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Synthesis of 1,4-Naphthoquinone Methides via Acid-Catalyzed Cascade Cyclizations of Benzannulated Enediynyl Alcohols

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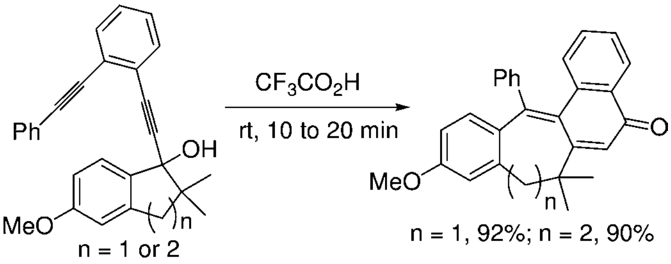
ABSTRACT



Treatment of benzannulated enediynyl alcohols with trifluoroacetic acid at room temperature promoted a cascade sequence of cyclization reactions, leading to 1,4-naphthoquinone methides. The transformation involved an unusual two-carbon ring expansion from the cyclic alcohols and the construction of the *p*-quinone methide ring from an acyclic system along the reaction pathway.

p-Quinone methides are reactive compounds implicated in many chemical and biological processes.[1] They have also found useful applications in a variety of areas, including serving as cationic dyes and pH-sensitive indicators.[2] For *p*-benzoquinone methides without substituents on the exocyclic methylene group, the molecules are often too reactive to be isolated in pure form. On the other hand, a large number of α,α-diarylmethylene-substituted *p*-benzoquinones have been isolated.[3] Similarly, the diaryl-substituted 1,4-naphthoquinone methides are relatively stable and can be isolated.[4] Several synthetic methods for the diaryl-substituted *p*-quinone methides have been developed. Most of the methods involved the preparation of triarylmethyl precursors for subsequent transformations.[1] The use of the Wittig reactions for condensations with *p*-benzoquinones[5] and 1,4-naphthoquinones[6] has also been reported. In our investigations of the cascade cyclization reactions of benzannulated enediynyl alcohols,[7] a serendipitous discovery led to the development

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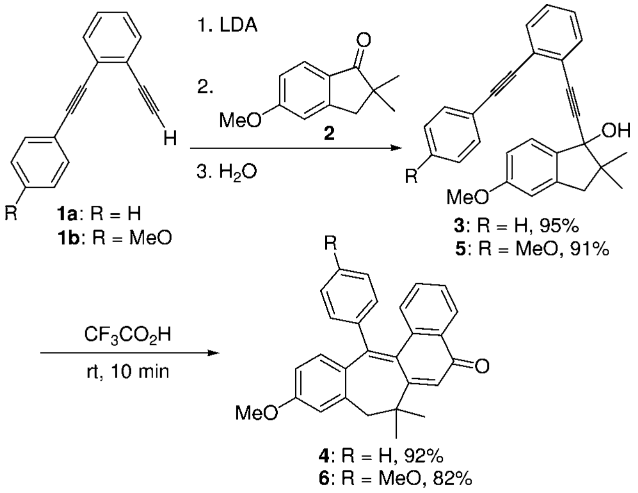
of a new synthetic pathway to 1,4-naphthoquinone methides bearing two aryl substituents at the exocyclic methylene group under a mild acidic condition at room temperature.

Treatment of the benzannulated enediyne **1a** with lithium diisopropylamide (LDA) to form the corresponding lithium acetylide followed by condensation with 1-indanone **2** produced the benzannulated enediynyl alcohol **3** after aqueous workup (Scheme 1). On exposure to trifluoroacetic acid at room temperature for 10 min, **3** was smoothly transformed to 1,4-naphthoquinone methide **4** in 92% isolated yield. Similarly, **6** was obtained from **1b** and **2**. Several other examples of using different combinations of benzannulated enediynes and aryl ketones to form 1,4-naphthoquinone methides are shown in Figure 1. The transformations from **8** to **9** and from **11** to **12** occurred within 20 min at room temperature. In the cases of **15** and **18**, the reaction mixtures were stirred at room temperature for 60 min. The transformation to 1,4-naphthoquinone methides by this method is particularly efficient for cyclic aromatic ketones bearing a methoxyl group at the position para to the keto group and involves an unusual two-carbon ring expansion. It is also worth noting that unlike other reported methods, this new synthetic pathway involves the formation of the *p*-quinone methide ring system from an acyclic precursor.

