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Allenyl Azide Cycloaddition Chemistry. Synthesis of Pyrrolidine-Containing Bicycles and Tricycles via the Possible Intermediacy of Azatrimethylenemethane Species

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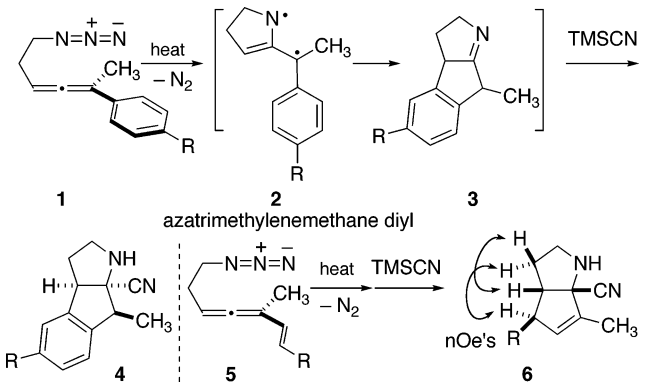
The emergence of azatrimethylenemethane (ATMM, cf. **2**) diyl cyclization chemistry can stimulate the development of new strategies for the construction of polycyclic nitrogen-containing species, much as the exploration of the parent trimethylenemethane diyl's reactivity has fueled much progress in polyquinane synthesis.[1] This chemistry might evolve from an initial intramolecular allene azide dipolar cycloaddition reaction (Scheme 1). Herein we report that both 1-aryl- and 1-vinyl-substituted 5-azidoallene substrates **1** and **5**, respectively, do indeed furnish transient imine products (e.g., **3**) en route to isolable polycyclic pyrrolidine derivatives **4** and **6**, respectively.

Speculation about the role of ATMM diyl intermediates in various rearrangement processes has appeared sporadically,[2] but the seminal investigations of Quast on triazoline decomposition chemistry provided the first systematic and convincing evidence in support of the existence of this elusive species.[3,4] In addition, this earlier work also revealed that (1) direct, *inter*molecular azide/allene cycloaddition was not a viable route to ATMM precursor triazolines due to incompatible reaction regiochemistry[3c,4] and (2) facile ATMM closure to an iminocyclopropane may render diyl capture (e.g., **2** → **3**) problematic.

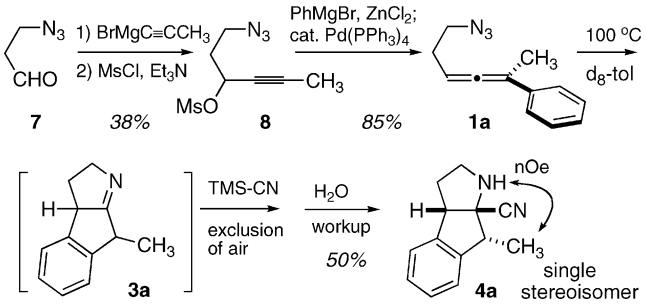
It is possible that both of these concerns could be alleviated by resorting to an intramolecular variant of the allene azide cycloaddition.[5] Tethering the reactive components together should overcome the inherent and undesired regiochemical bias for this cycloaddition.[5a] The use of terminally *di*substituted allenes **1** and **5** thwarts a ready triazoline alkene isomerization/aromatization pathway and opens up the possibility of intercepting Quast chemistry to generate a putative ATMM diyl intermediate **2**. A second benefit of intramolecularity becomes apparent when evaluating the prospects for closure of **2** to furnish an iminocyclopropane as per the Quast studies. Similar cyclopropane formation is likely to be energetically prohibitive in this bicyclic system,[3g,6] and thus alternative diyl trapping chemistry may now be expressed.

Scouting experiments to test this plan began with the phenyl-substituted allenyl azide **1a**, available from the acrolein azide addition product **7**[7] in a few well-precedented steps (Scheme 2).[8] This cyclization substrate was heated to 100 °C in a deoxygenated, dilute C_7D_8 solution (~0.06 M) with ^{1}H NMR monitoring. Clean conversion to a new species was observed over the course of 5 h, and preliminary spectroscopic analysis provided ^{1}H and ^{13}C NMR evidence that supported the structural assignment shown as imine **3a** (imine at δ 183.3; methyl doublet at δ 1.85 (J = 7.6 Hz)). Only a single stereoisomer was detectable, but no assignment of relative stereochemistry was made. All attempts to isolate this species were frustrated by its sensitivity to oxygen and moisture, but rapid addition of the crude imine solution to an excess of TMS-CN did provide a new tractable product whose spectral data pointed to the cyanoamine structure **4a**. The stereochemistry of this product was

Scheme 1



Scheme 2



established by dnOe studies, and a diagnostic enhancement is shown in Scheme 2.

The formation of tricycle **4a** is consistent with the ATMM-based reaction cascade proposed in Scheme 1. Mechanistic speculation about this reaction sequence begins with the intramolecular allene azide cycloaddition, which generates the regiochemically desired and hence labile triazoline **9** (Scheme 3). Expulsion of N_2 as per the Quast work would be expected to deliver the key ATMM diyl intermediate **10**, whose cyclization chemistry finds precedent in earlier work.[6b,9] In principle, an ATMM diyl intermediate could cyclize through resonance form **10a** (e.g., at nitrogen) to furnish a pyrrolizidine-type product **12**. That cyclization through the imine resonance form **10b** is favored might be a reflection of the stability of the imine function in **10b**, which would place greater spin density at carbon in the ATMM diyl construct. A zwitterionic resonance form **10c**[10] may also contribute to the structure and chemistry of the putative ATMM intermediate derived from **1a**.[11] Irrespective of the mechanistic subtleties, this encouraging result prompted further exploration of the scope of this process, as detailed in Table 1.

