

# One-Pot Synthesis of Trisubstituted Triazenes from Grignard Reagents and Organic Azides

Abdusalom A. Suleymanov, 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

**ABSTRACT:** A simple and versatile method for the preparation of linear, trisubstituted triazenes is reported. The procedure is based on the reaction of Grignard reagents with 1-azido-4iodobutane or 4-azidobutyl-4-methylbenzenesulfonate. These organic azides enable the regioselective formation of triazenes via an intramolecular cyclization step. The new method can be used for the preparation of aryl, heteroaryl, vinyl, and alkyl triazenes. The synthetic utility of vinyl triazenes is demonstrated by acidinduced C–N, C–O, C–F, C–P, and C–S bond-forming reactions.

risubstituted linear triazenes have been investigated extensively in the context of synthetic organic chemistry.<sup>1</sup> Among other things, triazenes have been used as traceless linkers in solid-phase organic synthesis,<sup>2</sup> for surface grafting of small molecules,<sup>3</sup> as cross-coupling partners,<sup>4</sup> as directing groups for C-H activation reactions,<sup>5</sup> as precursors for diazonium salts<sup>6</sup> and diazocompounds,<sup>7</sup> and as starting materials for N-heterocycles<sup>8</sup> and polycyclic aromatic hydrocarbons (PAHs).9 Most efforts have focused on 1-aryl-3,3dialkyl triazenes, which are accessible by coupling of aryldiazonium salts with secondary amines (see Scheme 1, eq 1).<sup>1–9</sup> Triazenes with alkyl, vinyl, or alkynyl substituents in the 1-position cannot be prepared in this fashion, because the corresponding diazonium salts are unstable. A high-yield synthesis for trialkyl triazenes was introduced by Michejda and co-workers.<sup>10</sup> Coupling of alkylmagnesium or lithium

# Scheme 1. Different Routes for the Synthesis of Trisubstituted Linear Triazenes $^{a}$

$$Ar - \stackrel{+}{N \equiv N} + H \stackrel{R'}{N} \xrightarrow{-H^+} Ar - \stackrel{R'}{N'} \xrightarrow{R'} (1)$$



<sup>a</sup>Data taken from refs 1, 10, and 11.



compounds with azides gives disubstituted triazenes, which are then alkylated (Scheme 1, eq 2). A limitation of this approach is the fact that two isomers are formed in roughly equal amounts. We have recently introduced a new method for the synthesis of triazenes. Coupling of Grignard reagents with lithium amides and nitrous oxide was shown to give triazenes in good yields (Scheme 1, eq 3).<sup>11</sup> Importantly, the one-pot procedure can be used to prepare triazenes with vinyl and alkynyl substituents in 1-position. A potential disadvantage of the method is the utilization of gaseous N<sub>2</sub>O, which is not a standard reagent in synthetic chemistry laboratories.<sup>12</sup> Below, we describe a variation of the azide route of Michejda.<sup>13</sup> The new method allows one to prepare trisubstituted triazenes with aryl, heteroaryl, vinyl, or alkyl groups in the 1-position as single isomers in one-pot reactions.

Our investigations were inspired by studies of Michejda and co-workers on the reaction of alkyl Grignard reagents with 1-azido-3-chloropropane (compound A1 in Scheme 2). Depending on the reactions conditions, they observed the formation of either N-alkylazimines<sup>14</sup> or cyclic triazenes (Scheme 2, eqs 1 and 2).<sup>13</sup> The latter were formed by cyclization of linear, disubstituted triazenes. We hypothesized that by lengthening the spacer between the azide group and the halogen, we might favor the formation of linear, instead of cyclic triazene (Scheme 2, eq 3). In order to facilitate the cyclization step, we replaced the chloro atom with iodo or tosyl functions.<sup>25</sup> The corresponding azide reagents A2 and A3 (Scheme 2) are readily accessible in two simple steps from commercially available chemicals. In some cases, the utilization of the OTs-substituted azide A3 turned out to be advantageous, because it facilitated the workup of the reactions (for details, see the Supporting Information (SI)).