Scheme 1



Using the transformation from **3** to **4** as an example, a proposed reaction mechanism is outlined in Scheme 2. The acid-catalyzed transformation of the propargylic alcohol moiety in **3** through cationic intermediates **3a** and **3b** could produce the α,β-unsaturated ketone system in **3c**. A subsequent carbon−carbon bond formation between one of the acetylenic carbons and the β-carbon of the enone system to form a new six-membered ring could lead to **3d**. The carbocationic center in **3d** could be captured by an electron-rich π bond of the methoxyl-substituted benzene system to form **3e** having a strained cyclobutenyl ring. A subsequent carbon−carbon bond cleavage with the relief of the ring strain could then lead to 1,4-naphthoquinone methide **4** with an unusual two-carbon ring expansion.

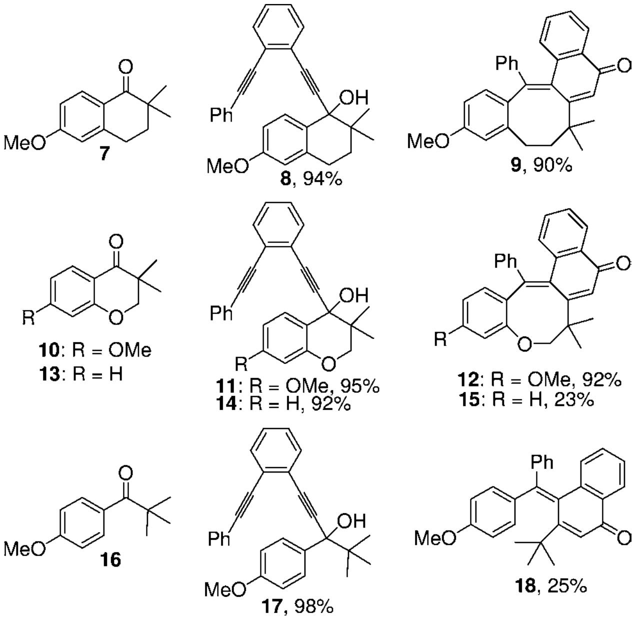
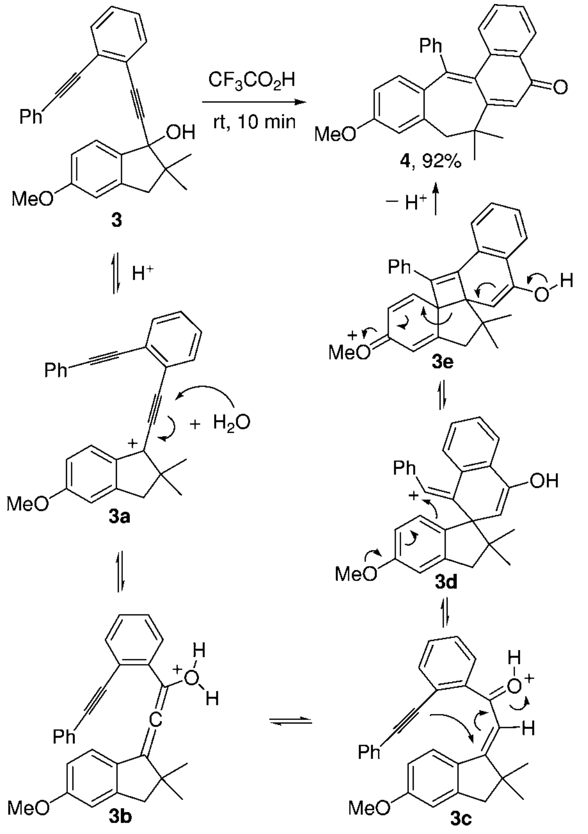


Figure 1. Structures of aryl ketones, benzannulated enediynyl alcohols, and 1,4-naphthoquinone methides.

