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Cyclization Cascades Initiated by 1,6-Conjugate Addition

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Abstract

Dienyl diketones containing tethered acetates selectively undergo two different 1,6-conjugate addition-initiated cyclization cascades. One is a 1,6-conjugate addition/cyclization sequence with incorporation of the nucleophile, and the other is catalyzed by DABCO and is thought to proceed via a cyclic acetoxonium intermediate. The reaction behavior of substrates lacking the tethered acetate was also studied. The scope of both types of cyclization cascades, the role of the amine additive, and the factors controlling reactivity and selectivity in the two different reaction pathways is discussed.

Functionalized cyclopentenones containing quaternary stereogenic carbon centers are valuable building blocks for the preparation of interesting small molecules. Efficient, catalytic methods for the assembly of these targets via Nazarov cyclization have been studied extensively in recent years,¹ and capitalize on the conservation of orbital symmetry² as a means to control relative stereochemistry. Typically, either a Bronsted or a Lewis acid is used to promote the 4 π cationic electrocyclization.

Recently, we reported that 1,6-conjugate addition of a nucleophile to dienyl diketone **1** could initiate Nazarov cyclization, via pentadienyl cation **2** (Scheme 1).³ Further study of nucleophile-initiated cyclization of this kind has revealed a new type of cascade cyclization, which occurs under neutral reaction conditions, yet produces a stereochemical result consistent with cationic electrocyclization. In this communication, we describe the two reaction pathways available to dienyl diketones upon treatment with nucleophiles, and present a mechanistic rationale for the unusual reactivity observed.

A series of diketone substrates of type **4** were prepared for examination in the conjugate addition-initiated reaction. Substrates in which R1 = H were of particular interest, since conrotatory cyclization would install adjacent tertiary and all-carbon quaternary centers stereospecifically in these systems.

We found that conjugate addition-initiated Nazarov cyclization proceeded smoothly with pyrrolidine to give products of type **5** (Table 1, entries 1 and 3), and with dimethyl malonate to give products of type **6** (entries 2 and 4-7, and 9). Both triethylamine and DABCO (1,4-diazabicyclo[2.2.2]octane) could be used as the basic additive for the reaction of substrate **4b** (entries 3 and 4). As would be expected in an electrocyclic reaction, only a single diastereoisomer was observed in each case. These reactions occur at ambient temperature, employ inexpensive reagents and catalysts, and are neither air-nor moisture-sensitive.

In the case of dienyl diketone **4c**, a dramatic change in reaction outcome was observed when DABCO was used instead of Et₃N as the basic additive (Table 1, entry 8). None of the

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Supporting Information. Experimental procedure and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>

expected product **6c** was obtained; instead, a new type of cyclization cascade took place resulting in cyclopentenone **7** (74 % yield, Table 2). Strangely, no incorporation of the malonate nucleophile had occurred. This result is especially surprising in light of the entry 5 result, in which use of DABCO as the basic additive uneventfully produced malonate adduct **7b** (entry 4 vs. 5; Table 1).

When malonate was excluded from the reaction, the yield of product **7** improved to 92% (Table 2, entry 1). Further experimentation revealed that treatment of **4c** with Y(OTf)₃ and various amine bases also led to formation of **7** in good yield. While Et₃N facilitated the reaction to some extent (20% yield; entry 2), long reaction times and elevated temperatures were required. Nucleophilic bases such as DMAP, DBU and DABCO (entries 3 and 4) were found to be efficient promoters. Still, DABCO was the optimal promoter, and we were interested to find that when the Lewis acid was excluded, an even higher yield of **7** was obtained (entry 6, 97% yield). Furthermore, DABCO facilitated the reaction at catalytic levels (entries 7-9), operating with catalyst loading as low as 1 mol % (54 % yield). However, 10 mol % was found to be the optimal loading, both in terms of yield (96%) and reaction time (1 hour). The reaction was equally efficient when run open to air.

Once optimized conditions were identified, substrate scope was evaluated (Table 3). Acetate **4d** cyclized efficiently to produce cyclopentenone **8** in nearly quantitative yield (entry 2). Treatment of secondary acetates **4e** and **4f** gave **9** and **10**, respectively, as single diastereoisomers (entries 3 and 4). Figure 1 shows the key nOe correlations used to assign the stereochemistry of compound **9**. Acetate **4g** underwent cyclization to give cyclopentenone **11** in 84% yield (entry 5). For this experiment, elevated temperature was required to facilitate the reaction.

