Activated Alkynes

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1-Alkynyltriazenes as Functional Analogues of Ynamides

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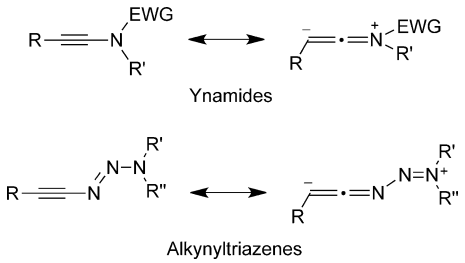
Abstract: *The chemical reactivity of 1-alkynyltriazenes has been investigated and is found to parallel the reactivity of ynamides. The similarity in reactivity of these two classes of compounds is demonstrated by addition reactions with acids, by cycloaddition reactions with ketenes, tetracyanoethene, and cyclopropanes, as well as by intramolecular cyclization reactions. The presence of reactive triazene groups in the products enables 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 the preparation of 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 standard alkynes. On the other hand, ynamides are significantly more stable than ynamines,[1d] and accordingly 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 by simple and atom-economic synthetic routes; b) they should be reactive enough to enable 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. Herein, we demonstrate that 1-alkynyltriazenes possess the characteristics outlined above.

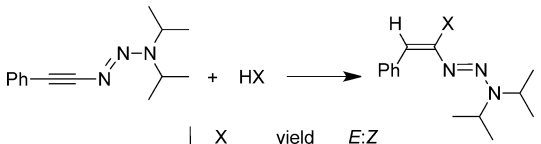
Research in our laboratory is directed towards the development of useful synthetic procedures involving nitrous oxide (N_2O, "laughing gas").[3] Recently, we have discovered that it is possible to prepare 1-alkynyltriazenes by reaction of lithium amides with nitrous oxide and alkynyl Grignard reagents.[4] This simple method allows access to 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 on these compounds is as a result of the fact that 1-alkynyltriazenes are difficult to prepare using 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 examined the reaction of 3,3-diisopropyl-1-(phenylethynyl)triazene with HCl (Scheme 2). 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. Similar hydrohalogenation reactions are known for ynamides.[7] Hydrohalogenation reactions with ynamides can be conveniently performed by utilization of MgX_2 in wet organic solvents (HX generated in situ).[7] This method also worked for our triazenes and provided the addition products **1**–**3** in good yields (Scheme 2) with a preferred formation of the *E* isomer. The *E* isomer of compound **1** was also characterized by X-ray crystallography (see the Supporting Information).

Ynamides are sufficiently reactive to allow the addition of simple carboxylic acids.[8] Similarly, benzoic acid or acetic acid could be added to 3,3-diisopropyl-1-(phenylethynyl)triazene



	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. Reaction conditions for HX = HCl, HBr, or HI: MgX_2, wet CH_3CN, RT, 24 h. Reaction conditions for HX = HO_2CR: toluene, 100 °C, 24 h.

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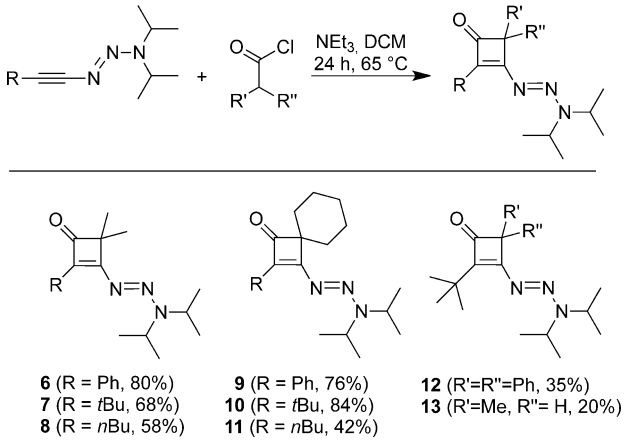
(toluene, 100 °C, 24 h) to give products **4** (91 % yield) and **5** (94 % yield). Again, the *E* isomer was obtained as the major product isomer (Scheme 2).

