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Cyclobutenediones as Precursors to Quinones and Cyclopentenones

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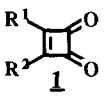
Introduction

For many years, cyclobutenediones **1** and benzocyclobutenediones **2** were studied as theoretically interesting molecules without any obvious potential for use in the intentional design of complex organic molecules.[2] Within the last 10 years this situation has begun to change. A variety of simple, yet powerful, methods have been developed that allow the conversion of cyclobutenediones and benzocyclobutenediones into highly functionalized quinones and cyclopentenone derivatives (Scheme 1). This article will highlight the synthetic potential of some of these recent reactions, and demonstrate that substituted cyclobutenediones are readily available starting materials.



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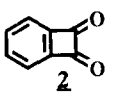

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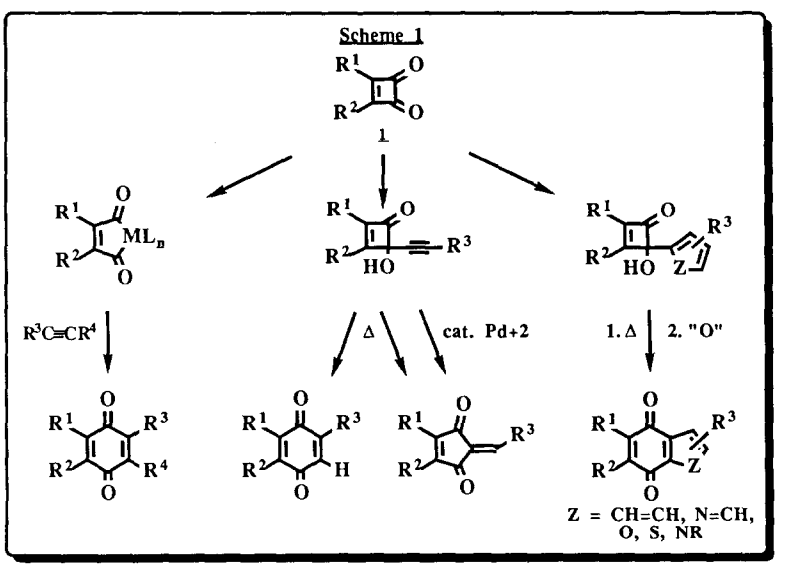
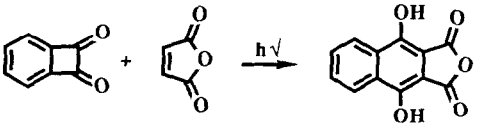


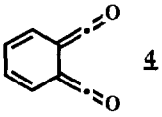
Discussion

Although Staab and Ipaktschi showed that benzocyclobutenedione and maleic anhydride upon irradiation would undergo a Diels-Alder reaction to afford the adduct **3** in good yield (eq. 1), attempts by these workers and others to extend this chemistry to other olefinic and acetylenic substrates led to very low yields of Diels-Alder adducts or gave alternative products.[3] This interesting reaction is presumed to proceed via a bisketene **4** generated by photolysis of the benzocyclobutenedione.



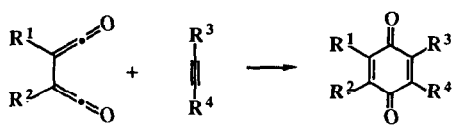
(eq. 1)

