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Activated Alkynes

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1-Alkynyltriazenes as Functional Analogues of Ynamides**

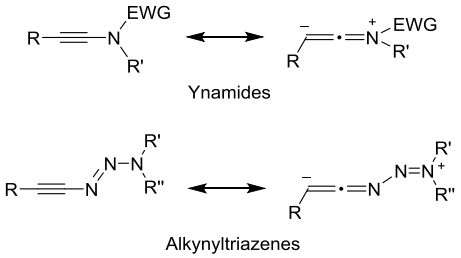
*Florian G. Perrin, Gregor Kiefer, Loic Jeanbourquin, Sophie Racine, Daniele Perrotta, Jérôme Waser, Rosario Scopelliti, and Kay Severin**

***Abstract**: Recently, we have reported a procedure which allows preparing 1-alkynyltriazenes by a simple one-pot-reaction. Here, we show that the chemical reactivity of 1-alkynyltriazenes parallels what has been observed for ynamides. The similarity in reactivity of these two classes of compounds is demonstrated by addition reactions with acids, by cycloaddition reactions with ketenes, tetracyanoethene, and cyclopropanes, as well as by intramolecular cyclization reactions. The presence of reactive triazene groups in the products allows subsequent transformations. Overall, our results suggest that 1-alkynyltriazenes should become valuable reagents in synthetic organic chemistry.*

Following the development of efficient synthetic routes for ynamides, these compounds have emerged as extremely useful building blocks for synthetic organic chemistry.[1] The unique reactivity of ynamides is related to the nitrogen atom adjacent to the alkyne function, which renders the triple bond more reactive compared to what is observed for plain alkynes. On the other hand, ynamides are significantly more stable than ynamines.[1d] Accordingly, they are much easier to work with.

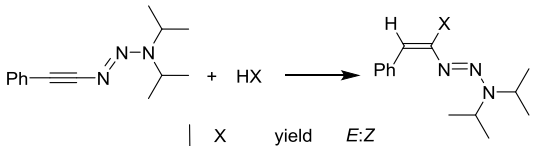
The development of functional analogues of ynamides offers the possibility to further advance the field of alkyne chemistry.[2] Ideally, these analogues should display the following characteristics: a) they can be prepared via simple and atom economic synthetic routes; b) they should be reactive enough to allow different chemical transformations under mild conditions; c) they should be stable enough to allow easy handling; d) they should provide access to compounds which cannot be prepared with ynamides. Here, we demonstrate that 1-alkynyltriazenes possess the characteristics outlined above.

Research in our laboratory is directed towards the development of useful synthetic procedures involving nitrous oxide (N_2O, 'laughing gas').[3] Recently, we have discovered that it is possible to prepare 1-alkynyltriazenes by reaction of lithium amides with nitrous oxide and alkynyl Grignard reagents.[4] This simple methodology allows accessing a variety of 1-alkynyltriazenes in good yields. While aromatic triazenes have been studied extensively in the context of synthetic organic[5] and medicinal chemistry,[6] the chemistry of 1-alkynyltriazenes is completely unexplored. The lack of studies about these compounds is due to the fact that 1-alkynyltriazenes are difficult to prepare via the classic synthetic routes for triazenes.[5] We hypothesized that 1-alkynyltriazenes might display a reactivity similar to ynamides, because comparable resonance structures can be formulated for these types of N-atom substituted alkynes (Scheme 1).



Scheme 1. Resonance structures of ynamides and 1-alkynyltriazenes. EWG = electron-withdrawing group.

First, we have examined the reaction of 3,3-diisopropyl-1-(phenylethynyl)triazene with HCl. Aromatic triazenes are sensitive to acids and the triazene group is typically replaced upon addition of strong acids.[5] In contrast, we observed the 1,2-addition of HCl to the triple bond in the reaction with the 1-alkynyltriazene (Scheme 2). Similar hydrohalogenation reactions are known for ynamides.[7] For the latter, the reactions can be conveniently performed by utilization of MgX_2 in wet organic solvents (HX generated in situ).[7] This methodology also worked for our triazenes and provided the addition products **1**-**3** in good yields with a preferred formation of the *E* isomer. For compound **1**, this isomer was also characterized by X-ray crystallography (see Supporting Information).