The aryl-substituted substrates **1b**−**e** were designed to probe the influence of electronic effects on the overall efficiency of this multistep process. Both relatively electron-rich (**1b** and **1c**) and relatively electron-deficient (**1d** and **1e**) aryl rings were examined,

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Scheme 3

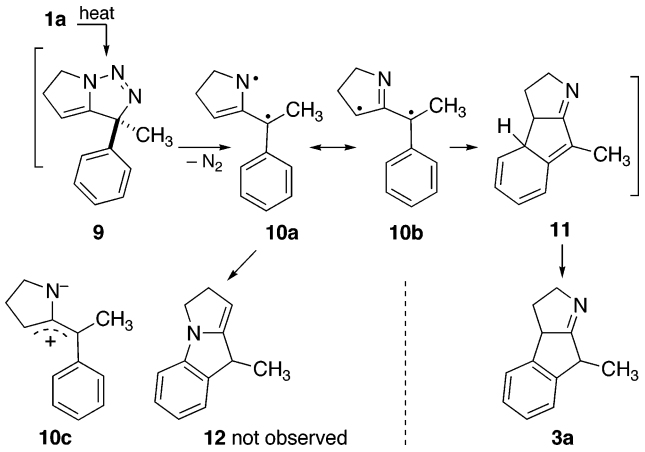

Table 1. Yield of Cyclization/Reorganization Products Formed from Aryl-Substituted Allenyl Azides

	azido(aryl)allene **1**		pyrrolidinyl nitrile **4**	
entry	R =		yield (%)[a]	
1	−H	**1a**	50	**4a**
2	$-OCH_3$	**1b**	52	**4b**
3	$-CH_3$	**1c**	63	**4c**
4	−Cl	**1d**	47	**4d**
5	$-CO_2Et$	**1e**	37	**4e**

[a] Yield of isolated, chromatographically pure product.

Table 2. Yield of Cyclization/Reorganization Products Formed from Alkene-Substituted Allenyl Azides

	azido(alkenyl)allene **5**		pyrrolidinyl nitrile **6**	
entry	R =		yield (%)[a]	
1	−H	**5a**	96	**6a**
2	−Ph	**5b**	84	**6b**
3	$-CO_2Et$	**5c**	90	**6c**

[a] Yield of isolated, chromatographically pure product.

and in all cases the desired pyrrolidinyl cyanide products **4b**−**e** were formed in moderate yield. Analysis of the crude thermolysates by ^{1}H NMR spectroscopy revealed that a single stereoisomer of the imine product was present (5% detection limit) in each case. The stereochemical assignments of **4b**, **4c**, and **4e** followed from comparison of their ^{1}H and ^{13}C NMR spectral data with those of **4a**, whose stereochemistry was secured by dnOe spectroscopy, and with those of **4d**, whose structure was assigned unambiguously on the basis of single-crystal X-ray analysis (see Supporting Information).[12] Evaluation of this limited data set suggests that electron-rich aryl rings provide product with marginally higher yields. It is not immediately apparent where along this complex reaction cascade this electronic influence becomes manifest, but it is possible that formation of the presumably electron-deficient ATMM diyl intermediate **10** (Scheme 3) is favored when the attached aryl ring can better satisfy the diyl's electron demand. This hypothesis is consistent with a contribution of zwitterionic character (cf. **10c**) to the ATMM intermediate.

The vinyl-substituted allenyl azide substrates **5a**−**c** extend this transformation to nonaromatic products (Table 2). In this instance, cyclization/N_2 extrusion/cyclization furnishes bicyclic products **6a**−**c**, respectively, with the alkene positioned adjacent to the cyanoamine center, as opposed to the alkene-isomerized versions. The newly formed secondary stereogenic centers in **6b** and **6c** emerged as single diastereomers, and the assignment as syn to the adjacent ring fusion hydrogen was based upon key difference nOe measurements (cf. Scheme 1). A model for the evolution of syn stereochemistry upon 1,5-pentenediyl closure in a related system has been advanced earlier,[6b] and the formation of both **6b** and **6c** is in accord with the expectations of that model.

In summary, a heretofore unexplored cascade cyclization sequence evolving from the thermolyses of allenyl azides has been developed. Incorporation of aryl rings or alkenyl appendages leads to tricyclic or bicyclic pyrrolidine products, respectively, following cyanide trapping of an unstable imine.

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Supporting Information Available: Experimental procedures and characterization data for **1a**−**e**, **4a**−**e**, **5a**−**c**, **6a**−**c**, and **8** and X-ray-derived structural depiction of **4d** with accompanying data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) CCDC 259790 contains the supplementary crystallographic data for this communication. These data can be obtained online free of charge (or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1 EZ, U.K.; Fax (+44) 1223−336−033; or deposit@cccd.cam.ac.uk).

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