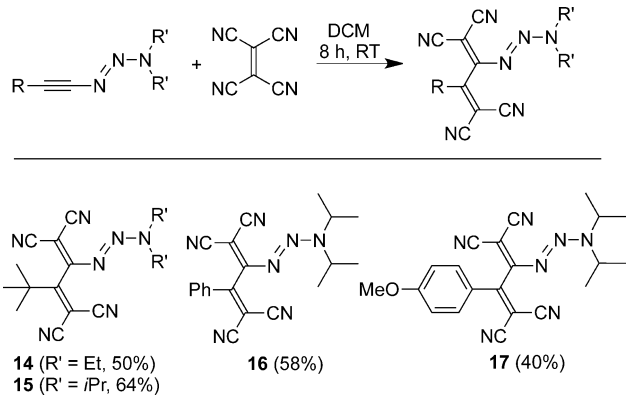
Encouraged by these first test reactions, we have examined more complex transformations. Ynamides[9] and their analogues, such as *N*-alkynylated sulfoximines,[10] are known to undergo [2+2] cycloaddition reactions with ketenes to afford functionalized cyclobutenones. We have investigated the reaction of 3,3-diisopropyl-1-(phenylethynyl)triazene with dimethylketene (generated in situ by dehydrohalogenation of isobutyryl chloride). As in the case of ynamides, we observed the formation of a cyclobutenone (**6**), which was isolated in 80 % yield (Scheme 3). It should be noted that



Scheme 3. Synthesis of substituted cyclobutenones by reaction of 1-alkynyltriazenes with ketenes. The ketenes were generated in situ from acyl chlorides.

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 cyclobutenone derivatives **7**–**13**, it possible to vary the triazene as well as the ketene coupling partner, even though a low yield of isolated product 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 X-ray crystallographic analysis of a crystal of compound **9** (see the Supporting Information).

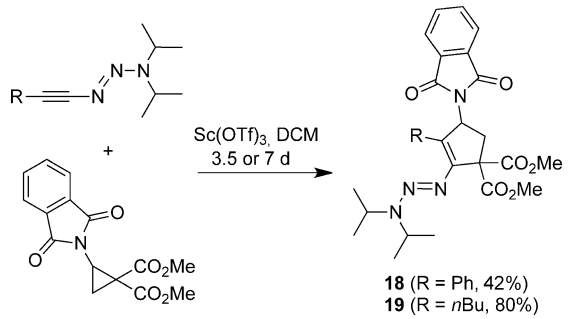
Activated alkynes (for example *N*,*N*-dimethylanilino-substituted alkynes) are known to react with tetracyanoethylene (TCNE) to give 1,1,4,4-tetracyanobuta-1,3-diene derivatives.[12] The products have received considerable interest because of their optical properties. Recently, it was reported that 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 (Scheme 4). As in the case of ynamides, a clean transformation into the corresponding tetracyanobutadienes (**14**–**17**) was obtained when the starting materials were mixed in dry dichloromethane (DCM) at room temperature. The reactions can be performed with triazenes derived from aliphatic as



Scheme 4. Reactions of 1-alkynyltriazenes with tetracyanoethylene.

well as aromatic alkynes, and variations of the dialkylamine component are also possible.

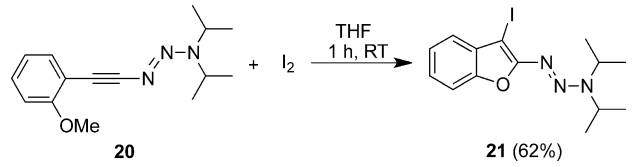
Donor–acceptor cyclopropanes are useful building blocks in Lewis acid catalyzed [3+*n*] cycloadditions to yield heterocycles or carbocycles.[14] Recently, Johnson et al. described a $Sc(OTf)_3$-catalyzed [3+2] annulation of activated cyclopropanes with ynamides.[15] However, versatile aminocyclopropanes[16] as reaction partners were not employed. Cyclopentene derivatives **18** (42 % yield) and **19** (80 % yield) were obtained by reaction of 1-alkynyltriazenes with an aminocyclopropane (Scheme 5). The regioselectivity of the prod-



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

ucts, with the triazene functional group next to the ester groups, was confirmed by single-crystal X-ray analysis of a crystal of **18** (for details see the Supporting Information). These results demonstrate that 1-alkynyltriazenes are compatible with a strong Lewis acid such as $Sc(OTf)_3$.

