Convenient Access to Hydroquinone and Quinone Derivatives from Cyclobutenedione Units

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An important synthetic method providing access to a variety of heterocyclic and polycyclic quinones and hydroquinones is described. The key transformation involves the thermal ring expansion of cyclobutenedione derivatives to quinone/hydroquinone units. The synthetic utility and recent applications of this method in natural product synthesis are also discussed.

Introduction

Thirty years ago, cyclobutenediones were only studied as theoretically interesting molecules without much thought towards their potential use in building complex structures.^[1–3] Late in the 1980s, these compounds started to find their way into synthetic organic chemistry via their conversion to highly functionalized benzoquinones and cyclopentenones.^[1] During the studies of unsaturated ketenes,^[4,5] Moore and coworkers discovered one of the most important uses of

cyclobutenediones while carrying out the thermolysis of 4-alkynyl-4-hydroxycyclobutenones. These compounds were able to undergo 4π-electrocyclic ring opening to the corresponding enynylketenes, which subsequently ring close to form diradical intermediates. These intermediates then rearrange to form quinone or hydroquinone derivatives via either radical addition or homolytic substitution, offering a convenient synthetic method to access polycyclic compounds containing quinone/hydroquinone moieties from cyclobutenediones.^[4–20]

Thermal Ring Expansion of 4-Alkynyl-4-Hydroxycyclobutenones

In preliminary versions of this transformation,^[4,5] simple 4-alkynyl-4-hydroxycyclobutenones were converted to quinone derivatives (Scheme 1). First, the readily available cyclobutenediones^[1,21–23] **1** were transformed into 4-alkynyl-4-hydroxycyclobutenones **2** by straightforward nucleophilic addition to one of the carbonyl groups.^[6–9,12–16,18] **2** were then heated with or without transition metal catalysts to perform a ring expansion-cyclization to produce the highly functionalized quinones **5**,^[4,5] which could be easily reduced to give hydroquinone derivatives. This process was later proved to be a cascade reaction involving several highly reactive intermediates: the conjugated ketene **3** and the benzenoid diradical **4** (Scheme 1).^[6–19]

Scheme 1. Quinone derivatives from cyclobutenediones.

Modifications for Enhanced Synthetic Utility

Exploiting the radical character of this cascade reaction, many improvements have been made to develop the synthetic value for this type of transformation.^[7–20] The most obvious and prevalent method is to attach radical acceptors at suitable positions on the precursor molecule in order to get a further radical cyclization to occur.^[8,10,11,13,14,18,20] (a and b, Scheme 2). Another simple yet useful method is to replace the original alkynyl group with an unsaturated cyclic or heterocyclic fragment^[7,9,12,15–17,19] (c, Scheme 2). Both of these lead to convenient syntheses of polycyclic and heterocyclic compounds containing quinone/hydroquinone moieties (Scheme 2).

Scheme 2. Polycyclic and heterocyclic compounds from cyclobutenediones.

Recent Applications

The thermal ring expansion of substituted cyclobutenones to quinone and hydroquinone derivatives has recently been employed in numerous syntheses of natural products and bioactive compounds.^[7,8,12,14,18,24,25] Alkaloids assoanine^[14] and cribrastatin **6**^[24] along with diterpenes (–)-colombiasin **A**^[25] and (–)-elisapterosin **B**^[25] (Scheme 3) are selected examples of a potentially broad class of such naturally occurring compounds that could be prepared by this method. This effective and convenient transformation, termed Moore rearrangement, will be among the first choices for future synthetic strategies of biologically valuable organic compounds containing quinone/hydroquinone moieties.^[26,27]

Scheme 3. Examples of natural products synthesized using the Moore rearrangement.

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