrophilic addition or cycloaddition reactions at the C≡C bond.

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[21] In the light of this ab inito study, it seems unrealistic to utilize 1-azido-2-dimethylaminoethyne as a hypergolic fuel for hypergolic bipropellant mixtures.[22] Moreover, the report[23] on the synthesis and isolation of (ethylsulfanyl)ethynyl azide is highly questionable. In this case, it has also been shown that the presented NMR data are incompatible with the structure,[10] and several attempts to reproduce the generation of the latter azide were unsuccessful.[3a,8]

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[25] **Caution!** The azide **1a** is a highly volatile and explosive compound that can be safely used in cold solution. However, recondensation under reduced pressure can lead to an explosion (protective shield). The explosive properties of **1a** are similar to those of diazomethane. For potential hazards in handling hydrazoic acid and organic azides, see: T. Keicher, S. Löbbecke in *Organic Azides*: *Syntheses and Applications* (Eds.: S. Bräse, K. Banert), Wiley, Chichester, **2010**, pp. 3–27.

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