Scheme 2



The proposed reaction mechanism is supported by the observation that on exposure to trifluoroacetic acid, the benzannulated enediynyl alcohol **19** produced the α,β-

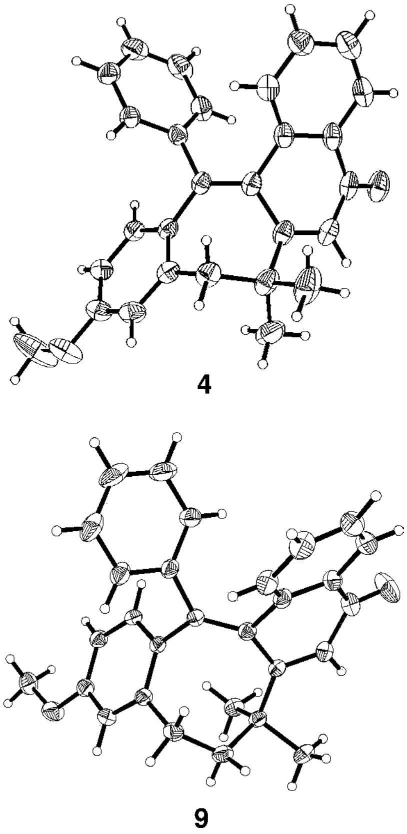
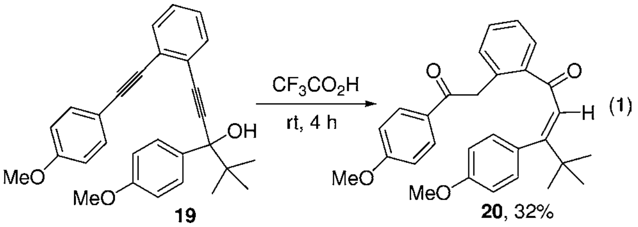


Figure 2. ORTEP drawings of the crystal structures of **4** and **9**.

unsaturated ketone **20** with the second acetylenic group being hydrated to form a keto group (eq 1). Apparently, in this case the rate of hydration of the second acetylenic group bearing a 4-methoxyphenyl substituent is faster than that of attacking the β-carbon of the enone system as shown in **3c**. The presence of a methoxyl group in **3** is crucial to the success of the reaction. Without the methoxyl group, a complex mixture of products was observed. Presumably, the presence of a *p*-methoxyl group in **3a** further stabilizes this carbocationic species and may also facilitate the capture of the carbocationic center in **3d**. In addition, without the α,α-dimethyl group in **3** simple dehydration occurred to form an indene derivative.



The X-ray crystal structures of **4** and **9** indicate that the phenyl substituents are oriented essentially perpendicular to the exocyclic carbon−carbon double bond of the *p*-quinone methide system (Figure 2). In the case of **9**, the eight-membered ring adopts a tub-like conformation, causing the benzene ring of the *p*-methoxyphenyl group also to orient essentially perpendicular to the exocyclic carbon−carbon double bond. For **4**, the ^{1}H NMR signals of the aliphatic *gem*-dimethyl and methylene hydrogens and the aromatic hydrogens on the phenyl substituent are broad at room temperature, indicating a relatively slow rate of ring inversion of the 7-membered ring and a slow rate of rotation of the phenyl substituent on the NMR time scales. At −40 °C, however, two singlets from the *gem*-dimethyl group and a distinct AB coupling pattern of the methylene hydrogens could be clearly discerned. A similar dynamic NMR phenomenon was also observed for **9**. In addition, the tub-like conformation of the eight-membered ring in **9** causes one of the methyls of the *gem*-dimethyl group to be located in the magnetically shielding region of the *p*-methoxyphenyl group. As a result, its ^{1}H NMR signal exhibits a significant upfield shift, appearing at $\delta = 0.43$.

The UV−vis absorption spectra of **4** and **9**, recorded in CH_3CN (5.0×10^{-5} M), reveal absorption bands in the visible region with maxima at 397 and 402 nm, respectively (Figure 3). This is similar to what was observed for the 1,4-naphthoquinone methide having two phenyl substituents on the exocyclic methylene group, which exhibits an absorption maximum at 400 nm.[4] Bathochromic shifts were observed for **6** ($\lambda_{max} = 410$ nm) bearing an additional *p*-methoxyl substituent and **12** ($\lambda_{max} = 413$ nm) having an additional *O*-alkoxyl substituent. On exposure of **4** to increasing concentration of sulfuric acid, an absorption band with maximum at 559 nm emerges with increasing intensity, which is attributable to the formation of the corresponding triarylmethyl cation (Figure 4).[8] Similar absorption bands were observed for **6** ($\lambda_{max} = 570$ nm), **9** ($\lambda_{max} = 615$ nm), and **12** ($\lambda_{max} = 609$ nm) on exposure to sulfuric acid with pronounced bathochromic shifts for the cases of **9** and **12** bearing an eight-membered ring (Figure 5). As a result, the