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Scheme 2. Reactions of the Azides A1–A3 with Grignard Reagents



The reaction between phenylmagnesium bromide (2 equiv) and A2 in THF at 50  $^{\circ}$ C for 2 h followed by aqueous workup gave triazene 1 in 71% isolated yield. <sup>1</sup>H NMR monitoring of the reaction indicates the initial formation of a magnesium triazenide salt. The addition of water then induces cyclization, presumably via a linear, disubstituted triazene (for details, see the SI).

Employing other arylmagnesium halides in the reaction with A2 or A3 enabled the formation of the aromatic triazenes 2-6 in good isolated yields (Scheme 3). The heteroaromatic triazenes based on 3-methylthiophene (7) or *N*-methylindole (8) were obtained from the corresponding heteroaryl bromides in 54% or 61% yield, respectively. The procedure can also be

Scheme 3. Synthesis of Aromatic Triazenes from Grignard Reagents and A2 or  $A3^a$ 



<sup>*a*</sup>Reaction conditions: Grignard reagent (1 equiv) and A2 or A3 (0.5–1.2 equiv) in THF (0.2–1.0 M) at 50 °C for 2–12 h. <sup>*b*</sup>The Grignard reagent was generated by metalation of the corresponding arene using TMPMgCl·LiCl (1.1 equiv). <sup>*c*</sup>Azide A2 was recovered.

employed for the synthesis of ferrocenyl triazene 9, which was isolated in 59% yield. Direct C–H magnesiation of benzo[b]-thiophene, thiophene, and thieno[2,3-b]thiophene with the Knochel–Hauser base TMPMgCl·LiCl,<sup>15</sup> followed by the addition of A2 or A3 gave the S-heteroaromatic triazenes 10–12 in 40%–73% yields. In addition to the standard analytical techniques, the structure of 11 was confirmed by X-ray crystallography. Electron-deficient aromatic Grignard reagents G1 and G2 did not give the desired products. The azide reagent A2 was recovered in these cases.

The synthesis of 1-12 demonstrates that aromatic and heteroaromatic triazenes are accessible in synthetically interesting yields via the new azide route. It is worth comparing our procedure to the standard method for synthesizing aromatic triazenes, which relies on the coupling of secondary amines with aryl diazonium salts (see Scheme 1, eq 1). The latter are typically prepared from aromatic amines by diazotization. The factor for choosing one method over the other could be the price or the availability of the respective starting material. The aryl bromides used for the preparation of Grignard reagents are generally less expensive than the corresponding aryl amines. For example, 9-bromophenan-threne, which was used for the synthesis of 5, is ~300 times less expensive than 9-aminophenanthrene (for details, see the SI).

The triazenes 10-12 were prepared by direct magnesiation of the corresponding heteroarenes. Here, the azide route is particularly advantageous, because the corresponding aminothiophens are either not commercially available or very expensive.

Next, we investigated the synthesis of nonaromatic triazenes, which are not as easily available as aromatic ones. Our procedure enables the preparation of cyclic, as well as noncyclic vinyl triazenes (13-20) in moderate to good yields (see Scheme 4). The 1,2-disubstituted vinyl triazenes 17 and 18 were obtained as mixtures of E/Z stereoisomers. Various 1-alkyl triazenes (21-26) were prepared in yields between 29% and 68%. It is important to note that 1-alkyl triazenes tend to decompose upon chromatographic purification with silica gel, even when the latter is deactivated with NEt<sub>3</sub>. We found that much better results are obtained by using deactivated basic alumina for purification of 21-26. To the best of our knowledge, trisubstituted 1-alkyl triazenes have not yet been characterized by X-ray crystallography. The oily product 23 crystallized at -20 °C, and a structural analysis was performed. The N1–N2 double bond of 23 (1.266(5) Å) is slightly shorter than what was observed for the aryl triazene 11 (1.272(5) Å)and the vinyl triazenes 18-E (1.279(3) Å) and 20 (1.2743(13) Å). On the other hand, the N2–N3 single bond of 23 (1.328(5) Å) is longer, compared to that found for 11 (1.313(4) Å), 18-E (1.322(3) Å), and 20 (1.3214(14) Å) (for details, see the SI).