A mechanistic hypothesis consistent with the results shown in both Table 1 and Table 3 is presented in Scheme 2. In the absence of DABCO, 1,6-conjugate addition of either pyrrolidine or malonate leads to adducts **2** (Scheme 1), which undergo electrocyclization. In the presence of DABCO, 1,6-conjugate addition of DABCO^{4,5} to the dienyl diketone gives a zwitterionic DABCO adduct (see **12**, Scheme 2). We hypothesize that this species does not undergo 4 π electrocyclization, and if formed reversibly. Thus, when both malonate and DABCO are present, the malonate adduct **6b** is formed (Table 1, entry 5), and DABCO acts as a simple base. However, if the substrate has an acetate tether (like **4c-4g**, Table 3); another reaction pathway is available to DABCO adduct **12**. In these cases, we propose that the allylic quaternary ammonium moiety of **12** is displaced by the pendant acetate to produce cyclic zwitterion **13**, which contains a stereogenic center. The intramolecular S_N2 reaction is related to the anchimeric assistance acetates sometimes demonstrate during solvolysis,⁶ and glycosylation,⁷ but we could find only one example of a displacement reaction thought to proceed via a seven-membered acetoxonium intermediate.⁸ This stereocenter then controls the torquoselectivity of the subsequent electrocyclization, which produces spirocyclic zwitterions **14**. The ring stereochemistry is consistent with conrotatory closure, and analogous to the results of cyclization of the type **2** intermediate to cyclopentenones **5** and **6**. The cascade is concluded with intramolecular ether formation (Table 3). Remarkably, the proposal implies that seven, eight and nine-membered zwitterions **13** readily participate as intermediates in the cyclization cascades.

In conclusion, two different cyclization cascades can be carried out beginning with 1,6-conjugate addition to a dienyl diketone. One is Lewis acid-catalyzed, and involves incorporation of a nucleophile, producing highly substituted cyclopentenones containing a quaternary stereogenic center. The second is a novel, metal-free cascade catalyzed by 1,6-conjugate addition of DABCO, and involves three successive cyclizations: formation of a cyclic acetoxonium, putative 4 π electrocyclization, and opening of the acetoxonium to

form a cyclic ether. The stereochemical outcome of both reactions is consistent with conrotatory electrocyclization, even though the DABCO-catalyzed cyclization cascade must proceed via a zwitterionic rather than a cationic intermediate.⁹ The study of other varieties of conjugate addition-initiated cascade cyclizations is currently underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Key nOe correlations for compound **9**

Scheme 1.
Conjugate Addition-Initiated Nazarov Cyclization

Scheme 2.

Proposed Mechanism for 1,6-Conjugate Addition/Cyclization Cascades

Table 1Lewis Acid-catalyzed Conjugate Addition/Electrocyclization Cascade^a

entry	R ₁ =	nucleophile	base	yield (product; %)
1	4a , H	pyrrolidine	Et ₃ N	5a ; 87
2	4a , H	dimethylmalonate (DMM)	Et ₃ N	6a ; 83
3	4b , Me	pyrrolidine	Et ₃ N	5b ; 85
4	4b , Me	DMM	Et ₃ N	6b ; 78
5	4b , Me	DMM	DABCO ^b	6b ; 72
6	4c , (CH ₂) ₂ OAc	DMM	Et ₃ N	6c ; 89
7	4c	DMM	DABCO ^b	see Table 2
8	4d , (CH ₂) ₃ OAc	DMM	Et ₃ N	6d ; 87

Reaction Conditions:

^a diketone **4** added to a stirring solution of Y(OTf)₃ (1 mol %), LiCl (2 equiv.), base (1 equiv.), and the nucleophile in THF (1 M) at rt.^b DABCO = 1,4-diazabicyclo[2.2.2]octane

Table 2

Optimization of DABCO-Catalyzed Cyclization Cascade

entry	Lewis acid	base	catalyst loading (mol %)	yield (%)
1	Y(OTf) ₃	DABCO	100	92
2 ^b	Y(OTf) ₃	Et ₃ N	100	20
3 ^c	Y(OTf) ₃	DMAP	100	83
4	Y(OTf) ₃	DBU	100	64
5	Y(OTf) ₃	--	--	no reaction
6	--	DABCO	100	97
7	--	DABCO	10	96
8	--	DABCO	5	95
9 ^c	--	DABCO	1	54

^a All reactions run at 1 M concentration in THF at rt for 8 h, except when otherwise noted.^b Heating to 50 °C was required for the reaction to occur^c Reaction took 24 h to reach completion.

Table 3

Substrate Scope^{a,b}

entry	dienyl diketone	product	yield (%)
1			96%
2 ^c			98%
3 ^d			92%
4 ^e			91%
5 ^e			84%

^aReaction conditions: The diene was dissolved in THF (1 M) and DABCO (10 mol %) was added. The solution was stirred at rt until all starting material was consumed as judged by TLC.

^bReaction time was 1 h unless otherwise stated.

^cReaction time was 24 h.

^dReaction time was 8 h.

^eReaction was heated to 50 °C for 8 h.