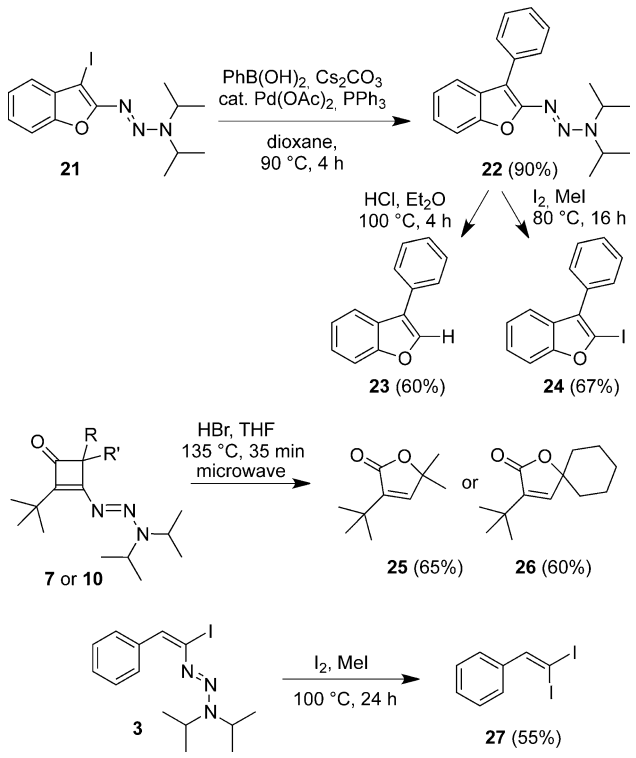
Next, we have investigated intramolecular cyclization reactions. The iodocyclization of alkynes is an efficient method for the synthesis of heterocycles.[17] Recently, it was shown that ynamides are suitable substrates for this type of chemistry, providing access to amide-functionalized benzofurans.[18] 1-Alkynyltriazenes can be used in similar fashion. To demonstrate this reactivity, we first synthesized the new 2-methoxyphenyl-substituted alkynyltriazene **20** using our N_2O procedure.[4] In the presence of iodine, the triazene is cleanly converted into the corresponding benzofuran **21**, which was isolated in 62 % yield (Scheme 6).



Scheme 6. Iodocyclization of an 1-alkynyltriazene.

Aromatic triazenes can be successfully employed in a variety of reactions because 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, it 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 benzofurans **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 heating the cyclobutenone in the microwave for 35 minutes in the presence of HBr (Scheme 7). The following mechanism seems plausible: an initial retro-electrocyclization gives a ketene, which is hydrolyzed to a carboxylic acid. Acid-induced rupture of the N–N single bond leads to the formation of a vinyl diazonium compound, which releases dinitrogen after intramolecular ring closure. It should be noted that spirocyclic butenolides such as **26** are of significant interest because this kind of subunit is found in numerous biologically active compounds, such as in the synthetic insecticides spirodiclofen and spiromesifen,[19] as well as in the natural products lambertellol A/B,[20] chlorothricolide,[21] and andirolactone.[22] The successful synthesis of butenolides **25** and **26** suggests that it is possible to access this important class of compounds in two steps starting from 1-alkynyltriazenes.



Scheme 7. Reactions of olefinic triazenes.

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).

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 study on scope and limitations 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 are activated alkynes, which undergo a variety of chemical transformations. The reactivity observed so far is reminiscent of what has been reported for ynamides. The extent of the similarity between 1-alkynyltriazene and ynamide reactivities needs to be examined in future studies, but it seems likely that the transformations reported herein are merely the tip of the iceberg with respect to possible reactions of 1-alkynyltriazenes. One interesting aspect of these reactions is the possibility to access triazenes, which would be otherwise difficult to synthesize. For example, it is unlikely that the olefinic triazenes described above (**1**–**19**) can be prepared by the standard synthetic route for triazenes. In view of the fact that aromatic triazenes have been investigated extensively as potential antitumor agents, it will be interesting to perform biological tests with these new olefinic triazenes. A second noteworthy point is the intrinsic reactivity of triazene-containing compounds. Despite the fact that the relative stability of the compounds means that handling and purification (for example, by chromatography) are quite straightforward, it is possible to substitute the triazene functionality with other groups, as demonstrated by the formation of compounds **23**–**27**. Taken together, our results suggest that 1-alkynyltriazenes should become valuable reagents for synthetic organic chemistry.

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Keywords: alkynes · cyclization · cycloaddition reactions · triazenes · ynamides

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[1] a) X.-N. Wang, H.-S. Yeom, L.-C. Fang, S. He, Z.-X. Ma, B. L. Kedrowski, R. P. Hsung, *Acc. Chem. Res.* **2014**, *47*, 560 – 578; b) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064 – 5106; c) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed.* **2010**, *49*, 2840 – 2859; *Angew. Chem.* **2010**, *122*, 2902 – 2921; d) C. A. Zificsak, J. A. Mulder, R. P. Hsung, C. Rameshkumar, L.-L. Wie, *Tetrahedron* **2001**, *57*, 7575 – 7606.

[2] T. Lu, R. P. Hsung, *ARKIVOC (Gainesville, FL, U.S.)* **2014**, 127 – 141.

[3] K. Severin, *Chem. Soc. Rev.* **2015**, *44*, 6375 – 6386.

