Synthesis of a New Family of 1,1-Diazidoethenes: One-Pot Construction of 4-Azido-1,2,3-triazoles via Nitrene Cyclization

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Supporting Information

ABSTRACT: The reaction of 4,4-dichloro-1,2-diazabuta-1,3-dienes with sodium azide has been studied and found to provide straightforward access to extremely rare 1,1-bisazides. It was demonstrated that these highly unstable compounds are prone to eliminate the N2 molecule to cyclize into 4-azido-1,2,3-triazoles bearing two aryl (heteroaryl) groups at positions 2 and 5. The formation of bisazides was confirmed by their trapping with cyclooctyne and B3LYP calculations. Most likely, the



elimination of nitrogen to form an intermediate nitrene is facilitated by the aza group via anchimeric-like participation. The reaction was found to be very general for the highly efficient synthesis of various 4-azidotriazoles. It was demonstrated that these heterocycles are highly attractive building blocks for subsequent preparation of 1,2,3-triazole-derived compounds.

The azide group is one of the most useful functional groups.¹ This fragment can easily be transformed into a variety of other fundamental substituents. As such, azides have broad application in industry and in the preparation of energetic materials. However, probably more important is the application of organic azides as precursors for subsequent transformation. Currently, this functional group is becoming more and more important in synthetic chemistry, materials science, and some biological applications due to its high utility in click chemistry. However, molecules containing two or more azide groups in the structure are less investigated.²

Recently, we devised a synthesis of a new type of 1,2-diaza-1,3-diene having two chlorine atoms at the C=C double bond.³ It has been demonstrated previously that 1,2-diaza-1,3dienes are highly universal building blocks in the construction of various heterocycles.⁴ However, dichloro-substituted heterodienes of this type are almost unknown in the literature, and data about their reactivity are still very sparse.⁵ Due to the presence of the electron-withdrawing aza group, these azadienes behave as highly reactive and versatile electrophiles.⁶ Having in hand these versatile building blocks, we started their systematic study. This paper is devoted to our investigation of the reaction of dichloro-1,2-diaza-1,3-dienes with sodium azide.

We expected a priori to obtain a new family of compounds having a 1,1-diazidoethene fragment in the structure. Currently, compounds having two or more azido groups in the structure are extremely rare. This is especially true for geminal vinyl bisazides. So far, only five 1,1-diazidoethenes have been reported in the literature due to the intrinsic instability of these compounds and lack of suitable synthetic methods.⁷ On the other hand, such molecules have a very rich synthetic chemistry that opens straightforward access to various nitrogen heterocycles.⁸ Recently, the chemistry of geminal di- and triazides was reviewed by Banert and Kirsch (Scheme 1).⁹

We proposed that the reaction of dichloro-1,2-diaza-1,3dienes 1 with sodium azide would provide new bisazides via the addition of an azide anion to the double bond with the carbon atom bearing two good leaving groups. However, our first experiments with 1a as a model electrophile in DMSO as a solvent at rt resulted in formation of totally different but very interesting product 3a. The corresponding 4-azido-substituted 1,2,3-triazole 3a was isolated in 75% yield. The structure of 3a was confirmed unambiguously by X-ray analysis (Scheme 2).

Notably, 1,2,3-triazoles having a substituent at position 2 are rare in comparison with 1-substituted 1,2,3-triazoles available by click reaction. Nowadays, 2-aryltriazoles attract significant attention as a novel type of blue-light-emitting fluorophore.¹⁰ Also the importance of triazoles in the fields of medicinal and material chemistry¹¹ makes them promising substrates for novel fluorophore development. One can see six nitrogen atoms in the structure of 3a. Formation of 3a can be explained by substitution of two chlorines with two azides (additionelimination sequence) followed by heterocylization via formation of nitrene and elimination of molecular nitrogen.

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Scheme 1. Known 1,1-Diazidoethenes and Expected Formation of a New Type of Bisazides 2





Figure 1. Scope of diazadienes 1. Influence of substituent at position 4 and molecular structure of 3f.

After exhaustive optimization of the model reaction with 2a (see Supporting Information), it was found that the reaction proceeds most efficiently with 3 equiv of sodium azide in DMSO at rt for 2 h to give model triazole 3a in 90% isolated yield. With the optimized reaction conditions in hand, the scope of this new reaction was investigated (Figure 1).

First, the influence of the nature of the substituents at position 3 (carbon atom) of the dichloro-1,2-diaza-1,3-dienes 1 was studied. Thus, a set of dienes 1 possessing both electronically and sterically different substituents was studied.

The transformation was found to be very general, demonstrating perfect efficiency with dienes 1 bearing either electron-rich or electron-poor substituents. The desired products were isolated in up to 95% yield. Apparently,



Figure 2. Scope of aryl groups at nitrogen of diazadienes 1.