3

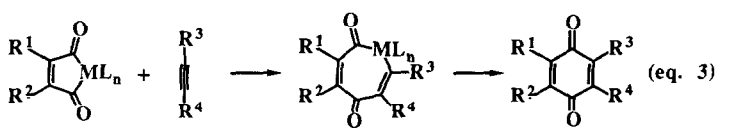


4

The concept of quinone synthesis by the [4 + 2] reaction of a bisketene with an alkyne would represent a very powerful synthetic entry to substituted quinones, if a general and high-yielding method could be found to join the reactants or their synthetic equivalents (eq. 2). The reaction of transition metal complexes of general structure **5** with alkynes by an insertion-elimination sequence was studied in our laboratories as a synthetic equivalent of the bisketene–alkyne approach to quinone synthesis (eq. 3).[4] Although a variety of different metallic species were investigated, cobalt complexes proved most useful for the synthesis of quinones. These compounds were readily available by the reaction of the low-valent cobalt reagent, $ClCo(PPh_3)_3$, with either benzocyclobutenediones or cyclobutenediones to form *phthaloyl*cobalt and *maleoyl*cobalt complexes such as **6** and **7**, respectively (eqns 4 and 5). Subsequent treatment of the bistriphenylphosphine species with one equivalent of dimethylglyoxime (dmg) in pyridine provided a high yield route to the dimethylglyoxime variants **8** and **9**. From the *phthaloyl*cobalt complex **8**, naphthoquinones such as those shown in Table 1 were prepared in high isolated yields simply by heating to 80°C in the presence of an alkyne and a mild Lewis acid such as $CoCl_2 \cdot 6H_2O$. Similar reactions in the benzoquinone series were explored by investigating the reaction of *maleoyl*cobalt complex **9** with unsymmetrical alkynes, and this chemistry demonstrated the high benzoquinone regioselectivity obtainable on reaction of an unsymmetrical alkyne with an unsymmetrical maleoylcobalt complex (Table 2). In order to maximize the regioselectivity in the benzoquinone synthesis most reactions were performed at room temperature in dichloroethane. Effective reaction rates were only achieved at room temperature in the presence of a strong Lewis acid such as $SnCl_4$ or $Zn(OSO_2CF_3)_2$.

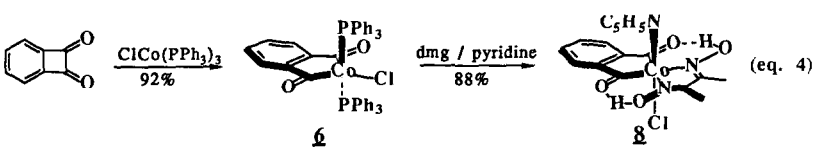


(eq. 2)



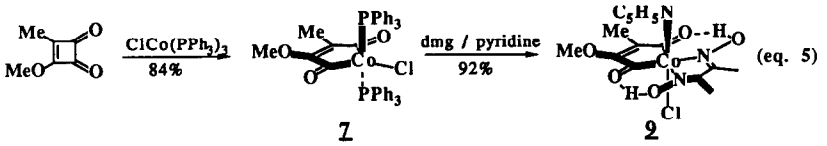
(eq. 3)

5



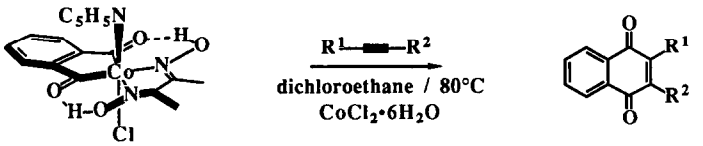
(eq. 4)

6 **8**



7 9

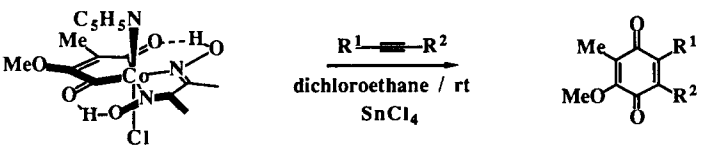
Table 1. Synthesis of Some Naphthoquinones From Phthaloylcobalt Complex 8 and Alkynes.



8

R^1	R^2	isolated yield
n-Bu	H	87
Et	Et	86
Me	CO_2Et	99
Et	OEt	85
Me	t-Bu	72
Me	$CH_2N(COMe)Ph$	70
Me	$CH_2CH=CMe_2$	94

Table 2. Regioselective Synthesis of Some Unsymmetrically Substituted Benzoquinones From Maleoylcobalt Complex 9 and Alkynes.



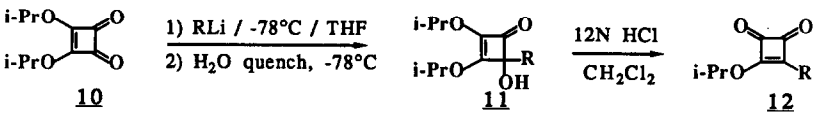
9

R^1	R^2	Lewis acid/temp	isolated yield	ratio of regioisome
n-Bu	H	$SnCl_4$/rt	65	10 : 1
Me	CO_2Et	$SnCl_4$/rt	62	20 : 1
EtO	Me	none/80°C	81	14 : 1
(Z)-MeOCH=CH	H	none/rt	50	20 : 1
CH_2SiMe_2-t-Bu	Me	$SnCl_4$/rt	51	20 : 1
$(CH_2)_2N(Bn)COCO_2Et$	H	$SnCl_4$/rt	65	7 : 1

