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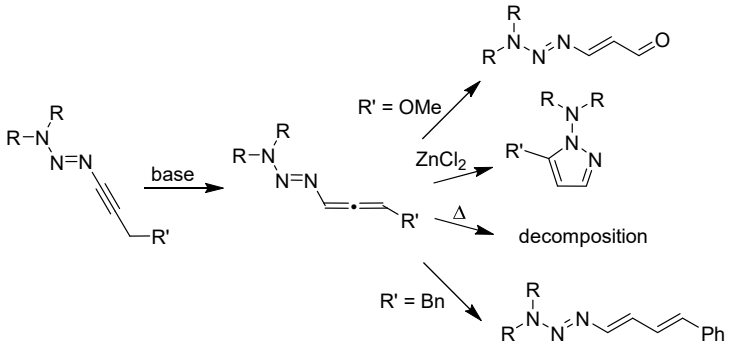
Synthesis and Reactivity of 1-Allenyltriazenes

Loïc N. Jeanbourquin, Rosario Scopelliti, Farzaneh Fadaei Tirani and Kay Severin*

Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland.

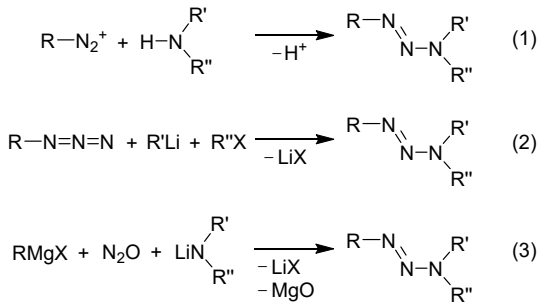
Supporting Information Placeholder



ABSTRACT: 1-Aryl-3,3-dialkyltriazenes have received considerable attention in the context of synthetic and medicinal chemistry. In contrast, the chemistry of other unsaturated triazenes is largely unexplored. The synthesis of 1-allenyltriazenes is described. This new class of compounds can be obtained by base-induced isomerization of 1-alkynyltriazenes. The latter are accessible by reaction of alkynyl Grignard reagents with lithium amides and nitrous oxide. 1-Allenyltriazenes were found to be thermally labile, but they can be stored without degradation at lower temperatures. In the presence of $ZnCl_2$, 1-allenyltriazenes rearrange into *N*-aminopyrazoles.

1-Aryl-3,3-dialkyltriazenes are popular building blocks in synthetic organic chemistry.[1] An attractive feature of these compounds is their stability under neutral and basic conditions, which allows functionalization of the arene with a variety of reagents, including highly basic organometallic compounds. Under acidic conditions, however, the triazene group can be replaced by numerous other functional groups. Another interesting aspect of aryltriazenes is the biological activity of some of these compounds. Two triazenes, dacarbazine and temozolomide, are currently used in the clinic to treat cancer, and many other aryltriazenes have been tested for their biological activity.[2] Given the importance of aryltriazenes, it may seem surprising that the chemistry of the closely related 1-alkenyl- and 1-alkynyl-3,3-dialkyltriazenes has hardly been investigated. However, there is a simple explanation: the standard procedures to synthesize aryltriazenes are difficult to extend to alkenyl- or alkynyltriazenes. 1-Aryl-3,3-dialkyltriazenes are typically obtained by coupling of an aryldiazonium salt with a secondary amine (Scheme 1, eq 1).[1] Diazonium salts of alkynes and alkenes are unstable,[3] and N-N coupling reactions with amines are thus problematic to realize. An alternative synthetic procedure of triazenes starts with azides (Scheme 1, eq 2),[1] but again, it is very difficult to handle the highly sensitive alkenyl- and alkynylazides.[4] We have recently reported a novel procedure for the preparation of triazenes, which relies on a rather unusual reagent in synthetic organic chemistry: nitrous oxide.[5,6] Reaction of N_2O with lithium salts of secondary amines and Grignard reagents gives triazenes in good yields (Scheme 1, eq 3). Importantly, this one-pot procedure allows accessing 1-alkenyl- or 1-alkynyl-3,3-dialkyltriazenes in a straightforward fashion. In continuation of these investigations, we turned our attention to 1-allenyltriazenes. To the best of our knowledge, 1-allenyltriazenes have not been prepared before.[7] We found that 1-allenyltriazenes can be obtained by base-induced isomerization of 1-alkynyltriazenes. Details of these findings are reported below.

