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Tandem Cycloaddition Reactions of Allenyl Diazo Compounds Forming Triquinanes via Trimethylenemethane Diyls

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Supporting Information

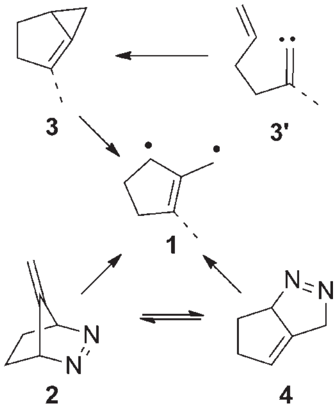
ABSTRACT: A tandem reaction strategy for forming triquinanes from linear allenyl diazo compounds through an intramolecular 1,3-dipolar cycloaddition reaction of an allenyl diazo group that generates a trimethylenemethane (TMM) diyl followed by an intramolecular [2 + 3] TMM diyl cycloaddition reaction has been developed. The new tandem cycloaddition reaction is readily applicable to the synthesis of complex molecules with high versatility and efficiency.

The concept of the ideal synthesis has been an important goal of organic synthesis.[1] Toward this goal, various aspects of economy of the synthesis have become the measures of the efficiency of synthetic routes to complex targets.[1b] These objectives are also in accord with the principles of green chemistry.[2] Multistep reactions in one synthetic operation[3] are known as tandem, domino, and cascade reactions. They satisfy the objectives of ideal synthesis and the principles of green chemistry. The reactions not only construct complex structures in a single operation but also eliminate isolation and purification steps of the intermediates.

Cycloaddition reactions have played a role in the development of tandem reactions. They rapidly increase architectural complexity and frequently occur with control of stereo- and regioselectivity. While trimethylenemethane (TMM)-mediated cycloaddition reactions have played a major role in cyclopentanoid synthesis,[4] they have not been used in the context of a tandem cycloaddition reaction. A synthetically viable TMM diyl was first observed by Koebrich in 1969.[5] The identity and properties of the TMM diyl were thoroughly studied by Berson from the late 1970s through the early 1980s.[6] On the basis of his studies, TMM diyl was successfully applied to the [2 + 3] cycloaddition reaction by Little.[7] The scope of the TMM diyl chemistry was also extended to the formation of six-, seven-, and eight-membered rings through various radical pathways.[8]

We recently reported a tandem reaction strategy for obtaining triquinanes from alkylidene carbenes via TMM diyls.[9] This tandem reaction strategy expanded the scope of TMM-mediated [2 + 3] cycloaddition reactions to the synthesis of angularly fused triquinanes.[10] TMM diyl (**1**) can be generated from methylene-2,3-diazabicyclo[2.2.1]hept-2-ene (**2**), bicyclo[3.2.1]hex-1-ene (**3**), or tetrahydrocyclopentapyrazole (**4**) (Scheme 1).[11] While all of these precursors to **1** were extensively studied, tetrahydrocyclopentapyrazole **4** was studied less than the other precursors, presumably because of the difficulty of preparing **4**. We envisioned that the tetrahydrocyclopentapyrazole structure could be accessed through a 1,3-dipolar cycloaddition reaction between a diazo compound and an allene, and we designed a tandem cycloaddition reaction strategy for obtaining triquinane structures from substrates containing olefin, allene, and diazo functional groups (Scheme 2). Herein we report an efficient tandem cycloaddition reaction strategy for the formation of triquinanes via TMM diyls.

Scheme 1. Generation of Methylcyclopentene TMM Dyl 1



The tandem cycloaddition reaction strategy could produce linearly fused as well as angularly fused triquinanes by altering the substitution pattern on the allene functionality. The diazo group of **I** or **IV** would undergo an intramolecular cycloaddition reaction with the allene to form **II** or **V**, respectively. Tetrahydrocyclopentapyrazole **II** or **V** would lose N_2 to generate TMM diyl **III** or **VI**, which would undergo another [2 + 3] cycloaddition reaction to produce the triquinane structure.[6b]