With the development of a method of benzoquinone synthesis from metal complexes of general structure **5**, the need for a simple and efficient route to substituted cyclobutenediones, the organic precursors to maleoylmetal complexes, became apparent. Our studies of cyclobutenedione synthesis culminated recently in a very simple preparation of generally substituted cyclobutenediones starting from commercially available squaric acid.[5] The synthetic sequences and results are depicted in Tables 3 and 4. Basically, substituted cyclobutenediones are available by treating diisopropylsquarate **10**, a crystalline ester of squaric acid, with organolithium nucleophiles followed by processing with acid. Addition of one organolithium nucleophile generates the 1,2-adducts **11** and acid treatment provides a route to the semisquaric acid derivatives **12** shown in Table 3. Standard acid catalyzed hydrolysis and

reesterification allows the isopropyl group of **12** to be replaced with other alkoxy substitutents. Differentially disubstituted cyclobutenediones are available by the sequential addition of two different organolithium reagents to diisopropylsquarate as shown in Table 4. Addition of either $LiAl(O\text{-}t\text{-}Bu)_3H$ or MeLi to diisopropylsquarate gives an isolable 1,2-adduct that is protected as the t-butyldimethylsilyl ether **13** in Table 4. A second organolithium reagent can be added and after treatment of the intermediate double adducts **14** with acid, the disubstituted cyclobutenediones **15** are isolated.

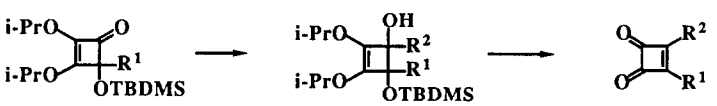
Table 3. Addition of Organolithium Reagents to Diisopropyl squarate.



10 **11** **12**

compound	R	yield 11 (%)	yield 12 (%)
a	H	89	65
b	Me	97	92
c	n-Bu	80	88
d	t-Bu	83	95
e	Ph	93	89
f	2-thienyl	98	96
g	C≡CPh	84	98
h	C≡CBu	82	88
i	C≡CTMS	70 (22% C≡CH)	93
j	4'-(C_6H_4C≡CTMS)	88	90

Table 4. Synthesis of Differentially 3,4-Disubstituted-3-Cyclobutene-1,2-diones.

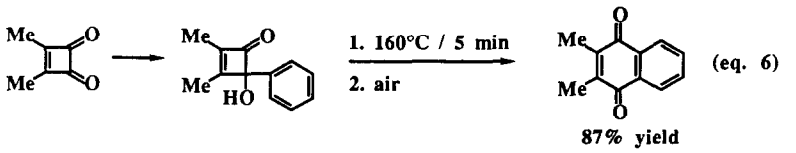


13 **14** **15**

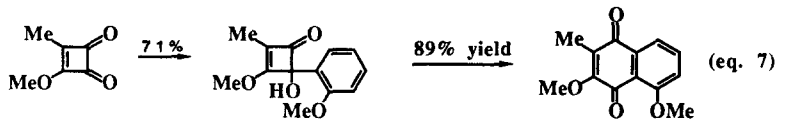
compound	R^1	R^2	yield 14 (%)	yield 15 (%)
a	H	Me	81	88
b	H	n-Bu	80	94
c	H	t-Bu	85	90
d	H	2-thienyl	96	90
e	Me	Me	91	96
f	Me	n-Bu	---	79
g	Me	t-Bu	---	96
h	Me	Ph	---	78

The ready availability of numerous cyclobutenediones opened the way for the development of other synthetic applications of these highly functionalized starting materials. During the course of a study of the reactions of 2,3-dimethyl-4-hydroxy-4-phenylcyclobut-2-enone, prepared by the addition of PhLi to 3,4-dimethylcyclobut-3-ene-1,2-dione, a simple synthesis of ring-fused quinones was uncovered.[6] After heating to 160°C in xylene and exposing to air, the 4-hydroxy-4-phenylcyclobutenone was converted into 2,3-dimethyl-1,4-naphthoquinone in 87% yield (eq. 6). This reaction turned out to be very general; 4-hydroxycyclobutenones bearing an unsaturated substituent at the 4-position rearranged on heating followed by oxidation to give ring-fused quinones. Some typical examples are

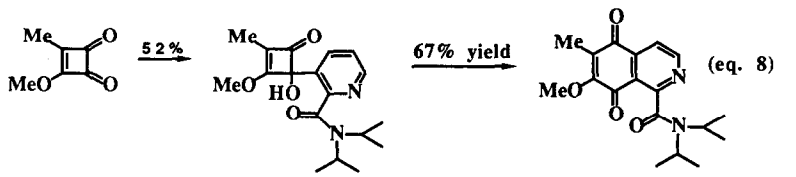
shown in equations 7 – 10. The reaction is presumed to proceed via a vinylketene intermediate (Scheme 2).