Scheme 1. Synthetic Routes for the Preparation of Triazenes.

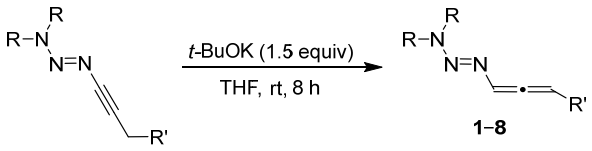


Studying the chemical reactivity of 1-alkynyltriazenes, we observed that these compounds behave as functional analogues of ynamides.[8] For example, the addition of acids to 1-alkynyltriazenes was found to give 1,2-addition products, rather than products resulting from an acid-induced cleavage

of the triazene function. Similar 1,2-additions are known for ynamides.[9]

Under basic conditions, *N*-propargylamides can isomerize to allenamides,[10] a class of compounds which has received considerable attention in recent years.[11] It has been suggested that, depending on the nature of the amide group, allenamides are thermodynamically more stable than ynamides, and that the two isomers form an equilibrium under basic conditions.[12] These results suggested to us that it might be possible to prepare 1-allenyltriazenes by a base-induced isomerization of 1-alkynyltriazenes. To examine this hypothesis, we performed NMR-scale test reactions. Solutions of 3,3-dicyclohexyl-1-prop-1-yn-1-yltriazene in THF-d_8 (~ 60 mM) were treated with 1.5 equivalents of different bases, and the mixtures were analyzed by ^{1}H NMR spectroscopy after a reaction time of 8 h. Whereas *t*-BuOLi, BuLi, potassium bis(trimethylsily)amide (KHMDS), and 1,8-diazabicyclo[5.4.0]undec-7-enen (DBU) did not result in an isomerization, the addition of *t*-BuOK gave the corresponding allene in high yield. Subsequently, we attempted the synthesis of 1-allenyltriazenes with *t*-BuOK on a preparative scale. Different 3,3-dicyclohexyl and 3,3-diisopropyl-1-alkynyltriazenes were successfully converted to the corresponding 1-allenyltriazenes (Table 1, entries 1–7). Purification of the products was complicated by the fact that small amounts of starting materials remained in the reaction mixture, even if the concentration of the base was increased or if the reaction time was prolonged. Since the alkyne and the allene display similar polarity, column chromatography resulted in some loss of product. Still, we were able to isolate the allenes **1**–**7** in the form of oily compounds in yields between 57% and 77%. Attempts to prepare the phenyl-substituted allene **8** were hampered by the low stability of the product. When the reaction was performed at –40 °C with 0.75 equiv of *t*-BuOK, a rather clean formation of **8** was observed (81% yield according to ^{1}H NMR). However, we were not able to isolate **8** in pure form.

Table 1. Synthesis of the 1-Allenyltriazenes 1–8.



compound	R	R'	yield [%][a]
1	Cy	H	69
2	Cy	Et	68
3	Cy	Pr	77
4	*i*Pr	Et	74
5	*i*Pr	Pr	76
6	*i*Pr	Cy	68
7	iPr	$(CH_2)_2$Ph	57
8	*i*Pr	Ph	81[b,c]

[a] Isolated yields unless stated otherwise. [b] Yield determined by ^{1}H NMR using mesitylene as an internal standard. [c] The reaction was performed at –40 °C with 0.75 equiv *t*-BuOK.

A predisposition for a thermal decomposition was also observed for the alkyl-substituted allenes **1**–**7**, even though they are more stable than **8**. Storage of the compounds at room temperature resulted in noticeable decomposition after a few days. At –28 °C, however, the allenes are stable for several weeks.

The stability at elevated temperatures was investigated by heating solutions of allenes **1**, **2** or **4** (~ 0.1 M) in toluene-d_8 to 90 °C. The allenes were found to decompose with half-lives between 4 and 8 h. In all three cases, were able to detect the corresponding dialkylamine (Cy_2NH and iPr_2NH), along with some other unidentified decomposition products. Heating toluene solutions of **5** or **7** gave similar results: significant decomposition occurred within hours, and iPr_2NH was identified as one of the products.