The designed tandem cycloaddition reaction strategy was first executed with linear substrate **5a** (Table 1). When **5a** in toluene solution was heated at 110 °C,[12] exceptionally clean conversion was observed. The desired linearly fused triquinane **6a** was obtained in 83% yield (Table 1, entry 1). Though the reaction is believed to follow the tandem cycloaddition reaction sequence shown in Scheme 2, no intermediate was observed. A similar reaction of allenyl azide was also reported to proceed through the corresponding triazole intermediate to produce tetrahydropentapyrrole, but the intermediate was not observed. It was calculated that the loss of N_2 from the triazole intermediate is an exothermic process.[13] Indirect evidence for the formation of the intermediate **II** was obtained when substrates with different

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Scheme 2. Tandem Reaction Sequence of Allenyl Diazo Compounds To Give Triquinanes

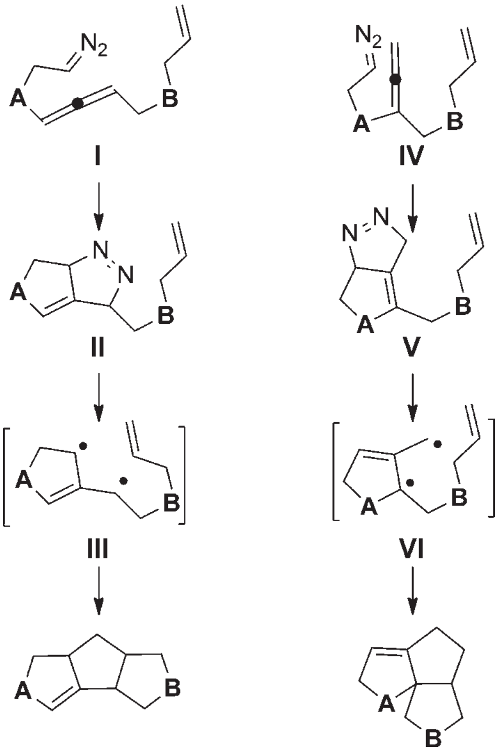
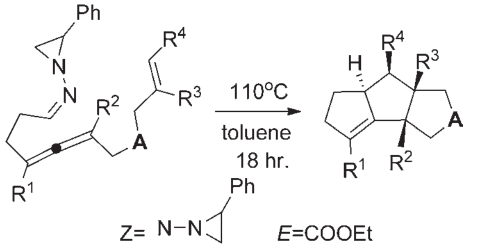
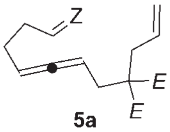
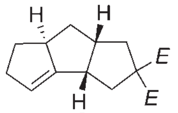
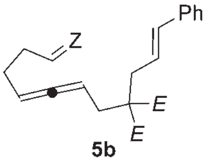
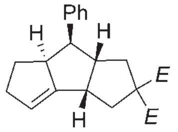
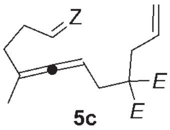
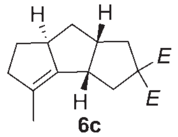
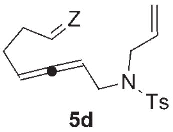
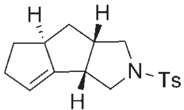
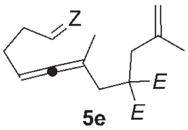
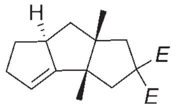


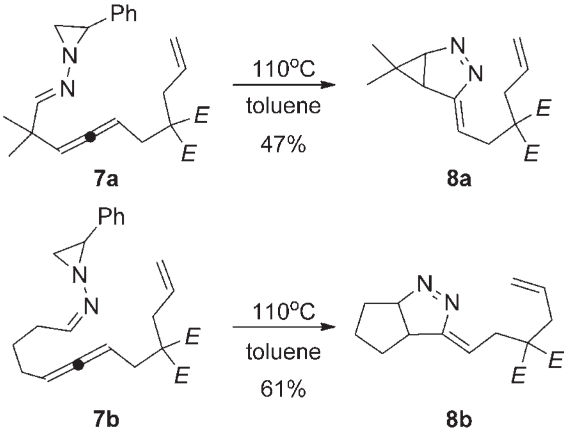
Table 1. Tandem Reaction of Linear Substrates To Give Linearly Fused Triquinanes



entry	substrate	product	yield[a]
1	 5a	 6a	83%[b]
2	 5b	 6b	86%
3	 5c	 6c	84%
4	 5d	 6d	82%[b]
5	 5e	 6e	70%

[a] Isolated yields. [b] Obtained as 7:1 mixture with the syn-cis isomer.