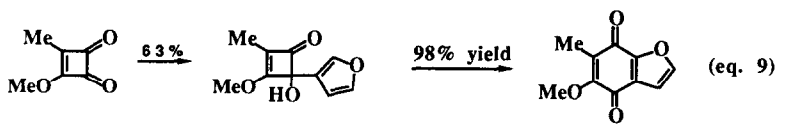
(eq. 6)



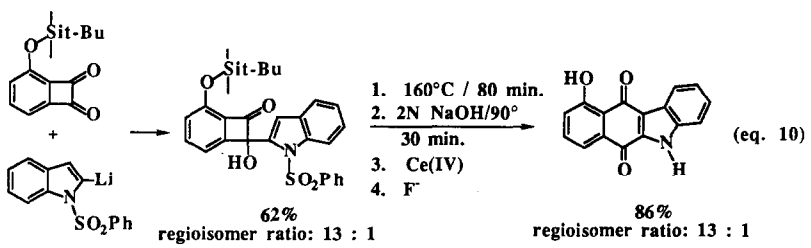
(eq. 7)



(eq. 8)

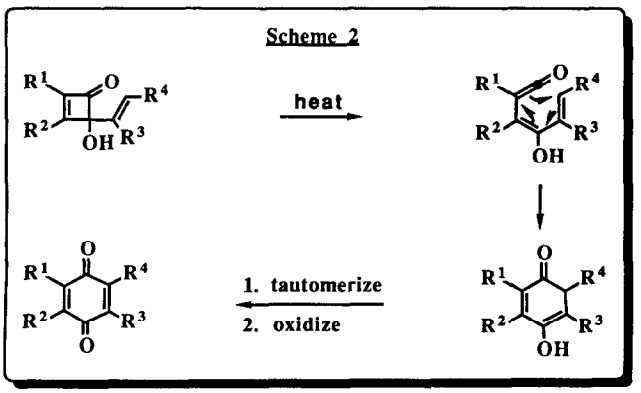


(eq. 9)

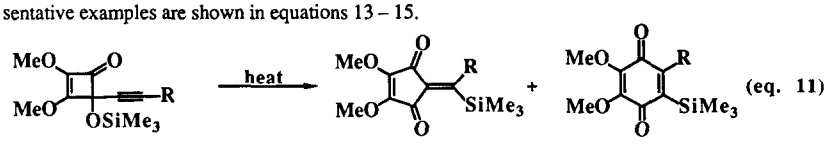


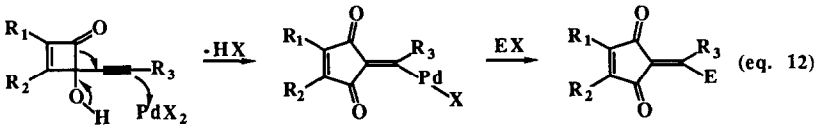
(eq. 10)

Scheme 2

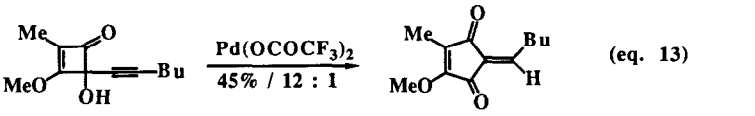


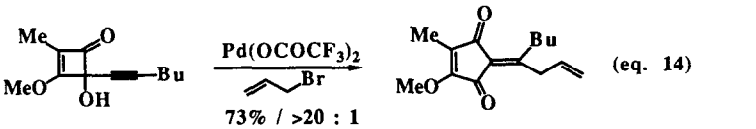
During the course of his study of unsaturated ketenes, Moore explored the thermolysis of 4-alkynyl-4-hydroxycyclobutenones and discovered a novel rearrangement leading to either benzoquinones or alkylidene cyclopentenediones (eq. 11).[7] The outcome of the reaction was dependent on the alkyne substitutent R. An alternative and more general route to alkylidene cyclopentenediones was achieved when the 4-alkynyl-4-hydroxycyclobutenones were exposed to a catalytic amount of Pd(+2) (eq. 12).[8] This palladium induced ring expansion provides a general route to alkylidene cyclopentenediones and related molecules with exceptional control over the stereochemistry of the newly formed exocyclic double bond. The reaction is presumed to proceed via a vinylpalladium intermediate **16** that either suffers protonation or undergoes reaction with substrates added to the reaction mixture. Representative examples are shown in equations 13 – 15.

