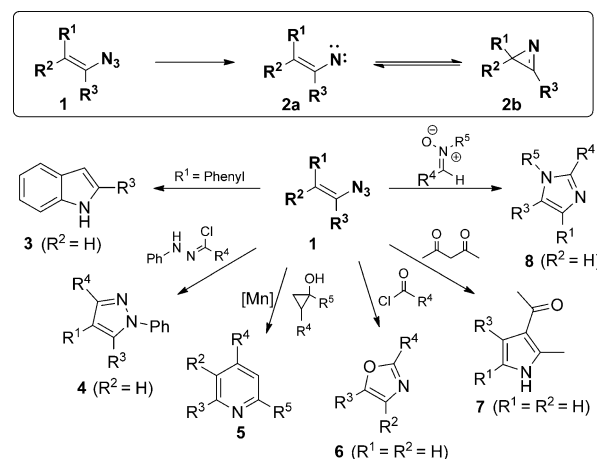


Vinyl and Alkynyl Azides: Well-Known Intermediates in the Focus of Modern Synthetic Methods

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azidation · cyanocarbenes · cyclopropanation ·
hypervalent iodo compounds · vinyl nitrenes

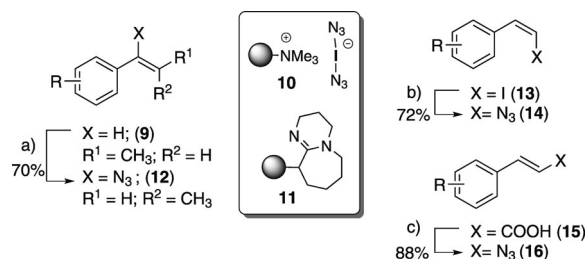
1-Azidoalkynes and **1-azidoalkenes**, which have for a long time been regarded as “sleepers” of the reactive azido species, recently showed their full potential in interesting procedures, and have now emerged as important substance classes. In particular, the handling of these problematic azides (explosiveness, toxicity, ephemerality, low selectivity/high reactivity) hampered, and still hampers, the development of synthetically useful reactions. Although they can be traced back quite a long time in the literature,^[1] 1-azidoalkynes and -alkenes gained increased attention only recently as a result of novel synthetic methods, characterizations, and new possible modes of reaction. 1-Azidoalkenes (**1**; more precisely azido vinylidenes), for example, are known as precursors of 1-azidoalkynes (**21**). Additionally, derivatives thereof containing various substitution patterns form intermediates for the formation of many nitrogen heterocycles. In the syntheses of heterocycles, vinyl azides very often appear in the form of their synthetic synthon, the vinyl nitrene (**2a**), which is in equilibrium with the corresponding azirine (**2b**); the name diazoenamine is, therefore, an adequate description of compounds **1** that can be easily transformed into compounds **2a** or **2b** by heating or photolysis (Scheme 1).^[2] Important progress has been made over the last few years through the conversion of 1-azidoalkenes into nitrenes with loss of molecular nitrogen. This enabled many easy protocols to be developed for the syntheses of indoles (**3**), pyrazoles (**4**), pyridines (isoquinolines) (**5**), oxazoles (**6**), pyrroles (**7**), and imidazoles (**8**; Scheme 1).^[2] This list is only a selection of the recent developments made concerning the chemistry of vinyl azides. Beyond these, similar protocols including metal catalysis are known for the syntheses of, for example, lactams and azabicyclic systems (Mn^{III}),^[3] or for the synthesis of isoquinolines (Rh-Cu)^[4] and indoles (Rh₂^{II}).^[5] Decomposition of the azide unit to **2a** can be avoided by a slight variation of the reaction conditions (low temperature, base). In consequence,



Scheme 1. Selected synthetic reactions with vinyl azides^[2]

1,4,5-trisubstituted triazoles have been synthesized by the use of compounds containing 1,3-dicarbonyl groups in copper-free 1,3-dipolar cycloadditions.^[2f]

A main drawback of vinyl azides up to now was the limited access to them: in the past, vinyl azides mostly had to be generated by reaction of IN₃ (synthesized in situ from NaN₃ and ICl) with alkenes.^[6] As a consequence of new developments during the last few years, chemists are now able to synthesize vinyl azides in a regio- and stereospecific manner and in very good yields without the need to use highly explosive reagents. The solid-supported (with ion-exchange resins as the cation) bisazido(I)iodate (**10**; Scheme 2) is a readily available reagent (obtained through easy protocols) for haloazidations of alkenes. In particular, its application in



Scheme 2. New approaches to vinyl azides. a) **10**, **11**; b) CuI, NaN₃, L-proline; c) NaN₃, PhI(Tfa)₂, TEAB.^[7–9] TEAB = tetraethylammonium bromide, Tfa = trifluoroacetoxy.