Scheme 3. Effect of the Tether Length in the Diazo−Allene Cycloaddition Reaction

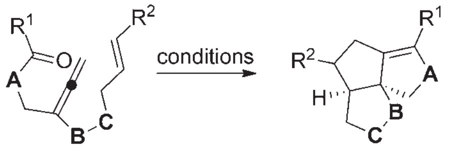


lengths of the tether between the aziridinyl imine and allene functionalities were subjected to the same reaction conditions (Scheme 3). When substrate **7a** bearing a two-carbon tether was subjected to the reaction conditions, cyclopropylpyrazole **8a** was obtained without further rearrangement.[14] The substrate with a four-carbon tether, **7b**, produced cyclopentapyrazole **8b** instead of anticipated cyclohexapyrazole compound. Selectivity for five-membered ring formation from the intramolecular cycloaddition reaction was in accord with the outcomes of other cycloaddition reactions of allenes.[15] In both cases, the first cycloaddition reaction products with pyrazole rings were isolated. These results support the existence of intermediate **II** in the tandem cycloaddition reaction pathway leading to the triquinane product.

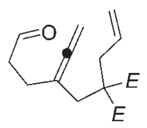
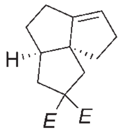
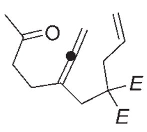
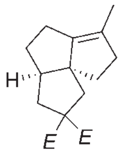
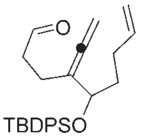
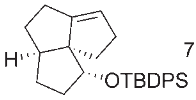
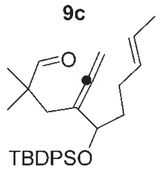
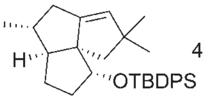
Table 1 shows that the new tandem reaction protocol is quite versatile and efficient in comparison with previous synthetic methods using the TMM diyl cycloaddition reaction.[7,9] The reaction tolerates various substitution patterns, as the trisubstituted allenes **5c** and **5e** produced the corresponding linearly fused triquinanes **6c** and **6e** in good yield. The formation of **6e** is noteworthy since the product contains consecutive quaternary carbon centers at the ring junction, which poses high steric congestion. The relative stereochemistry of the products was confirmed through correlation spectroscopy (COSY) and nuclear Overhauser effect (NOE) experiments for all the products and comparison of the spectroscopic data of **6c** with previously reported ones.[16]

Given the wide applicability and high efficiency of the tandem reaction strategy for the synthesis of linearly fused triquinanes, the synthetic strategy was also applied to the synthesis of angularly fused triquinanes. Though the alkylidene carbene-mediated TMM diyl [2 + 3] cycloaddition showed limited efficiency for the formation of angularly fused triquinanes in our previous report,[10] it appeared that the low efficiency of the tandem reaction was not due to the strain energy associated with the TMM diyl

Table 2. Tandem Reaction of Linear Substrates To Give Angularly Fused Triquinanes



