

Silver-Promoted Reactions of  
Bicyclo[3.2.1]octadiene Derivatives

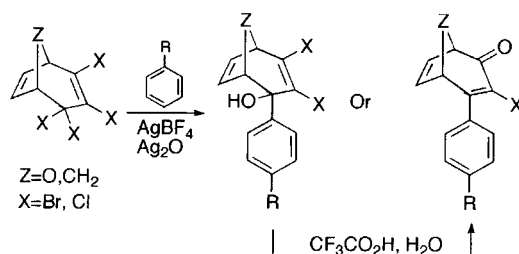
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## ABSTRACT



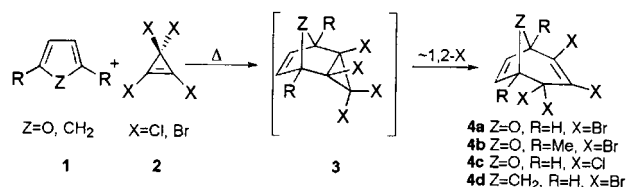
Highly substituted bicyclo[3.2.1]octadiene building blocks are easily prepared from tetrachloro- or tetrabromocyclopropene through reaction with cyclic dienes. These polyhalogenated derivatives can serve as precursors to a variety of functionalized bridged bicyclic compounds. Herein, we report on the generation and reaction of electrophilic species with silver ion.

It has long been recognized that bridged bicyclic compounds can serve as key synthetic building blocks because of the diversity of structures available from these intermediates.<sup>1</sup> We have been interested in the use of the bicyclo[3.2.1]octene nucleus as a precursor to various carbocyclic<sup>2</sup> and heterocyclic<sup>3</sup> ring systems through cleavage of one of the three unique bridges. Typically, these types of bicyclic molecules are constructed by the reaction of cyclic dienes with oxyallyl cation equivalents generated by decomposition of halogenated ketones.<sup>4</sup>

However, it has also been known for some time that tetrahalocyclopropenes can be directly converted to a series of analogous bicyclo[3.2.1]octadiene derivatives by reaction with various dienes. Tobey and West<sup>5</sup> first reported in 1966 that both tetrachloro- and tetrabromocyclopropene **2** were

extremely reactive dienophiles and underwent Diels–Alder reaction with furan and cyclopentadiene under thermal conditions (Scheme 1).

Scheme 1. Synthesis of Bicyclo[3.2.1]octadienes



Interestingly, the primary cycloadduct **3**, containing a cyclopropane fused onto a bicyclo[2.2.1]heptene system, was not observed in the reaction. Instead, the initial cycloadduct had spontaneously rearranged through migration of a halide ion to give halogenated bicyclo[3.2.1]octadiene derivative **4**. In contrast to mechanistic studies,<sup>6</sup> little effort has been

† To whom questions regarding X-ray structure should be addressed.

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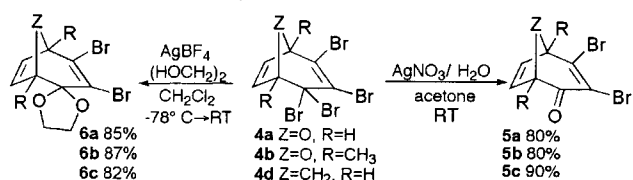
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extended to studying the synthetic potential of these highly functionalized bicyclic adducts. From a synthetic perspective, these are interesting derivatives that possess a seven-membered carbocyclic ring that is functionalized at every position. Herein, we wish to report our studies on functionalization of some of these derivatives through reactions promoted by the use of silver ion.

Although there have been few studies on chemical transformations of the halogenated cycloadducts, Tobey and Law were able to show that the tetrachloro adducts could be hydrolyzed to the 1,3-diketone in fair yield by treatment with strong acid.<sup>7</sup> In an attempt to find more mild hydrolytic conditions, silver-promoted<sup>8</sup> ionization of the allylic halides was examined (Scheme 2). Treatment of the tetrabromo

**Scheme 2.** Synthesis of Ketones and Ketals



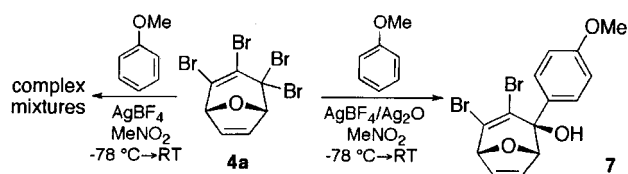
adduct of furan **4a** with an aqueous solution of silver nitrate lead to rapid hydrolysis of the geminal dibromide group to produce the ketone **5a** in very good yield. This type of hydrolysis worked equally well on the adduct of 2,5-dimethylfuran **4b** and cyclopentadiene **4d** to give the highly versatile dibromo enone moiety.