	X	yield	*E*:*Z*
1	Cl	75%	96:4
2	Br	60%	93:7
3	I	60%	> 99:1
4	$PhCO_2$	91%	95:5
5	$MeCO_2$	94%	88:12

Scheme 2. Addition of acids to 1-alkynyltriazenes. For HX = HCl, HBr or HI: MgX_2, wet CH_3CN, RT, 24 h; for HX = HO_2CR: toluene, 100 °C, 24 h.

Ynamides are sufficiently reactive to allow the addition of simple carboxylic acids.[8] In a related fashion, benzoic acid or acetic acid could be added to 3,3-diisopropyl-1-(phenylethynyl)triazene (toluene, 100 °C, 24 h) to give the products **4** (yield: 91%) and **5**

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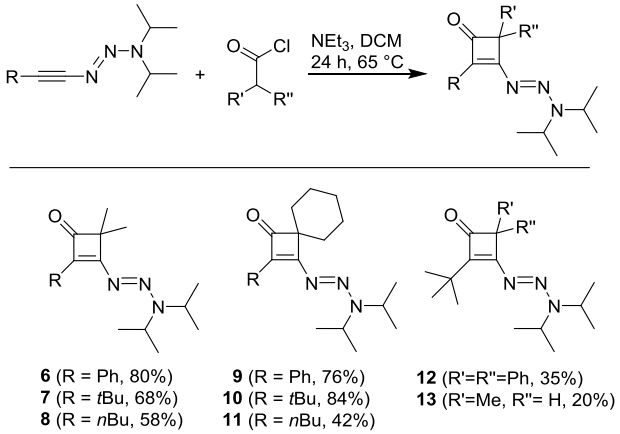
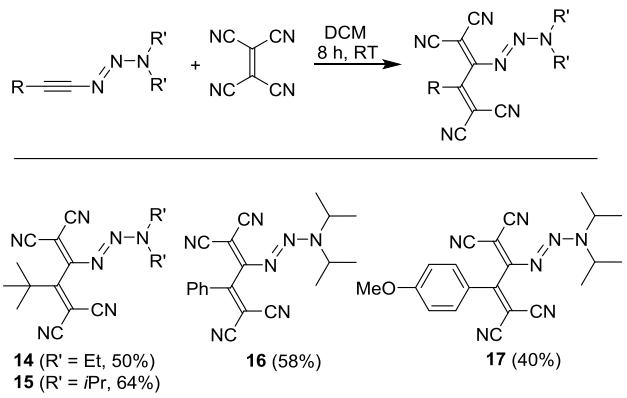
(yield: 94%). Again, the *E* isomer was obtained as the major product isomer (Scheme 2).

Encouraged by these first test reactions, we have examined more complex transformations. Ynamides[9] and their analogs such as *N*-alkynylated sulfoximines[10] are known to undergo [2+2] cycloaddition reactions with ketenes to afford functionalized cyclobutenones. We have investigated the reaction of 3,3-diisopropyl-1-(phenylethynyl)triazene with dimethylketene (generated in situ be dehydrohalogenation of isobutyryl chloride). As in the case of ynamides, we observed the formation of a cyclobutenone (**6**), which could be isolated in 80% yield (Scheme 3). It should be noted that cycloaddition reactions between non-activated ketenes and alkynes are difficult to achieve.[11] The clean formation of cyclobutenone **6** thus confirms the high reactivity of 1-alkynyltriazenes. As evident by the successful formation of the cyclobutenones **7**–**13**, it possible to vary the triazene as well as the ketene coupling partner, even though a low isolated yield was obtained in some cases (Scheme 3). In all cases, we obtained only one isomer. The trans position of the keto group and the triazene group was confirmed by a crystallographic analysis of compound **9** (see Supporting Information).



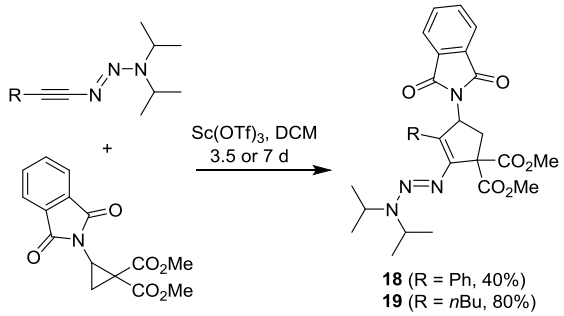
Scheme 3. Synthesis of substituted cyclobutenones by reactions of 1-alkynyltriazenes with ketenes, generated in situ from acyl chlorides.