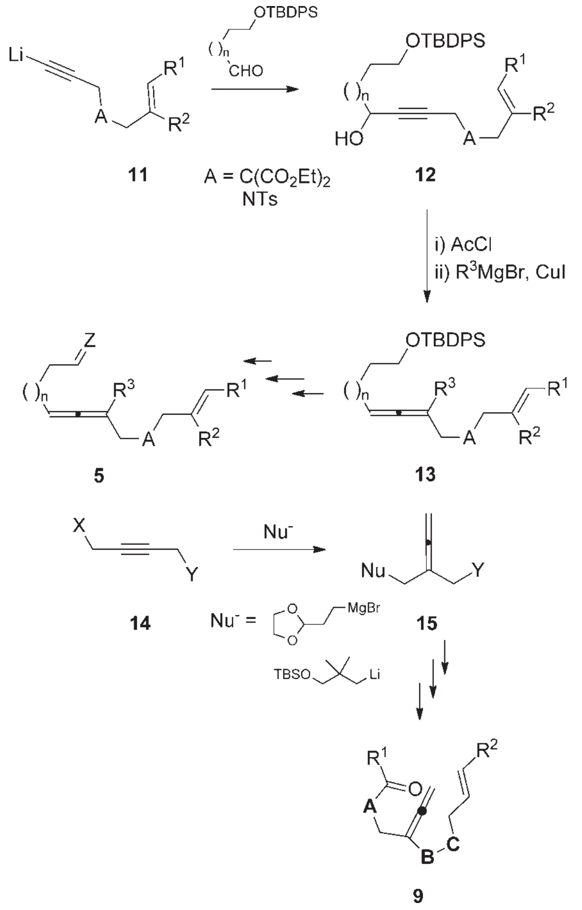
E=COOEt

entry	substrate	conditions[a]	product	yield[b]
1	 **9a**	A	 **10a**	93%
2		B		98%
3	 **9b**	A[c]	 **10b**	84%
4	 **9c**	A	 **10c**	78%
5	 **9d**	A	 **10d**	45%
6		B		61%

[a] Conditions A: 2-phenylaziridin-1-amine, CH_2Cl_2, toluene, 110 °C, 12 h. Conditions B: NH_2NHTs/MeOH, NaH/toluene, 110 °C, 4 h. [b] Isolated yields. [c] Xylene, 160 °C, 12 h.

cycloaddition reaction. Thus, it was hoped that the current tandem cycloaddition route could produce angularly fused triquinanes efficiently. When aldehyde **9a** was subjected to the tandem cycloaddition reaction sequence after aziridinyl imine formation, angularly fused triquinane **10a** was obtained in 93% yield (Table 2, entry 1), which is a dramatic improvement over the yield of the alkylidene carbene-mediated TMM diyl cycloaddition reaction.[10] The diazo intermediate could also be generated from the corresponding ketone **9b**, though the reaction was slower than that of **9a**. A higher temperature was required in order to form the diazo group with a rate comparable to that for formation of the diazo functionality from aldehyde imines. This result expands the substrate scope and flexibility of the process. The substituent on the allenyl group can be exchanged with the substituent at the diazo group for the same product. As demonstrated in the previous report, the cycloaddition reaction can be stereoselective. The substrate with the substituent on the tether, **9c**, produced angularly fused triquinane **10c** stereoselectively.[17]

Scheme 4. Representative Synthetic Pathways Leading to the Substrates



When the sterically demanding substrate **9d** was subjected to the tandem cycloaddition reaction conditions after formation of the aziridinyl imine, angularly fused triquinane **10d** was obtained with a significant amount of byproducts (Table 2, entry 5). The main byproducts appeared to be the products of the unexpected intermolecular cycloaddition reaction between the TMM diyl intermediate and styrene, the latter being generated from the aziridinyl imine during the formation of the diazo group. To eliminate the side reaction, the aziridinyl imine was replaced by the sodium salt of tosylhydrazone as the precursor for the diazo functional group.[18] When **9a** was subjected to reaction conditions B (Table 2, entry 2), the reaction produced angularly fused triquinane **10a** almost quantitatively. The reaction time was substantially shorter than for conditions A, which implies that the rate determining step of the tandem reaction is formation of the diazo group. When the new procedure was applied to substrate **9d**, the tandem reaction proceeded smoothly to produce angularly fused triquinane **10d** in good yield without the formation of byproducts (Table 2, entry 6).

Substrates for the tandem cycloaddition reaction can be readily prepared in straightforward manners (Scheme 4). Typically, substrates for the linear triquinanes were prepared from **11** through cuprate addition to form allene **13** via alkynol **12**. Substrates for the angular triquinanes were prepared from allenyl intermediate **15** obtained from activated 1,4-butynediol.

In conclusion, we have developed a tandem cycloaddition route to triquinanes from linear substrates via a cycloaddition reaction of TMM diyls generated from the 1,3-dipoar cycloaddition reaction of allenyl diazo compounds. The current tandem reaction shows versatility, efficiency, and wide applicability to complex natural product synthesis, as the tricyclic compounds can be obtained from linear substrates with various substitution patterns.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Synthetic schemes for the substrates, experimental details, and spectral data (including COSY and NOE spectra) for the cycloaddition reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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