It was also possible to employ a diol in the reaction to directly produce the protected form of the dibromo enone (Scheme 2). To avoid competitive hydrolysis, anhydrous silver tetrafluoroborate in dichloromethane was required. Under these conditions, the corresponding dioxolanes **6a–c** were produced in high yields. The use of Lewis acid to promote conversion of a carbon–bromine bond to a carbon–oxygen bond prompted us to examine if a similar process could be used to effect the formation of carbon–carbon bonds.

Initial attempts to promote arylation of the furan-derived bromide **4a** were unsuccessful with a variety of Lewis acid catalysts. Treatment of an anisole solution of **4a** with highly reactive catalysts such as aluminum chloride or titanium tetrachloride led to extensive decomposition of the materials, while milder Lewis acids such as boron trifluoride etherate failed to promote any reaction. The facility of the silver-promoted hydrolysis of the bromides suggested that silver salts<sup>9</sup> may also be used to promote the arylation reaction (Scheme 3).

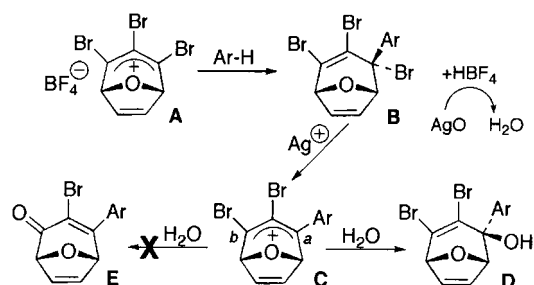
Attempts to effect arylation with silver tetrafluoroborate and a large excess of anisole were sluggish and produced a

**Scheme 3.** Silver-Promoted Arylation



complex mixture of products.<sup>10</sup> One conceivable complication was that the initial product of the arylation contains a more reactive allylic bromide than the starting compound. This halide would be susceptible to further ionization and subsequent reaction of the cation. We were also concerned that the reaction became highly acidic, which could promote alternative reactions. In an attempt to provide an acid scavenger, an equivalent of silver oxide was added to the reaction mixture. Under these conditions, a monoarylated product was isolated in very high yield, and its structure was determined to be the tertiary carbinol **7**. The compound was formed with a very high preference for the para isomer with only minor amounts of the ortho product detected in the crude NMR. A possible pathway to arrive at the adduct involves initial formation of the allylic cation **A** upon treatment with silver (Scheme 4).

**Scheme 4.** Possible Mechanism for Arylation



Attack of anisole on the symmetrical cation should initially give **B**<sup>11–12</sup> and an equivalent of tetrafluoroboric acid that is neutralized by silver oxide. Bromide **B** is poised for a second ionization to give the highly stabilized cation **C**. Water, generated from silver oxide, can intercept this nonsymmetrical allylic cation at position *a* to give *exo*-alcohol **D** or at *b* to give **E** after collapse of the initially formed bromohydrin. Although **E** would appear to be the most stable adduct, the addition of water was completely selective for formation of the benzylic alcohol. This preference may reflect a greater localization of the cationic charge at this position. With an efficient set of reaction conditions determined, a study of the arylation reaction was undertaken with several different aromatic nucleophiles (Table 1).

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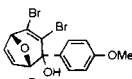
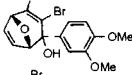
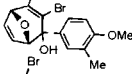
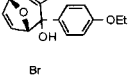
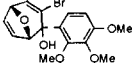
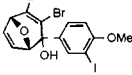
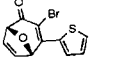
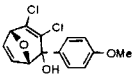
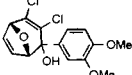
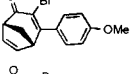
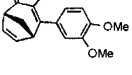
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(10) GC-MS and crude NMR data indicated that the products of the reaction contained multiple aryl rings and a cleaved oxo-bridge.

(11) Compound **B** has not been observed in any of the reactions.

(12) AM1 calculations indicate that the *exo* and *endo* adducts from anisole only differ by 0.88 kcal/mol in favor of the *exo* arene.

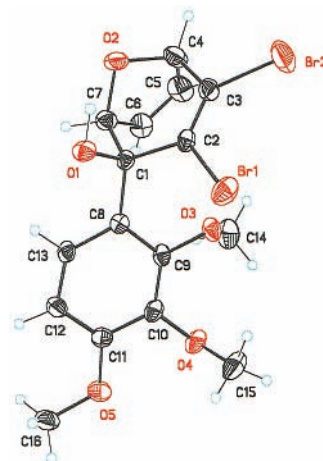
**Table 1.** Silver-Promoted Arylation Reactions

halide	arene <sup>a</sup>	product	yield <sup>b</sup>
<b>4a</b>	benzene	<b>5a</b>	N/A <sup>c</sup>
<b>4a</b>	toluene	<b>5a</b>	N/A <sup>c</sup>
<b>4a</b>	anisole	 <b>7</b>	87%
<b>4a</b>	veratrol	 <b>8</b>	75%
<b>4a</b>	2-methyl anisole	 <b>9</b>	70%
<b>4a</b>	anethole	 <b>10</b>	76%
<b>4a</b>	1,2,3-trimethoxy benzene	 <b>11</b>	82%
<b>4a</b>	<i>o</i> -iodoanisole	 <b>12<sup>d</sup></b>	32%
<b>4a</b>	thiophene	 <b>13<sup>e</sup></b>	79%
<b>4c</b>	anisole	 <b>14</b>	68%
<b>4c</b>	veratrol	 <b>15</b>	64%
<b>4d</b>	anisole	 <b>16</b>	77%
<b>4d</b>	veratrol	 <b>17</b>	67%