The attempted preparation of the alkynyl triazene 27 has failed. Instead, the reaction between (phenylethynyl)-magnesium bromide and A3 gave triazole 28 (see Scheme 4).<sup>16</sup>

It is worth noting that monosubstituted and disubstituted vinyl triazenes can also be prepared by our previously reported  $N_2O$ -based method.<sup>11</sup> The synthesis of trisubstituted vinyl triazenes, however, was found to be problematic. For example, the preparation of **29** (a structural analogue of **19**) from LDA,  $N_2O$ , and the corresponding vinylmagnesium bromide gave a yield of only 15% (Scheme 5). The attempted synthesis of **30** (a structural analogue of **20**) failed completely.

Scheme 4. Synthesis of Non-aromatic Triazenes from Grignard Reagents and  $A3^{a}$ 



"Reaction conditions: Grignard reagent (1.25-2.00 equiv) and A3 (1.00 equiv) in THF (0.2-1.0 M) at 50 °C for 4–12 h. <sup>b</sup>The *E*-isomer was analyzed by X-ray crystallography. 'Not detected.

Scheme 5. Synthesis of Vinyl Triazenes from LDA, N<sub>2</sub>O, and Vinyl Grignard Reagents



So far, very few studies about the reactivity of vinyl triazenes have been reported.<sup>17,18</sup> The available data point to the fact that vinyl triazenes can be used as vinyl cation surrogates.<sup>19</sup> The possibility to use vinyl triazenes for electrophilic vinylation reactions was corroborated by acid-induced cleavage reactions of triazene **20** (see Scheme 6).

Addition of HF·Py to a solution of 20 in DCM rapidly gave vinyl fluoride 31, which could be isolated in 54% yield (the high volatility of the product compromises the yield). Tetrasubstituted fluoroalkenes such as 31 can be obtained by reaction of ketones with a lithiated  $\alpha$ -fluorobenzyl phosphonate, but the latter reagent is thermally instable, and its formation requires the utilization of diethylaminosulfur trifluoride.<sup>20</sup> A reaction of 20 with methanol in the presence of trifluoroacetic acid (TFA) gave the tetrasubstituted enol ether 32. The reported procedure for the synthesis of 32 is based on methylation of the corresponding enolate, which usually gives a mixture of C- and O-alkylation.<sup>21</sup> Treatment of 20 with TFA in butanethiol rapidly gave the corresponding vinyl sulfide 33 in 73% yield. Tetrasubstituted vinyl sulfides can be accessed otherwise via a Wittig olefination of thioesters.<sup>22</sup> Vinyl sufide 33 was easily converted to the corresponding vinyl sulfone 34 by oxidation



with *meta*-chloroperoxobenzoic acid (*m*-CPBA). In the presence of TFA, vinyl triazene **20** reacts with acetonitrile to give enamide **35** as a product of a Ritter-type reaction. Most of the previously published methods for the synthesis of tetrasubstituted enamides are known to be metal-catalyzed.<sup>23</sup> The success of the above-mentioned reactions inspired us to try a Michaelis-Arbuzov-type vinylation of trialkyl phosphites. Indeed, TFA-induced reaction of **20** with P(OEt)<sub>3</sub> led to vinyl phosphonate **36** in 30% isolated yield. To the best of our knowledge, this reaction represents the first metal-free synthesis of a tetrasubstituted alkenyl phosphonate.<sup>24</sup>

In summary, we have developed a simple and general method for the synthesis of linear, trisubstituted triazenes from Grignard reagents and 1-azido-4-iodobutane or 4-azidobutyl-4-methylbenzenesulfonate. These organic azides enable the regioselective formation of triazenes via an intramolecular cyclization step. The method allows the preparation of aromatic, as well as nonaromatic triazenes. Importantly, it provides access to vinyl triazenes, which are difficult to prepare otherwise. These triazenes can be used for electrophilic vinylation reactions, as demonstrated by the acid-induced replacement of the triazene function with fluoride, alkoxide, sulfide, amide, and phosphonate. The mild, metal-free reaction conditions, and the rapid formation of the desired products underline the potential of vinyl triazenes in synthetic organic chemistry.

## ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b01214.

Experimental details and analytical data of the new compounds (PDF)

#### **Accession Codes**

CCDC 1825041, 1825043, 1825046, and 1836098 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/ data\_request/cif, or by emailing data\_request@ccdc.cam.ac. uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

AUTHOR INFORMATION

#### **Corresponding Author**

\*E-mail: kay.severin@epfl.ch. ORCID <sup>©</sup>

Kay Severin: 0000-0003-2224-7234

# Notes

The authors declare no competing financial interest.