Activated alkynes (e.g. *N*,*N*-dimethylanilino-substituted alkynes) are known to react with tetracyanoethylene (TCNE) to give 1,1,4,4-tetracyanobuta-1,3-diene derivatives.[12] The products have received considerable interest because of their optical properties. Recently, it was reported that ynamides are also able to react with TCNE to give tetracyanobutadienes.[13] This report prompted us to examine the reaction of 1-alkynyltriazenes with TCNE. As in the case of ynamides, a clean transformation into the corresponding tetracyanobutadienes (**14**–**17**) was observed when the starting materials were mixed in dry dichloromethane at room temperature (Scheme 4). The reactions can be performed with triazenes derived from aliphatic as well as aromatic alkynes, and variations of the dialkylamine part are also possible.



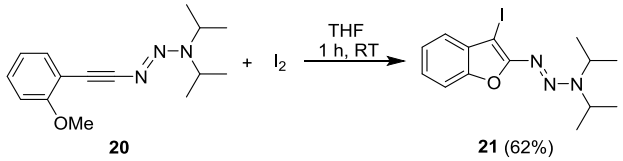
Scheme 4. Reactions of 1-alkynyltriazenes with tetracyanoethylene.

Donor-acceptor cyclopropanes are useful building blocks in Lewis acid catalyzed [3+n] cycloadditions to yield heterocycles or carbocycles.[14] Recently, Johnson et al. described a $Sc(OTf)_3$ catalyzed [3+2] annulation of activated cyclopropanes with ynamides.[15] However, the use of versatile aminocyclopropanes[16] as reaction partners were not reported in this work. We were able to obtain the cyclopentene derivatives **18** (yield: 42%) and **19** (yield: 80%) by reaction of 1-alkynyltriazenes with an aminocyclopropane (Scheme 65). The depicted regioselectivity, with the triazene function next to the ester groups, was confirmed by a crystallographic analysis of **18** (for details see SI). These results demonstrate that 1-alkynyltriazenes are compatible with a strong Lewis acid such as $Sc(OTf)_3$.



Scheme 5. Synthesis of substituted cyclopentenes by reactions of 1-alkynyltriazenes with cyclopropanes.

Next, we have investigated intramolecular cyclization reactions. The iodocyclization of alkynes represents an efficient tool for the synthesis of heterocycles.[17] Recently, it was shown that ynamides are suited substrates for this type of chemistry providing access to amide-functionalized benzofurans.[18] 1-Alkynyltriazenes can be used in similar fashion. To demonstrate this point, we have first synthesized the new 2-methoxyphenyl-substituted alkynyltriazene **20** using our N_2O methodology.[4] In the presence of iodine, the triazenes cleanly converts into the benzofuran **21** (isolated yield: 62%).

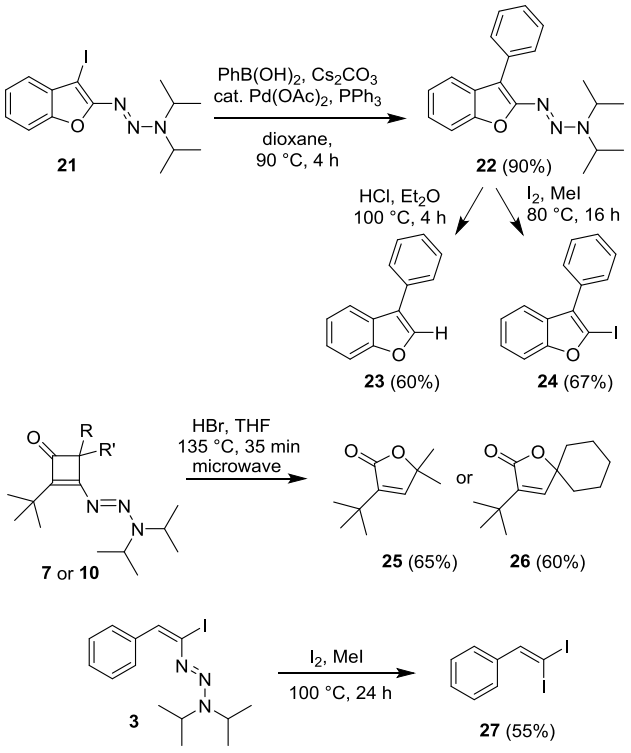


Scheme 6. Iodocyclization of an 1-alkynyltriazene.

