A New Approach to the Nazarov Reaction via Sequential Electrocyclic Ring Opening and Ring Closure

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The Nazarov reaction, a well-established method for generation of new cyclopentenone rings from dienone precursors, has enjoyed considerable recent attention.[1] Particular focus has been placed on its use in tandem or domino processes,[2] catalytic approaches,[3] and strategies for stereocontrol in the electrocyclization step.[4] As typically practiced, the Nazarov reaction begins with a 1,4-dien-3-one, which is activated with protic or Lewis acid to form a pentadienyl cation. We are interested in alternative methods for generation of Nazarov-type pentadienyl systems which may permit novel trapping pathways or greater functional group compatibility. Here we describe a novel Nazarov process in which 2-chloro-3-silyloxypentadienyl cations capable of electrocyclization are generated from readily available dichlorocyclopropane precursors.

Dihalocyclopropanes are known to undergo 2π disrotatory electrocyclic opening under thermal conditions or treatment with silver(I).[5] The resulting 2-chloroallyl cations can be trapped by halide or solvent, aromatic compounds,[6] or internal nucleophiles.[7] We envisioned a variation of this process as a potential complementary method for accessing the Nazarov intermediate: if ring-opening chemistry could be carried out on alkenyl-substituted dihalocyclopropanes 1, pentadienyl cations 2 potentially capable of undergoing 4π electrocyclization would result (Scheme 1). Simple dihalogenated vinylcyclopropanes undergo thermal rearrangement to dihalocyclopentenes;[8] however, these may occur via a homolytic pathway. To the best of our knowledge, the corresponding cationic process is unknown.[9]

Computations have shown that the presence of an alkenyl substituent on C-2 of a 1,1-dihalocyclopropane should increase the rate of electrocyclic opening relative to hydrogen.[10] The presence of an oxygen-containing group on the same carbon (Y = OR) should also accelerate ring opening and would furnish a pentadienyl cation quite analogous to the Nazarov intermediate formed from 1,4-dien-3-ones.[11] Silyl ethers were chosen for initial investigation, as the cyclization products 4 would be expected to undergo facile desilylation to the corresponding cyclopentenone. Thus, cyclopropanes 6 were prepared via dichlorocyclopropanation of the readily available 2-triisopropylsilyloxydienes[12] 5 under phase-transfer conditions[13] (Table 1). Cyclopropanation reactions generally occurred in high yield, especially in the case of disubstituted silyl enol ethers (entries 1−5). Silyloxydiene 5f did not react cleanly under phase-transfer conditions and underwent direct conversion to chlorodienone 7f when treated with potassium *t*-butoxide in chloroform (entry 6). Although the anticipated dichlorocyclopropane 6f is the likely precursor of 7f, none of this material was isolated. Use of more labile silyl ethers (e.g., triethylsilyl) also led to the unwanted formation of dienones 7 during purification or the subsequent ring-opening step.

With cyclopropanes 6a−e and 6g,h in hand, the possibility of effecting Nazarov cyclization by sequential electrocyclic ring opening and closure could now be examined.[14] Dihalocyclopropanes can be ionized thermally or with various Lewis acids, especially
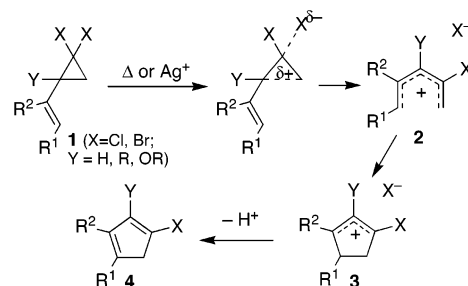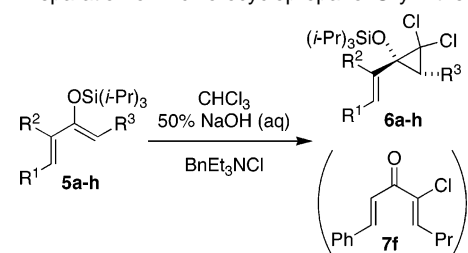
Scheme 1

*Table 1.* Preparation of Dichlorocyclopropanol Silyl Ethers 6[a]

entry	diene[b]	R¹	R²	R³	product	yield (%)[c]
1	5a	H	H	H	6a	93
2	5b	(CH₃)₂CH	H	H	6b	95
3	5c	Ph	Me	H	6c	90
4	5d	(CH₂)₄		H	6d	91
5	5e	(CH₂)₃		H	6e	92
6	5f	Ph	H	Pr	7f	55[d]
7	5g	Ph	Me	Pr	6g	87
8	5h	Ph(CH₂)₂	H	H	6h	71

[a] Silyloxydienes 5 were dissolved in CHCl₃ (0.12 M) with benzyltriethylammonium chloride (20 mol %), and the resulting solution was stirred vigorously at room temperature with 50% aqueous NaOH (190 equiv) until 5 was deemed consumed (TLC). [b] See Supporting Information for preparation of dienes 5. [c] All yields are based on isolated product after chromatography. [d] *t*-BuOK/CHCl₃ used in place of PTC conditions.