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### REFERENCES

 (1) For recent reviews, see: (a) Dong, W.; Chen, Z.; Xu, J.; Miao, M.; Ren, H. Synlett 2016, 27, 1318–1334. (b) Zhang, Y.; Cao, D.; Liu, W.; Hu, H.; Zhang, X.; Liu, C. Curr. Org. Chem. 2015, 19, 151–178.
 (c) Kölmel, D. K.; Jung, N.; Bräse, S. Aust. J. Chem. 2014, 67, 328– 336. (d) Kimball, D. B.; Haley, M. M. Angew. Chem., Int. Ed. 2002, 41, 3338–3351.

(2) Bräse, S. Acc. Chem. Res. 2004, 37, 805-816.

(3) (a) Hansen, M. N.; Farjami, E.; Kristiansen, M.; Clima, L.; Pedersen, S. U.; Daasbjerg, K.; Ferapontova, E. E.; Gothelf, K. V. J. Org. Chem. 2010, 75, 2474–2481. (b) Lu, M.; Chen, B.; He, T.; Li, Y.; Tour, J. M. Chem. Mater. 2007, 19, 4447–4453. (c) Hudson, J. L.; Jian, H.; Leonard, A. D.; Stephenson, J. J.; Tour, J. M. Chem. Mater. 2006, 18, 2766–2770. (d) Chen, B.; Flatt, A. K.; Jian, H.; Hudson, J. L.; Tour, J. M. Chem. Mater. 2005, 17, 4832–4836.

(4) For selected examples, see: (a) Dai, W.-C.; Wang, Z.-X. Org. Chem. Front. 2017, 4, 1281–1288. (b) Li, W.; Wu, X.-F. Org. Biomol. Chem. 2015, 13, 5090–5093. (c) Saeki, T.; Son, E.-C.; Tamao, K. Org. Lett. 2004, 6, 617–619. (d) Sengupta, S.; Sadhukhan, S. K. Org. Synth. 2002, 79, 52.

(5) (a) Wang, D.; Cui, S. Tetrahedron 2016, 72, 2725–2730. (b) Xu,
L.; Yang, W.; Zhang, L.; Miao, M.; Yang, Z.; Xu, X.; Ren, H. J. Org.
Chem. 2014, 79, 9206–9221. (c) Wang, C.; Chen, H.; Wang, Z.;
Chen, J.; Huang, Y. Angew. Chem., Int. Ed. 2012, 51, 7242–7245.
(d) Voica, A.-F.; Mendoza, A.; Gutekunst, W. R.; Fraga, J. O.; Baran, P.
S. Nat. Chem. 2012, 4, 629–635.

(6) (a) Zhang, Y.; Hu, H.; Liu, C.-J.; Cao, D.; Wang, B.; Sun, Y.; Abdukader, A. Asian J. Org. Chem. 2017, 6, 102–107. (b) Cao, D.; Zhang, Y.; Liu, C.; Wang, B.; Sun, Y.; Abdukadera, A.; Hu, H.; Liu, Q. Org. Lett. 2016, 18, 2000–2003. (c) Liu, C.; Lv, J.; Luo, S. Z.; Cheng, J.-P. Org. Lett. 2014, 16, 5458–5461.

(7) Dao, H. T.; Baran, P. S. Angew. Chem., Int. Ed. 2014, 53, 14382–14386.

(8) (a) Sun, H.; Wang, C.; Yang, Y.-F.; Chen, P.; Wu, Y.-D.; Zhang, X.; Huang, Y. J. Org. Chem. 2014, 79, 11863–11872. (b) Fang, Y.; Wang, C.; Su, S.; Yu, H.; Huang, Y. Org. Biomol. Chem. 2014, 12, 1061–1071. (c) Wang, C.; Sun, H.; Fang, Y.; Huang, Y. Angew. Chem, Int. Ed. 2013, 52, 5795–5798. (d) Goeminne, A.; Scammells, P. J.; Devine, S. M.; Flynn, B. L. Tetrahedron Lett. 2010, 51, 6882–6885.