Scheme 3. One-Pot Protocol



Figure 3. Synthesis of 3 bearing a heterocyclic substituent.

electronic factors in the aryl substituent at position 3 of the diazadienes did not affect the heterocyclization as all dienes 1 were smoothly converted into azidotriazoles 3. The reaction with a 2-naphthalenyl derivative also proceeded well to give 3m in 89% yield. However, the influence of steric hindrance was more pronounced. For example, the reaction with substrates 1 bearing a substituent in the *ortho*-position demonstrated somewhat lower yields. In the case of 2,6-disubstituted substrates, yields of 3k,l dropped to 34%.

Next, the influence of the nature of the substituent at position 1 of the starting dienes was studied. It was found that in contrast to previous results, almost no effect on the reaction was observed. Therefore, practically any aryl substituent can be installed at position 2 of the target azidotriazole 3 (Figure 2).

We also attempted to perform the synthesis of **3** using a much more attractive one-pot protocol (Scheme 3). The one-pot protocol opened very efficient access to azidotriazoles starting from easily available benzaldehydes and hydrazines.

For example, **3a,f,g,h** were synthesized in reasonably good yields (up to 67%) without additional optimization. Significant

Scheme 4. Conversions of the Azide Group and Molecular Structure of 4d



Scheme 5. Proof of Bisazide Generation



growth of molecular complexity is observed for this one-pot multistep procedure (Scheme 3).

Also, the possibility to synthesize azidotriazoles 3 bearing a heterocyclic substituent was investigated. The reaction was

Scheme 6. DFT Calculations of the Reaction Mechanism and X-ray Structure of 6a⁴



found to be applicable for the synthesis of many pyridine 3ab-ad and quinoline 3ae derivatives. It has been found previously that thienyl- or furyl-derived dichloro-1,2-diaza-1,3-dienes 1 are very unstable, and these derivatives cannot be isolated in pure form due to their rapid degradation at rt. Nevertheless, using this one-pot protocol, the corresponding furan- and thiophene-substituted azidotriazoles 3af-3ah were prepared successfully in up to 60% isolated yield (Figure 3).

Apparently, triazoles **3** are synthetically attractive building blocks due to the presence of the azido group in the structure. Thus, the synthetic usefulness of these heterocycles was investigated (Scheme 4).

For example, Cu-catalyzed click reaction provided the corresponding bistriazole 4a very efficiently in 86% isolated yield. In contrast, similar ruthenium-catalyzed cycloaddition gave no results. Most likely, chelation of ruthenium prevented this type of cycloaddition. Reaction with malonodinitrile (Dimroth triazole synthesis) opened access to another type of bistriazoles. The corresponding product 4b was isolated in 70% yield. It was demonstrated that the azido group in 3a could be reduced directly to the amine 4c in 95% yield. Alternatively, iminophosphorane 4d can be prepared in quantitative yield by the reaction of 3a with PPh₃. Finally, the possibility to prepare another phosphorus derivative 4e was demonstrated using a reaction with triethyl phosphite. The corresponding amide 4e was isolated in 96% yield (Scheme 4).

Finally, initial efforts have been made to bring insight into the possible mechanism of this reaction. We decided to confirm real formation of the bisazides as short-living highly reactive compounds. Toward this aim, reaction of **1a** was performed in the presence of an excess cyclooctyne at 60 °C. Strain-promoted azide–alkyne [3 + 2] cycloaddition (SPAAC) reaction was successful for trapping the short-lived azides.^{9,12} The corresponding bistriazole **5a** was isolated in 60% yield as a result of a SPAAC reaction of the intermediate bisazide **2a** with cyclooctyne (Scheme 5).



^aThese energies are based on an assumption that Cl⁻, and other byproducts do not participate in the subsequent steps.

In addition, DFT calculations were performed to gain a deeper insight into the reaction mechanism. It should be noted that the obtained results are in perfect agreement with data obtained by theoretical calculation (Scheme 6). Cyclization of bisazide 2a into azidotriazole has a quite low activation barrier (16.5 kcal/mol). Moreover, stepwise substitution was confirmed by isolation of 4-chlorotriazole 6a as the minor product. An alternative pathway for formation of 3a by transformation of 3-chlorotriazole 6a has a much higher activation energy for this step (35.6 kcal/mol). Therefore, cyclization of 2a into azidotriazole 3a is much faster than the formation of 3a from 6a.

In summary, the reaction of 4,4-dichloro-1,2-diazabuta-1,3dienes with sodium azide has resulted in the formation of corresponding 1,1-bisazides as highly reactive intermediates. As a result, after elimination of molecular nitrogen, 4-azido-1,2,3triazoles were prepared in up to 95% yield. The formation of bisazides was confirmed by SPAAC with cyclooctyne and B3LYP calculations. It was demonstrated that 4-azido-1,2,3triazoles are highly attractive building blocks for subsequent preparation of various 1,2,3-triazole-derived compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b03227.

Experimental details, optimization of reaction conditions, characterization of products, X-ray data, copies of NMR spectra of all products, and calculations details (PDF)

Accession Codes

CCDC 1871724–1871726 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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