The success of aromatic triazenes is due to the fact that they are very stable under basic conditions and towards organometallic reagents, yet it is possible to substitute the triazene by a variety of functional groups using an appropriate activation method.[5] This intriguing mix of stability and reactivity is also found for the reaction products of 1-alkynyltriazenes. For example, is possible to use the 3-iodobenzofuran **21** in a Pd-catalyzed cross-coupling reaction with phenylboronic acid to give the arylated product **22** in 90% yield. The triazene function can then be removed by treatment with HCl/Et_2O or I_2/MeI to give the benzofuranes **23** and **24** (Scheme 7).

Another demonstration of the reactivity imparted by the triazene function is the successful conversion of the cyclobutenones **7** and **10** into the lactones **25** and **26**. This transformation was accomplished by a short heating step in the microwave using HBr (Scheme 7). The following mechanism seems plausible: an initial retroelectrocyclization gives a ketene, which is hydrolyzed to a carboxylic acid. Acid-induced rupture of the N-N single bond then provides a vinyl diazonium compound, which releases dinitrogen after intramolecular ring closure. It should be noted that spirocyclic butenolides such as **26** are of high interest because this kind of subunit is found in numerous biologically active compounds. Examples include the synthetic insecticides spirodiclofen and spiromesifen,[19] as well as the natural products lambertellol A/B,[20] chlorothricolide[21] and andirolactone.[22] The successful synthesis of the butenolides **25** and **26** suggests that it is possible to access this important class of compounds in two steps starting from 1-alkynyltriazenes.

The cleavage of the triazene function can also be accomplished for simple olefinic triazenes such as **3**. For example, heating of **3** with iodine in MeI provides the diiodostyrene **27** in 55% yield (Scheme 7).



Scheme 7. Reactions of olefinic triazenes.

To conclude, we have started to examine the chemical reactivity of 1-alkynyltriazenes, which can be prepared easily by a recently developed method.[4] On purpose, we have not performed a detailed scope-and-limitations study for one or two selected reactions. Instead, we have examined different types of reactions in order to obtain a first impression of the general reactivity. The results show that 1-alkynyltriazenes represent activated alkynes, which undergo a variety of chemical transformations. The reactivity observed so far is reminiscent of what has been observed for ynamides. The extend of the similarity between 1-alkynyltriazenes and ynamides needs to be examined in future studies, but it seems likely that the transformations described above a merely 'the tip of an iceberg' with respect to possible reactions of 1-alkynyltriazenes. One interesting aspect of these reactions is the possibility to access triazenes, which would be difficult to obtain otherwise. For example, it is unlikely that the olefinic triazenes described above (**1**-**19**) can be prepared by the standard synthetic route for tirazenes. In view of the fact that aromatic triazenes have investigated extensively as potential anti-tumor agents, it will be interesting to perform biological tests with these new olefinic triazenes in the future. A second noteworthy point is the intrinsic reactivity of triazene-containing compounds. Despite the fact that handling and purification is quite easy (e.g. via chromatography), it is possible to substitute the triazene function with other groups. This fact was exemplified by the formation of the compounds **23**–**27**. Taken together, our results suggest that 1-alkynyltriazenes should become valuable reagents for synthetic organic chemistry.

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Triazenes

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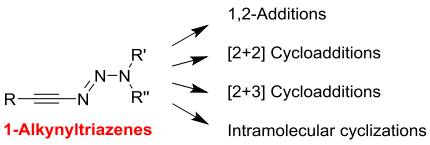

1-Alkynyltriazenes are activated alkynes with a reactivity profile similar to ynamides. The triazene function enables unique subsequent transformations.