halophilic silver(I) ion. Using 6a and 6c as test cases, a variety of conditions were surveyed. Heating 6a in acetonitrile caused efficient conversion to chlorodienone 7a (analogous to 7f) as did stirring with AgBF₄ in trifluoroethanol (TFE), while in CH₂Cl₂, it was converted to a complex mixture containing 9a. The more highly substituted 6c was subjected to several silver(I) salts (AgOTf, AgO₂CCF₃, AgBF₄) and other Lewis acids (AlCl₃, Et₂AlCl) in a variety of solvents, and it was found that AgBF₄ in CH₂Cl₂ gave the optimal conversion to the desired Nazarov cyclization product 8c. The other substrates 6a,b,d,e,g,h were then subjected to the same conditions (Table 2), with varying outcomes.

As noted above, 6a furnished 9a as part of a mixture that was not amenable to chromatographic purification. The presence of additional substituents on either the alkenyl moiety or the cyclopropane (entries 2−6) permitted clean conversion to the desired

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Table 2. AgBF$_4$-Mediated Rearrangement of Cyclopropanes **6**^{a}
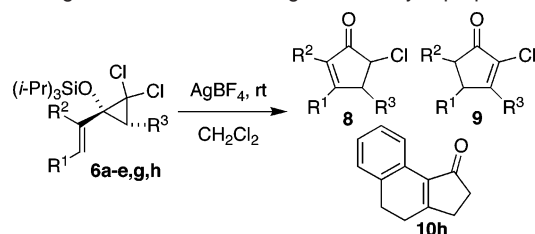
entry	substrate	R^1	R^2	R^3	products	yield (%)^b
1	**6a**	H	H	H	**9a**	c
2	**6b**	(CH$_3$)$_2$CH	H	H	**8b + 9b**	57^d
3	**6c**	Ph	Me	H	**8c**	70
4	**6d**	(CH$_2$)$_4$		H	**8d**	45
5	**6e**	(CH$_2$)$_3$		H	**8e**	74
6	**6g**	Ph	Me	Pr	**8g + 9g**	87^e
7	**6h**	Ph(CH$_2$)$_2$	H	H	**10h**	63^f

^{a} Cyclopropanes **6** were dissolved in CH$_2$Cl$_2$ or TFE (0.05 M) and stirred with AgBF$_4$ (1.5 equiv) at room temperature until complete consumption of starting material was observed (TLC). ^{b} Yields are based on isolated product after chromatography. ^{c} Compound **9a** was present in the crude reaction mixture, but decomposed during attempted chromatographic purification (silica or alumina). ^{d} Compounds **8b** and **9b** were isolated in a 1.7:1 ratio. Minor amounts of a dione resulting from trapping by adventitious water were also obtained (see Supporting Information). ^{e} All four possible regio- and stereoisomers were formed in the ratio 7.7:4.5:3:1 (**8g**(*cis*):**9g**(*cis*): **8g**(*trans*):**9g**(*trans*)). ^{f} The simple Nazarov cyclization product **8h** was not isolated.

cyclopentenones **8** or **9**.[15] In those cases lacking an additional alkyl substituent on the cyclopropane ring (entries 2−5), complete regioselectivity in the elimination step was seen in favor of the more substituted alkene product, except in the case of **6b**. This result contrasts with previous examples of fluorine-directed Nazarov cyclizations, in which preferential formation of an alkenyl fluoride was seen.[16] The presence of an additional alkyl group on the cyclopropane (entry 6) led to a mixture of regioisomers **8g** and **9g**, in each case as a pair of diastereomers.

The behavior of phenethyl-substituted substrate **6h** (entry 7) is especially notable. In this case, none of the expected cyclopentenone **8h** was isolated. Instead, tricyclic product **10h** was obtained in good yield. This product is assumed to form via electrophilic aromatic substitution involving the 2-silyloxycyclopentenyl cation formed upon electrocyclization. Such a pathway is precedented,[17] but the participation of a simple phenyl group is striking. Previous examples of the arene-terminated interrupted Nazarov reaction required the presence of at least one electron-donating substituent on the aromatic trap. The eventual formation of the tetrasubstituted alkene presumably arises via elimination of HCl and C=C migration.

We have described the first examples of an apparent sequential 2π electrocyclic opening/4π electrocyclic closure using alkenyldichlorocyclopropanes as pentadienyl cation precursors. The substrates are readily available via cyclopropanation of 2-silyloxydienes, and the process appears to be general. In one case possessing a remote aryl group, efficient interrupted Nazarov cyclization to a tricyclic product was seen. Further studies of this process are underway and will be disclosed in due course.

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Supporting Information Available: Experimental procedures and spectral data for cyclopropanes **6** and their rearrangement products. This material is available free of charge via the Internet at http://pubs.acs.org.

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