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Intermolecular [3 + 3]-Cycloadditions of Azides with the Nazarov Intermediate

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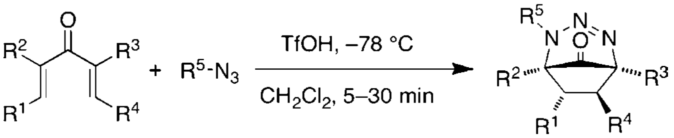
ABSTRACT



Tetrasubstituted 1,4-dien-3-ones undergo Nazarov cyclization at low temperature, followed by reaction with organic azides via an apparent [3 + 3]-cycloaddition to give bridged bicyclic triazenes. These products do not appear to be intermediates in the previously described Schmidt-type process to furnish dihydropyridones. The reaction typically occurs with high diastereoselectivity.

The Nazarov cyclization provides convenient access to cyclopentanoid products from acyclic precursors,[1] and has been shown to be an efficient tool in tandem and domino processes.[2] The initial electrocyclization process results in an oxyallyl cation subject to a variety of trapping modalities. Dienes[3] and electron rich olefins[4] have been shown to react in [4 + 3] and [3 + 2] cycloadditions, while aromatic systems[5] can trap the intermediate via Friedel−Crafts alkylations. Organic azides can capture the oxyallyl cation with subsequent Schmidt rearrangement to form dihydropyridones[6] or peroxy bridged indolizidinones.[7] This reactivity contrasts with the findings of Aubé and Desai,[8] who noted that azides participated in apparent [3 + 3]-cycloadditions with a simple oxyallyl cation to furnish a labile tetrahydrotriazine-5-one which then underwent rearrangement to a diazoketone or azepinone. *Intramolecular* [3 + 3] trapping of a more elaborate, photochemically generated oxyallyl zwitterion was reported by Schultz and co-workers.[9]

The synthetic value of the dihydropyridones obtained from Schmidt-type reactivity in the case of azide trapping of Nazarov intermediates was clear; however, a mechanistic rationale for the failure to observe [3 + 3]-adducts or products clearly arising from them was elusive. Conceivably, the nitrogen-insertion products **1** seen in these cases could arise from initially formed [3 + 3]-adducts **3**, followed by C−N bond cleavage and ring enlargement by a Schmidt-type mechanism (Scheme 1). The alternative N−N cleavage in analogy to the Aubé example might be suppressed in these cases due to the greater rigidity of bridged bicyclic cycloadducts **3**. However, if this were the case, isolation of at least

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(1) (a) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606. (c) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193–2206. (d) Nakanishi, W.; West, F. G. *Curr. Opin. Drug. Dicovery Dev.* **2009**, *12*, 732–751.

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(9) Schultz, A. G.; Macielag, M.; Plummer, M. *J. Org. Chem.* **1988**, *53*, 391–395.

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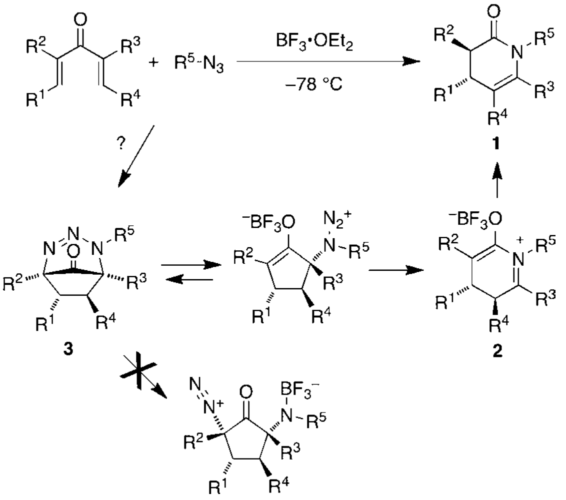
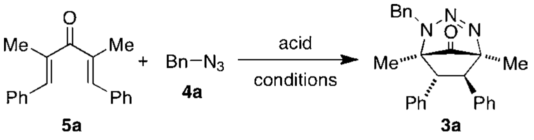
Scheme 1



minor amounts of the putative intermediate would be expected, yet cycloadducts **3** were never observed. Here we describe the effective trapping of the Nazarov intermediate by simple azides through Brønsted acid activation to provide access to remarkably stable bridged triazene cycloadducts.