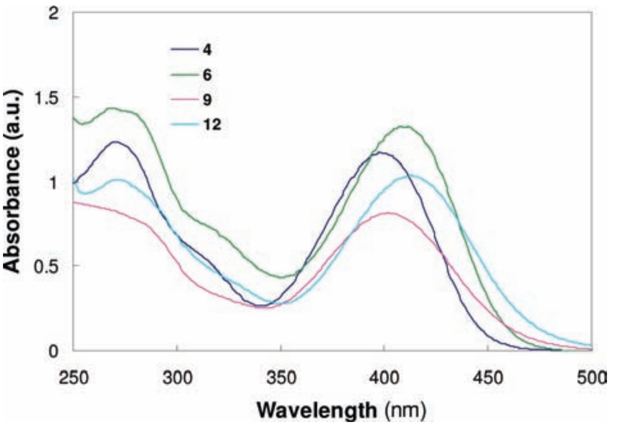


Figure 3. UV−vis absorption spectra of **4**, **6**, **9**, and **12** (5.0×10^{-5} M) in CH_3CN.

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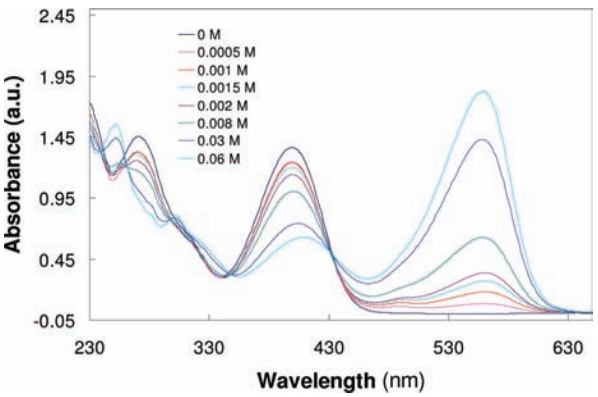

Figure 4. UV−vis absorption spectra of **4** (5.0×10^{-5} M) in CH_3CN with varying H_2SO_4 concentration.

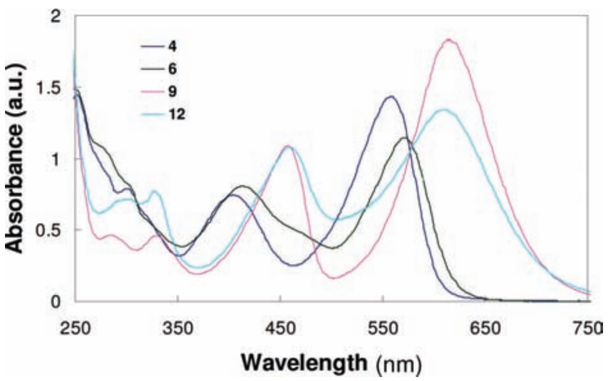

Figure 5. UV−vis absorption spectra of **4**, **6**, **9**, and **12** in CH_3CN containing sulfuric acid.

color of the solution turns red in the cases of **4** and **6** and turns green in the cases of **9** and **12**.[2c]

In conclusion, a new acid-catalyzed cascade cyclization pathway to transform benzannulated enediynyl alcohols to 1,4-naphthoquinone methides was discovered. For cyclic alcohols, the transformation involved an unusual two-carbon ring expansion. In addition, the *p*-quinone methide ring system was constructed from an acyclic precursor. Compared to the Schmittel cyclization reaction of the enyne-allene systems, derived from benzannulated enediynyl alcohols, leading to benzofluorenyl systems via biradical intermediates,[7,9] the current process proceeds through cationic intermediates, leading to 1,4-naphthoquinone methides.

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Supporting Information Available: All experimental procedures, NMR spectra, MS, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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