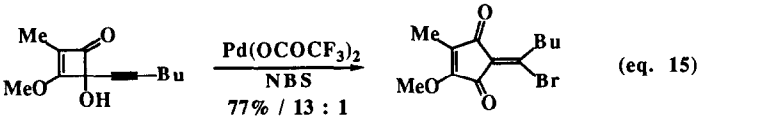




16

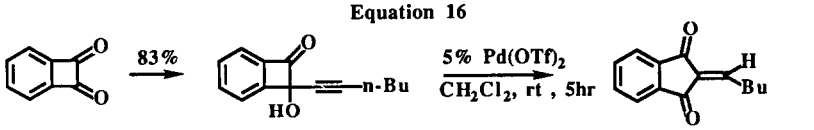






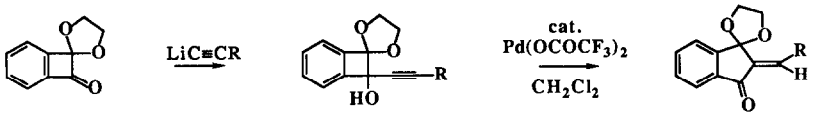
It also proved feasible to perform the palladium catalyzed rearrangement with benzo analogs of the cyclobutenones. Benzocyclobutenedione reacted with 1-lithio-1-hexyne to give 2-(1-hexynyl)-2-hydroxybenzocyclobutenone in 83% yield. Upon treatment with 5% $Pd(OCOCF_3)_2$ in methylene chloride at rt, the anticipated rearrangement to the 5-membered ring occurred and provided the alkylidene indandione in what appeared to be a high yield (eq. 16). However, the alkyldene indanedione was not stable to chromatography nor to distillation. The instability of the alkylidene indanedione was circumvented by preparing a monoketal of benzocyclobutenedione. Reaction with lithioalkynes provided the alkyne adducts and treatment with catalytic $Pd(OCOCF_3)_2$ in methylene chloride at rt induced the ring expansion and gave monoketals of alkylidene indandiones in high yield and with excellent exocyclic double bond stereoselectivity (Table 5).

Equation 16



unstable to chromatography

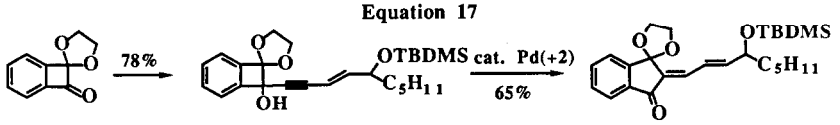
Table 5. Palladium Catalyzed Ring Expansion of 2-Alkynyl-2-hydroxybenzocyclobutenone Monoketals.



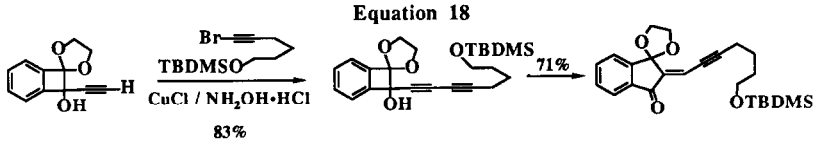
R	yield	conditions	yield	isomer ratio
n-C_4H_9	92	2.5% $Pd(OCOCF_3)_2$, 12h	91	36:1
n-C_6H_{13}	81	2.5% $Pd(OCOCF_3)_2$, 24h	51	26:1
c-C_6H_{11}	97	2.5% $Pd(OCOCF_3)_2$, 10h	75	>20:1
$SiMe_3$	84	2.5% $Pd(OCOCF_3)_2$, 12h	56	20:1
Ph	92	2.5% $Pd(OCOCF_3)_2$, 12h	89	20:1
CH_2OCH_3	90	2.5% $Pd(OCOCF_3)_2$, 12h	84	>20:1
$CH(OTBDMS)CH_3$	97	5.0% $Pd(OCOCF_3)_2$, 10h	66	18:1
$(CH_2)_2OTBDMS$	74	5.0% $Pd(OCOCF_3)_2$, 12h	75	22:1

The mild conditions of the palladium induced ring expansion of alkynylcyclobutenol derivatives has allowed a number of highly functionalized compounds to be prepared. Two of the more elaborate transformations we have conducted to date are shown in equations 17 and 18.

Equation 17



Equation 18



Conclusions

Although fairly strained and reactive, a variety of cyclobutenediones and benzocyclobutenediones can easily be prepared and manipulated and thus are valuable starting materials for the synthesis of highly functionalized organics such as quinones and cyclopentenones. With reasonable preparative routes to variously substituted cyclobutenediones now established, additional uses of these reactive small ring compounds in synthesis can be anticipated.

Acknowledgments

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---

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