(9) Zhou, J.; Yang, W.; Wang, B.; Ren, H. Angew. Chem., Int. Ed. 2012, 51, 12293-12297.

(10) (a) Sieh, D. H.; Wilbur, D. J.; Michejda, C. J. J. Am. Chem. Soc. **1980**, 102, 3883–3887. (b) Sieh, D. H.; Michejda, C. J. J. Am. Chem. Soc. **1981**, 103, 442–445.

(11) Kiefer, G.; Riedel, T.; Dyson, P. J.; Scopelliti, R.; Severin, K. Angew. Chem., Int. Ed. 2015, 54, 302–305.

(12) For a review about the utilization of nitrous oxide in synthetic chemistry, see: Severin, K. Chem. Soc. Rev. 2015, 44, 6375-6386.

(13) Schmidt, B. F.; Snyder, E. J.; Carroll, R. M.; Farnsworth, D. W.; Michejda, C. J.; Smith, R. H. J. Org. Chem. **1997**, 62, 8660–8665.

(14) Smith, R. H.; Pruski, B.; Day, C. S.; Pfaltzgraff, T. D.; Michejda, C. J. *Tetrahedron Lett.* **1992**, 33, 4683–4686.

(15) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. Angew. Chem., Int. Ed. 2006, 45, 2958–2961.

(17) (a) Lee, C. C.; Obafemi, C. A. Can. J. Chem. 1981, 59, 1636–1640. (b) Lee, C. C.; Ko, E. C. F. Can. J. Chem. 1976, 54, 3041–3044.
(c) Jones, W. M.; Maness, D. D. J. Am. Chem. Soc. 1970, 92, 5457–5464. (d) Jones, W. M.; Miller, F. W. J. Am. Chem. Soc. 1967, 89, 1960–1962.

(18) (a) Perrin, F.; Kiefer, G.; Jeanbourquin, L.; Racine, S.; Perrotta, D.; Waser, J.; Scopelliti, R.; Severin, K. *Angew. Chem., Int. Ed.* **2015**, *54*, 13393–13396. (b) Kossler, D.; Perrin, F.; Suleymanov, A. A.; Kiefer, G.; Scopelliti, R.; Severin, K.; Cramer, N. *Angew. Chem., Int. Ed.* **2017**, *56*, 11490–11493.

(19) For an overview about vinyl cation intermediates, see: (a) Hanack, M.; Carnahan, E. J.; Krowczynski, A.; Schoberth, W.; Subramanian, L. R.; Subramanian, K. J. Am. Chem. Soc. **1979**, 101, 100–108. (b) Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. R. Vinyl Cations; Academic Press: New York, 1979.

(20) (a) Allmendinger, T.; Fujimoto, R.; Gasparini, F.; Schilling, W.; Satoh, Y. Chimia **2004**, *58*, 133–137. (b) Tsai, H.-J.; Lin, K.-W.; Ting, T.-h.; Burton, D. J. Helv. Chim. Acta **1999**, *82*, 2231–2239.

(21) Jackman, L. M.; Lange, B. C. J. Am. Chem. Soc. 1981, 103, 4494-4499.

(22) Kumamoto, T.; Hosoi, K.; Mukaiyama, T. Bull. Chem. Soc. Jpn. 1968, 41, 2742–2745.

(23) For selected examples, see: (a) Guan, Z.-H.; Huang, K.; Yu, S.; Zhang, X. Org. Lett. **2009**, *11*, 481–483. (b) Han, J.; Jeon, M.; Pak, H. K.; Rhee, Y. H.; Park, J. Adv. Synth. Catal. **2014**, 356, 2769–2774.

(24) (a) Yuan, M.; Fang, Y.; Zhang, L.; Jin, X.; Tao, M.; Ye, Q.; Li, R.; Li, J.; Zheng, H.; Gu, J. Chin. J. Chem. 2015, 33, 1119–1123.
(b) Zhou, Y.; Ye, F.; Wang, X.; Xu, S.; Zhang, Y.; Wang, J. J. Org. Chem. 2015, 80, 6109–6118.

(25) The reaction between PhMgBr and 1-azido-4-chlorobutane, followed by aqueous workup, led to the formation of linear disubstituted triazene Ph $-N=N-NH-(CH_2)_4Cl$ .