Brønsted acid activation of the azide-interrupted Nazarov reaction was initially investigated as part of an effort to intercept the zwitterionic intermediate **2** presumed to form during ring-expansion. No trapping of this 1,4-dipole by intra- or intermolecular processes could be seen using the optimized BF_3•OEt_2 conditions described in the original study,[6] furnishing only the usual dihydropyridone products **1**. Using benzyl azide **4a** and prototypical dienone **5a**, several protic acids were examined in order to determine whether interrupted Nazarov reaction could be effected under these alternative conditions (Table 1). Starting materials were returned unchanged after stirring with trifluoroacetic acid, first at −78 °C and then at 0 °C. On the other hand, *p*-toluenesulfonic acid furnished an intractable mixture of products after 0.5 h at −78 °C. Although we were unable to detect any of the desired adduct after treatment with TsOH, the efficient consumption of starting materials at low temperature was promising, and other strong acids were examined. Bis(trifluoromethane)sulfonimide was found to consume starting materials to provide one main product, an apparent adduct of some sort, though clearly not the expected dihydropyridone. Instead, it seemed to be the elusive [3 + 3]-cycloadduct (**3a**), formed as a single diasteromer in 57% yield. A crystalline solid, **3a** was analyzed by single crystal X-ray diffraction analysis, which confirmed the initial structural assignment. Finally, trifluoromethanesulfonic acid was found to give **3a** in 78% yield after only 5 min at −78 °C, and these conditions were then used to examine the generality of this process with other substrates.[10]

Table 1. Evaluation of Brønsted Acids in Azide Trapping of the Nazarov Intermediate[a]

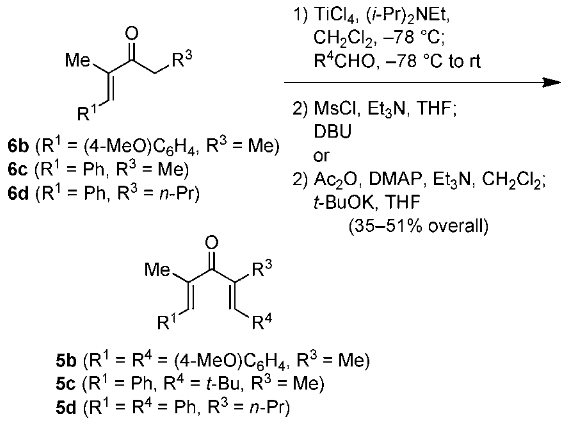


entry	conditions	yield **3a** (%)[b]
1	trifluoroacetic acid, CH_2Cl_2, −78 °C, 2 h; then 0 °C, 2 h	no conversion
2	*p*-toluenesulfonic acid, CH_2Cl_2, −78 °C, 0.5 h	intractable mixture
3	bis(trifluoromethane)sulfonimide, CH_2Cl_2, −78 °C, 0.25 h	57
4	trifluoromethanesulfonic acid, CH_2Cl_2, −78 °C, 5 min	78

[a] **4a** (2 equiv) and **5a** were stirred with 2.2 equiv of Brønsted acid in CH_2Cl_2 at the indicated temperature. [b] Yields are given for isolated products after chromatographic purification.

The scope of this unexpected cycloaddition process was probed using a variety of dienone substrates **5a−f**, both symmetrically and unsymmetrically substituted, along with azides **4a−c**. Previously unreported dienones **5b−d** were prepared from enones **6b−d** via aldol addition to the appropriate aldehydes and elimination of a suitably activated form of the *β*-hydroxyl group (Scheme 2).