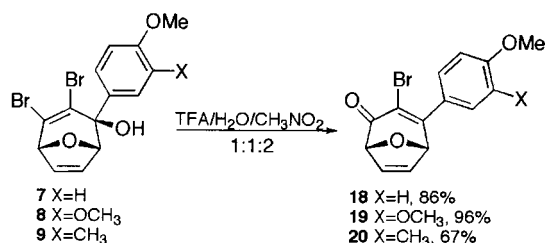
<sup>a</sup> Reaction conditions: 4 equiv of arene, 2 equiv of AgBF<sub>4</sub>, 2 equiv of Ag<sub>2</sub>O, MeNO<sub>2</sub>, -78° C → rt. <sup>b</sup> Isolated yields after chromatography. <sup>c</sup> Ketone **5a** formed in ~90% yield. <sup>d</sup> **5a** isolated in 65% yield. <sup>e</sup> Alcohol observed in crude mixture but converted to **13** upon silica gel chromatography.

When the reaction was attempted with less nucleophilic arenes such as benzene or toluene, the only product isolated was the bicyclic enone **5a**. It is proposed that this product arises from a competitive attack on the initially generated cation by adventitious water to produce the bromohydrin, which converts to the ketone with loss of acid. The equivalent of hydrobromic acid generated produces additional water upon reaction with silver oxide. The general trend observed showed that, with electron-rich aromatics such as veratrole, 2-methylanisole, anethole, and 1,2,3-trimethoxybenzene, the reaction proceeded in good yield to produce alcohols **7–11**. Less electron-rich arenes such as *o*-iodoanisole also produced the alcohol but accompanied by significant amounts of ketone **5a**. The tetrachloro cycloadduct **4c** was also sufficiently reactive and was converted to the tertiary carbinols **14** and **15** upon treatment with the silver salts and anisole or veratrole, respectively. The structure of the trimethoxyphenyl

adduct and *endo* orientation of the aromatic ring was confirmed through an X-ray structures analysis of alcohol **11** (Figure 1).

**Figure 1.** X-ray structure of alcohol **11**.

In all these cases, the only products observed were the tertiary alcohols, arising from capture of water at the benzylic position of the cation. However, in the case of thiophene a different level of activity was observed. Initially, in the crude reaction product, the analogous alcohol was observed. However, upon exposure to silica gel the adduct underwent spontaneous and complete rearrangement to the enone **13**. This facile rearrangement may reflect the greater ability of thiophene to stabilize the cation, thus making the addition of water more reversible and allowing equilibration to the more stable enone. Interestingly, when the carbon bridged adduct **4d** was treated under the arylation conditions, the only products observed were the ketones **16** and **17**. This may also reflect the ease of cation regeneration whereby the electron-withdrawing oxabridge destabilizes the cation while the methylene bridge does not, thereby allowing the equilibration to occur. These observations suggested that if conditions could be found that promoted reionization of the hydroxyl group, it may be possible to convert the alcohol adducts to the corresponding ketones. To examine this possibility, three of the alcohol adducts were exposed to acidic conditions (Scheme 5).

**Scheme 5.** Acid-Catalyzed Enone Formation

Treatment of alcohols **7–9** with a mixture of trifluoroacetic acid and water with nitromethane as a cosolvent promoted the complete conversion to the corresponding  $\beta$ -aryl enones **18–20** in high yield.

The reaction of tetrabromo- and tetrachlorocyclopropene with cyclic dienes provides a direct method for the synthesis of highly functionalized bicyclo[3.2.1]octadiene derivatives. These highly functionalized intermediates should prove useful for the synthesis of substituted cycloheptenes and should be a complimentary method with the traditional oxyallyl cation cycloaddition. It has been shown that the halogens positioned on the three-carbon bridge can be used to initiate the formation of cations. These reactive intermediates readily add oxygen and carbon based nucleophiles to

give novel bridged bicyclic compounds. Further studies on the reactions of these derivatives and applications to synthesis are ongoing.

**Acknowledgment.** The authors would like to thank the National Science Foundation and the University of Florida for partial support of this work. Dr. Ion Ghiviriga is thanked for assistance with NMR spectra.

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

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