Since 1-allenyltriazenes had not been described so far, we were interested to obtain structural information about this type of compound. The oily nature of the allenes at room temperature made a crystallographic analysis challenging. After several failed attempts, we were able to grow crystals of allene **4** at low temperature. A single crystal X-ray analysis revealed the typical *trans* configuration of the triazene function. The allene moiety is disordered over two orientations. Therefore, we will only discuss the bond lengths observed for the N_3 unit. As expected, the N1-N2 bond is longer than the N2-N3 bond (1.326(4) vs. 1.273(4)Å). These values are similar to what was observed for 1-alkenyl- and 1-alkynyltriazenes.[5] The N1-N2 bond is shorter than a typical N-N single bond (> 1.4 Å),[13] indicating some double bond character. The double bond character is evidenced by the NMR data of **4**: broad NMR signals are observed for the *i*Pr atoms, in line with a hindered rotation about the N-N(iPr)$_2$ bond. A similar behavior is observed for the other allenyltriazenes.

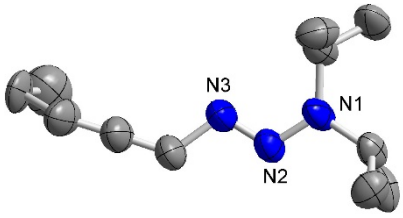
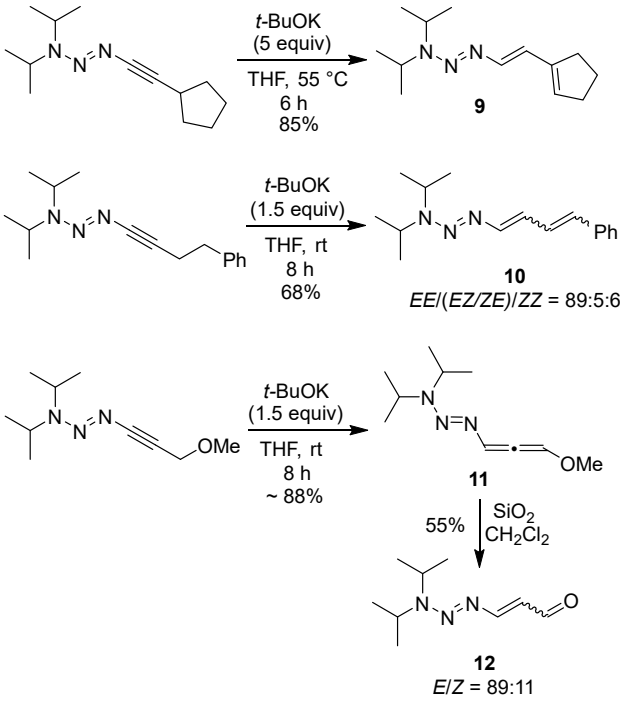


Figure 1. Molecular structure of the allenyltriazene **4** in the crystal. Only one of the two enantiomers is shown. Hydrogen atoms and lower occupancy disordered atoms are omitted for clarity. The thermal ellipsoids are at the 40% level. Selected bond lengths (Å): N1-N2 = 1.326(4), N2-N3 = 1.273(4).

Next, we have used a triazene with a cyclopentylethynyl group for the attempted synthesis of a trisubstituted allene. Under standard conditions (1.5 equiv *t*-BuOK, rt), only a minor conversion of the starting material was observed after several hours. More forcing reaction conditions (5 equiv *t*-BuOK, 55 °C) resulted in isomerization, but instead of the disubstituted allene, we were able to isolate the diene **9** in 85% yield (Scheme 2). In a similar fashion, the base-induced isomerization of a triazene with a 4-phenylbutynyl group resulted in the formation of the diene **10** (Scheme 2). Compound **10** was obtained as a mixture of stereoisomers, but the major *EE* isomer could be separated by column chromatography (yield: 61%). The *E* configuration of all three double bonds was confirmed by a crystallographic analysis (for details see Supporting Information, SI). Presumably, the dienes **9** and **10** are formed via intermediate allenes, but attempts stop the isomerization at the allene stage by variation of the reaction condi-

tions were not successful. To the best of our knowledge, compounds **9** and **10** represent first examples of 1,3-dienes with a triazene function in 1 position. Similar to 1,3-diene-1-carbamates[14] and 1,3-diene-1-amides,[15] they are expected to be an interesting substrates for Diels-Alder reactions.