Scheme 2



Symmetrical dienones **5a**,**b** reacted cleanly with azides **4a**,**b** to provide in each case a single [3 + 3]-cycloadduct **3** (Table 2). The stereochemical assignments for adducts **3b−d** were made based upon their close spectral analogy to the crystallographically characterized **3a**. Next, unsymmetrical dienone **5c** was examined (entries 5,6). This substrate required somewhat higher reaction temperature (−40 °C) to effect the initial Nazarov electrocyclization, presumably a result of the steric demand of the *t*-butyl substituent. Notwithstanding the higher temperature, reaction with **4a** and **4b** furnished in each case a single cycloadduct (**3e**,**f**) in moderate to good yield, indicating complete regio- and

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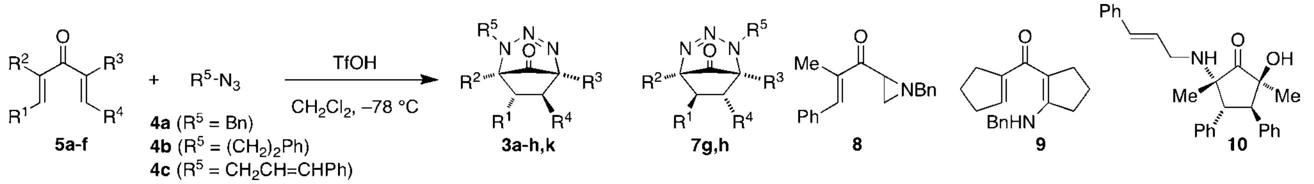
(10) Use of less than 2 equiv of acid led to diminished yields and incomplete consumption of starting materials.

Table 2. [3 + 3] Cycloadditions of Using Optimized Conditions[a]



entry	dienone	R^1	R^2	R^3	R^4	azide	R^5	product(s) (yield (%))[b]
1	**5a**	Ph	Me	Me	Ph	**4a**	CH$_2$Ph	**3a** (78)
2	**5a**					**4b**	CH$_2$CH$_2$Ph	**3b** (70)
3	**5b**	(4-MeO)C$_6$H$_4$	Me	Me	(4-MeO)C$_6$H$_4$	**4a**	CH$_2$Ph	**3c** (81)
4	**5b**					**4b**	CH$_2$CH$_2$Ph	**3d** (64)
5	**5c**	Ph	Me	Me	*t*-Bu	**4a**	CH$_2$Ph	**3e** (75)[c]
6	**5c**					**4b**	CH$_2$CH$_2$Ph	**3f** (62)[c]
7	**5d**	Ph	Me	*n*-Pr	Ph	**4a**	CH$_2$Ph	**3g/7g** (81, 1:2.2)
8	**5d**					**4b**	CH$_2$CH$_2$Ph	**3h/7h** (61, 1:2.1)
9	**5e**	Ph	Me	H	H	**4a**	CH$_2$Ph	**8** (52)[c]
10	**5f**	(CH$_2$)$_3$		(CH$_2$)$_3$		**4a**	CH$_2$Ph	**9** (57)[c]
11	**5a**	Ph	Me	Me	Ph	**4c**	CH$_2$CH=CHPh	**3k/10** (56, 1:1.58)

[a] General Procedure: TfOH (2.2 equiv) was added dropwise to a solution of **5** and **4** (2.0 equiv) in DCM at −78 °C. The reaction mixture was stirred at −78 °C and monitored for the disappearance of starting material by TLC analysis (5−30 min). The reaction was then quenched by addition of saturated NaHCO$_3$ solution and warmed to room temperature. [b] Yields are given for isolated products after chromatographic purification. [c] Reactions of dienones **5c**, **5e**, and **5f** were carried out at −40 °C, 0 °C and rt, respectively.

diastereoselectivity in the approach of the azide moiety to the unsymmetrical 2-hydroxycyclopentenyl cation intermediate. The indicated regiochemistry, assigned based upon HMBC correlations, is the result of approach of the azide with the alkyl substituent distal to the bulky *t*-butyl group. In contrast to **5c**, reaction of **5d** with **4a**,**b** was only marginally regioselective (entries 7,8), with a slight preference for approach of the azide with the alkyl group adjacent to the propyl chain rather than the methyl (ca. 2:1 **3g**,**h**:**7g**,**h**). However, in both cases, each regioisomer was formed as a single diastereomer.