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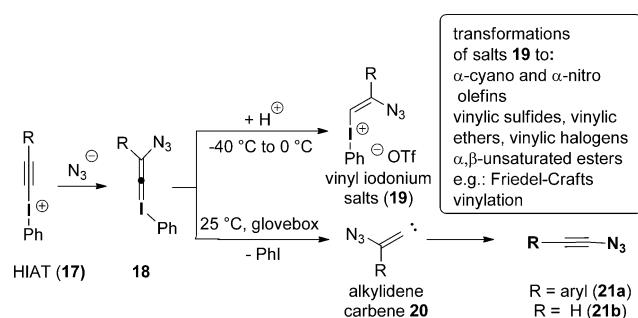
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flow synthesis avoids the release of explosive and toxic substances.^[7] An effective method for the synthesis of (*Z*)- β -azidostyrenes (**14**) and (*Z*)-1-azido alkenes through the Cu^I-catalyzed, proline-supported coupling of sodium azide with vinyl iodides was recently presented. The method described by Zhu and Ma^[8] can be used for the *Z*-selective synthesis of vinyl azides, whereas the variant by Telvekar et al. uses α,β -unsaturated carbonic acids for the formation of (*E*)-vinyl azides (**16**).^[9]

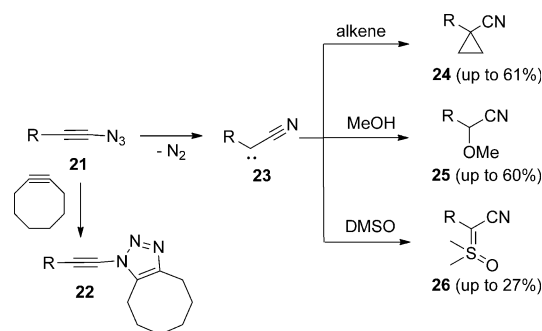
An alternative access to vinyl azides through reaction of hypervalent iodoniumalkynyl triflates (HIAT) with azides (according to Kitamura and Stang^[10]) has been advanced recently: After addition of an azide ion to the triple bond of the HIAT under formation of the ylene **18**, the vinyl iodonium salt (**19**) is formed *Z* selectively by protonation at low temperatures.^[11] This synthetic route chosen by Hyatt and Croatt and involving azido-iodoylenes enables access to diverse functionalized olefins (Scheme 3).



Scheme 3. Possible reactions of hypervalent iodonium alkynyl azide salts.^[10,12]

Furthermore, very short-lived 1-azidoalkyne intermediates (**21**) have been synthesized by the same synthetic route through changing the reaction conditions. Interest in these 1-azidoalkynes has been only of a theoretical nature for a long time. The few examples of practical applications were transformations into cyanocarbenes with a subsequent cyclopropanation or their direct application in 1,3-dipolar cycloaddition reactions. The 1-azidoalkynes (**21**) have been presumed to exist, for example, in the nowadays known reaction of 1-chloroalkynes with sodium azide, and have been verified through the formation of the expected secondary product. Their existence has been postulated several times, but could not be proven without doubt.^[13] In this new variant, phenyl- or pentyl-substituted hypervalent iodoniumalkynyl triflates are treated with tetrabutylammonium azide. The elimination of PhI occurs at room temperature and yields carbenes **20**, which can be converted into 1-azidoalkynes **21** by a 1,2-shift of the azide functionality in an inert atmosphere. While the confirmation of the synthesis of 1-azidoalkynes was still restricted in the study by Hyatt and Croatt to the characterization of the predicted products (**22**, **23**, **24**, Scheme 4), incontrovertible proof of a 1-azidoalkyne has been obtained by Banert, Auer, and co-workers, who treated hypervalent iodoniumalkynyl triflates with azides to give 1-azidoethyne, which could be fully characterized.^[14] The synthesis of this 1-azidoalkyne

species was achieved under very similar conditions to the ones chosen by Hyatt and Croatt: hexadecyltributylphosphonium azide (QN₃) was used as the azide source, as it is non-explosive and soluble in organic solvents, and was treated with phenyl iodoniumacetylene triflates or tetrafluoroborates in aprotic solvents at -40°C . After isolation and characterization of the target compound **21b**, a 1,3-dipolar cycloaddition with cyclooctyne (formation of triazole **22**) as well as a cyclopropanation by addition of alkenes (Scheme 4; the cyanocarbene **23** was postulated as an intermediate) was performed to complete the proof.



Scheme 4. Reactions and proof of 1-azidoalkynes **21**.^[11,14]

The spectroscopic verification of 1-azidoacetylene (**21b**) allowed an intermediate that had for many years only been predicted to eventually be proved. Hitherto published mechanistic descriptions concerning the formation of cyanocarbenes and their trapping products are thus now based on an assured background. The confirmed access to 1-azido-1-alkynes might result in new impulses to novel syntheses, and thus these compounds are likely to gain comparable synthetic importance as their azidoalkenyl analogues.

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