[4] G. Kiefer, T. Riedel, P. Dyson, R. Scopelliti, K. Severin, *Angew. Chem. Int. Ed.* **2015**, *54*, 302 – 305; *Angew. Chem.* **2015**, *127*, 306 – 310.

[5] a) D. K. Kölmel, N. Jung, S. Bräse, *Aust. J. Chem.* **2014**, *67*, 328 – 336; b) S. Bräse, *Acc. Chem. Res.* **2004**, *37*, 805 – 816; c) D. B. Kimball, M. M. Haley, *Angew. Chem. Int. Ed.* **2002**, *41*, 3338 – 3351; *Angew. Chem.* **2002**, *114*, 3484 – 3498.

[6] a) F. Marchesi, M. Turriziani, G. Tortorelli, G. Avvisati, F. Torino, L. De Vecchis, *Pharmacol. Res.* **2007**, *56*, 275 – 287; b) D. R. Newell, B. J. Foster, J. Carmichael, A. L. Harris, K. Jenns, L. A. Gumbrell, A. H. Calvert, *Triazenes: Chemical, Biological and Clinical Aspects*, Springer, Berlin, Heidelberg, **1990**, pp. 119 – 131.

[7] J. A. Mulder, K. C. M. Kurtz, R. P. Hsung, H. Coverdale, M. O. Frederick, L. Shen, C. A. Zificsak, *Org. Lett.* **2003**, *5*, 1547 – 1550.

[8] S. Xu, J. Liu, D. Hu, X. Bi, *Green Chem.* **2015**, *17*, 184 – 187.

[9] A. L. Kohnen, X. Y. Mak, T. Y. Lam, J. R. Dunetz, R. L. Danheiser, *Tetrahedron* **2006**, *62*, 3815 – 3822.

[10] R. Pirwerdjan, D. L. Priebbenow, P. Becker, P. Lamers, C. Bolm, *Org. Lett.* **2013**, *15*, 5397 – 5399.

[11] For cycloaddition reactions between alkynes and activated dichloroketenes, see: a) T. T. Tidwell, in *Science of Synthesis Vol. 23* (Ed.: R. L. Danheiser), Georg Thieme, Stuttgart, New York, **2006**, p. 101; b) A. Hassner, J. L. Dillon, *J. Org. Chem.* **1983**, *48*, 3382 – 3386; c) R. L. Danheiser, H. Sard, *Tetrahedron Lett.* **1983**, *24*, 23 – 26.

[12] S.-I. Kato, F. Diederich, *Chem. Commun.* **2010**, *46*, 1994 – 2006.

[13] M. Betou, N. Kerisit, E. Meledje, Y. R. Leroux, C. Katan, J.-F. Halet, J.-C. Guillemin, Y. Trolez, *Chem. Eur. J.* **2014**, *20*, 9553 – 9557.

[14] a) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem.* **2015**, *13*, 655 – 671; b) F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano, J. Waser, *Chem. Commun.* **2014**, *50*, 10912 – 10928; c) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504 – 5523; *Angew. Chem.* **2014**, *126*, 5608 – 5628; d) F. De Simone, J. Waser, *Synthesis* **2009**, 3353 – 3374; e) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051 – 3060; f) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321 – 347; g) H. U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151 – 1196.

[15] W. D. Mackay, M. Fistikci, R. M. Carris, J. S. Johnson, *Org. Lett.* **2014**, *16*, 1626 – 1629.

[16] F. de Nanteuil, J. Waser, *Angew. Chem. Int. Ed.* **2011**, *50*, 12075 – 12079; *Angew. Chem.* **2011**, *123*, 12281 – 12285.

[17] B. Godoi, R. F. Schumacher, G. Zeni, *Chem. Rev.* **2011**, *111*, 2937 – 2980.

[18] T. Okitsu, K. Nakata, K. Nishigaki, N. Michioka, M. Karatini, A. Wada, *J. Org. Chem.* **2014**, *79*, 5914 – 5920.

[19] R. Nauen, T. Bretschneider, A. Elbert, R. Fischer, R. Tiemann, *Pestic. Outlook* **2003**, *14*, 243 – 245.

[20] T. Murakami, Y. Morikawa, M. Hashimoto, T. Okuno, Y. Harada, *Org. Lett.* **2004**, *6*, 157 – 160.

[21] a) M. H. Lacoske, E. A. Theodorakis, *J. Nat. Prod.* **2015**, *78*, 562 – 575; b) W. R. Roush, R. J. Sciotti, *J. Am. Chem. Soc.* **1998**, *120*, 7411 – 7419.

[22] Y. Li, T. Thang, Y.-L. Li, *Tetrahedron Lett.* **2007**, *48*, 1503 – 1505.

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