Two other previously described dienones were studied. Lightly substituted dienone **5e** had previously been shown to undergo Nazarov cyclization in the presence of BF$_3$•OEt$_2$ followed by efficient and completely regioselective azide trapping via the Schmidt pathway to yield dihydropyridones.[6] In contrast, under the TfOH conditions **5e** reacted with benzyl azide to afford aziridine **8** (entry 9). Higher temperatures are required to achieve electrocyclization with less substituted dienones such as **5e**, and apparently a competing aziridination[11] occurs competitively at these temperatures.[12] Dicyclopentenyl ketone **5f** also failed to produce any of the expected [3 + 3]-adduct, instead furnishing enaminone **9** in moderate yield.[13] Again, the higher reaction temperature required for Nazarov cyclization of **5f**[4a,b] allows for alternative pathways involving **4a** and the starting dienone to intervene. Given the premature reaction with **4a** seen in the case of these two dienones, other azides were not examined.

Trapping by cinnamyl azide **4c** was also explored using dienone **5a** (entry 11). These reactants afford the usual dihydropyridone under Lewis acid conditions, and were expected to furnish [3 + 3]-adduct **3k**. While this product was indeed observed to be the primary component of the crude reaction mixture, attempted purification by silica gel chromatography resulted in a ca. 1:1.6 mixture of **3k** and a second product containing two exchangeable protons and with an apparent molecular formula indicating loss of N$_2$ and addition of water. The structure of this product was tentatively assigned as 2-hydroxy-5-aminocyclopentanone **10**. Trituration with hexane and recrystallization ultimately furnished crystalline material suitable for X-ray diffraction, which confirmed the assigned connectivity and established a *trans* relative stereochemistry between the two heteroatom substituents flanking the carbonyl. A similar hydrolysis product was reported by Schultz and co-workers for one of their intramolecular [3 + 3]-photocycloadducts,[9] apparently upon extended storage. Notably, we have not observed analogous hydrolysis behavior with any of the other [3 + 3]-adducts **3a**−**h** or **7g**,**h**, nor did pure **3k** seem to degrade during storage.

The complete diastereoselectivity observed in the formation of **10** suggests a possible internal delivery mechanism (Scheme 3). Ionic fragmentation of the triazene bridge of

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(11) (a) Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354–1355. (b) Li, J.; Fu, Y.; Guo, Q.-X. *Tetrahedron* **2008**, *64*, 11167–11174.

(12) The intermediacy of a triazoline [3 + 2]-cycloadduct in the formation of **8** cannot be ruled out, as Johnston has shown that acid-mediated extrusion of N$_2$ from triazolines to provide the aziridine can occur at temperatures as low as 0 °C: Hong, K. B.; Donahue, M. G.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 2323–2328.