Scheme 2. Synthesis of the Vinyltriazenes 9, 10 and 12.

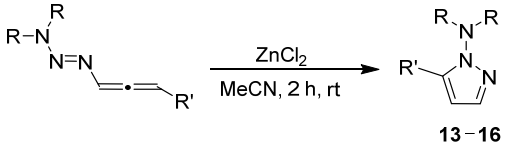


The addition of *t*-BuOK to a triazene with a methoxypropynyl group lead to the formation of the methoxy-substituted allene **11**, as evidenced by NMR spectroscopy (Scheme 3). Attempted purification by chromatography over SiO_2 resulted in hydrolysis to give the triazene-functionalized acrolein **12** as a mixture of isomers. Again, it was possible to separate the major *E* isomer by chromatography (yield = 38%). The proposed *E* configuration of the carbon-carbon double bond is supported by a $^3J_{H\text{-}H}$ coupling constant of 13.8 Hz (the *Z* isomer shows a value of 7.9 Hz). Similar to diene **10**, acrolein **12** is expected to be an interesting starting material for further transformation. It should be noted that the vinyl triazenes **10** and **12** are thermally more stable than the allenyltriazenes. Heating solutions of **10** or **12** in toluene-d_8 for 48 h at 90 °C resulted in negligible decomposition as evidenced by ^{1}H NMR spectroscopy.

First investigation regarding the chemical reactivity of 1-allenyltriazenes revealed that the Lewis acid $ZnCl_2$ is able to induce an isomerization into the corresponding aminopyrazole. It was thus possible to obtain the aminopyrazoles **13**–**16** in yields between 77 and 82% by addition of 1.1 eq. of $ZnCl_2$ to a solution of the respective allene in acetonitrile. The products were characterized by NMR spectroscopy and HR mass spectrometry. Compound **15** was also analyzed by single crystal X-ray diffraction (for details see SI). As a tentative mechanism for this reaction, we would like to propose a coordination of the nucleophilic β-C_{allene} carbon to zinc, followed by intramolecular C-N bond formation and 1,2-proton shift. Attempts to perform this rearrangement with catalytic amounts of $ZnCl_2$ were not successful. Presumably, the products are able to deactivate the Lewis acid by coordination to the metal.

Pyrazole derivatives are of interest because many exhibit interesting biological activities.[16] *N*-Aminopyrazoles, in particular, have been proposed as drugs against depression,[17] and they have been tested as acetylcholinesterase inhibitors[18] and as radical scavengers.[19] Furthermore, they represent valuable staring materials for the synthesis of 1,2,3-triazines.[17,20] *N*-Aminopyrazoles are typically obtained by amination of pyrazoles with hydroxylamine-*O*-sulfonic acid.[17,21] In case of asymmetric pyrazoles, the amination reaction gives a mixture of isomers, which need to be separated. Our method staring from allenyltriazenes represents a completely new approach for the synthesis of *N*-aminopyrazoles. It directly provides dialkylaminopyrazoles in good yields.

Table 2. Synthesis of the N-Aminopyrazoles 13–16.



compound	R	R'	yield [%][a]
13	*i*Pr	Et	78
14	*i*Pr	Cy	82
15	Cy	Et	77
16	Cy	H	84[b]

[a] Isolated yields [b] The reaction was performed at 70 °C.

In summary, we have shown that 1-allenyltriazenes can be prepared by based-induced isomerization of 1-alkynyltriazenes. The latter are easily accessible in a one-step reaction from lithium amides, alkynyl Grignard reagents, and nitrous oxide. The new allenes display only moderate thermal stability. This instability will limit their utility as a reagent in synthetic organic chemistry. Nevertheless, we think that it is worthwhile to study the reactivity of this class of compounds in more detail. The formation of the vinyl triazenes **9**, **10** and **12**, as well as the $ZnCl_2$-induced rearrangement into *N*-aminopyrazoles is first evidence that interesting new reactions can be discovered.

ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data of the new compounds. Crystallographic data for the compounds **4**, **10** and **15** in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* Email: kay.severin@epfl.ch.

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