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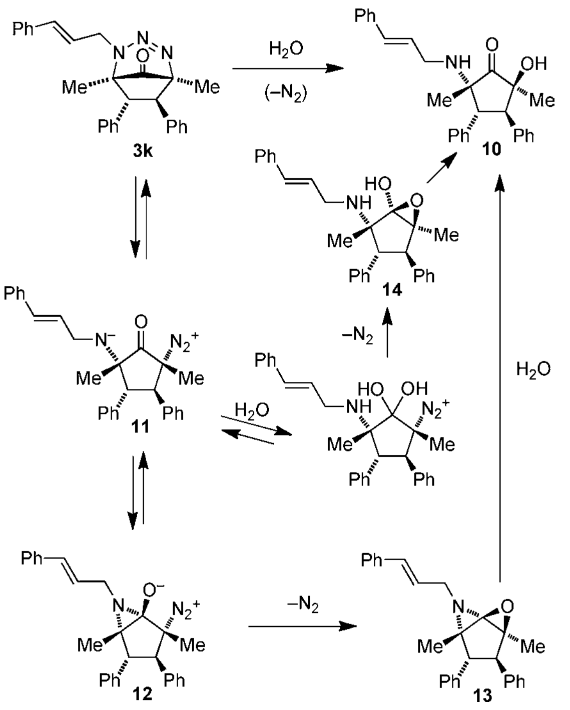
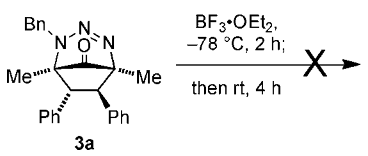
Scheme 3



3k to zwitterion **11** could permit equilibration with aziridine **12**,[14] which could then undergo epoxide formation to **13** with inversion at the diazonium-substituted center. **13** would be expected to suffer facile hydrolysis to **10**. Alternatively, hydrate formation from **11** would allow for internal displacement of N_2 to give **14**, which should readily rearrange to **10**. Attempts to fully convert the crude product to **10** via exposure to water or extended stirring with silica gel were unsuccessful. Given the variable ratios obtained in this capricious reaction, we did not examine the reaction of azide **4c** with other dienones. However, this unusual result and the reason for its limitation to the cinammyl-substituted case merit further study.

Finally, to address the question of whether [3 + 3]-adducts such as **3** are intermediates in the formation of 1,4-dipoles **2** and dihydropyridones **1** (see Scheme 1), we subjected a sample of **3a** to the conditions ($BF_3 \cdot OEt_2$, −78 °C) used to form **1a** from **5a** + **4a** (eq 1).[6] In the event, **3a** remained unconsumed, even after warming to rt.[15] In light of this result, we believe that nitrogen insertion products **1** arise from direct nucleophilic attack of the intermediate 2-oxidocyclopentenyl cations without the intermediacy of [3 + 3]-adducts **3**. The dramatically different outcomes in azide trapping seen under Lewis vs Brønsted acid conditions is intriguing. This difference may result from a greater propensity of the 2-hydroxycyclopentenyl cation to undergo a concerted cycloaddition process with azide in preference to nucleophilic trapping, or a greater rate of ring-expansion with expulsion of dinitrogen by the zwitterionic BF_3 complex following nucleophilic attack by azide.



(1)

We have found that treatment of a variety of dienones with organoazides in the presence of TfOH results in a new type of interrupted Nazarov reaction, furnishing bridged bicyclic triazenes via an apparent [3 + 3]-cycloaddition between the 2-hydroxycyclopentenyl cation that results from Nazarov electrocyclization and the azide 1,3-dipole. The reaction is remarkably stereoselective, and displays modest to high regioselectivity in unsymmetrical cases. An unusual and facile hydrolysis process was observed for one of the [3 + 3]-cycloadducts. Applications of this domino process and additional study of the origins of the high selectivity will be described in due course.

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Supporting Information Available: Experimental procedures, physical data and NMR spectra for all compounds and synthetic intermediates, and X-ray crystallographic data for **3a**, **3c** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] Intermediates related to **11** and **12** have previously been proposed by Aubé,[13c] Molander,[13b] and Sha: Sha, C.-K.; Ouyang, S.-L.; Hsieh, D.-Y.; Chang, R.-C.; Chang, S.-C. *J. Org. Chem.* **1986**, *51*, 1490–1494.

[15] Under the standard conditions, **4a** and **5a** are converted to **1a** in ca. 10 min.