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# Engaging the Pyridine-DMAD Zwitterion in a Novel Strategy for the Selective Synthesis of Highly Substituted Benzene and Cyclopentenedione Derivatives[†]

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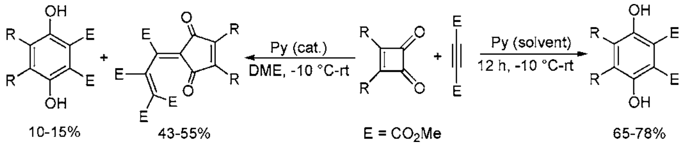
## ABSTRACT



**The pyridine-mediated reaction of dimethyl acetylenedicarboxylate and cyclobutene-1,2-diones affords selective access to either hexasubstituted benzene derivatives or cyclopentenedione derivatives depending on the concentration of pyridine.**

Oxygenated benzene derivatives, especially hydroquinones and quinones, are of exceptional value due to their useful chemical and pharmacological properties.[1] The commonly used methodologies for the synthesis of quinones include oxidation of phenols or hydroquinones using various oxidants such as cerium(IV) salts,[2] hydrogen peroxide,[3] manganese dioxide,[4] silver oxide,[5] etc. Two elegant approaches to the synthesis of quinones introduced in recent years and investigated in detail are (1) thermal cyclobutene ring opening reactions developed by Liebeskind,[6] Moore,[7] and Danheiser[8] and (2) the low valent cobalt mediated ring opening of cyclobutene-1,2-diones developed by Liebeskind.[9] The versatile Dötz reaction involving cycloaddition of metal carbenes leading to alkoxy phenols which serve as precursors for quinones is also noteworthy.[10]

Despite the success of the available methods, there is always a quest to develop newer and simpler methods for the synthesis of benzoquinones.[11] In view of this, and in the

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[†] This paper is dedicated to the memory of Professor R. H. Sahasrabudhey.

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context of our recent investigations on the reactivity of the zwitterion derived from pyridine and dimethyl acetylenedicarboxylate (DMAD) toward carbonyl compounds,[12] we reasoned that the zwitterion was likely to add to cyclobutenedione to form a tetrahedral intermediate with a propensity to undergo ring expansion via a concerted[13] or stepwise mechanism to deliver the quinone as the product (Figure 1). The results of our studies which reveal two pertinent and synthetically useful reactions, one involving a novel rearrangement, form the subject matter of this communication.

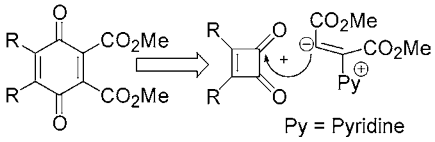
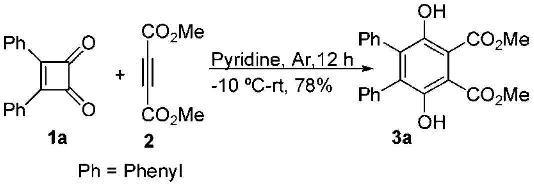


**Figure 1.** Retrosynthetic analysis.

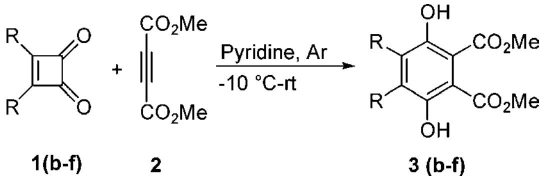
Our studies were initiated by the addition of dimethyl acetylenedicarboxylate (1.1 equiv) to a solution of 3,4-diphenylcyclobutene-1,2-dione[14] (1 equiv) in pyridine (2 mL) at −10 °C. The system was allowed to attain room temperature (∼30 °C) and was stirred for 12 h. Distillation of the solvent in vacuo followed by column chromatography afforded the hydroquinone **3a**, instead of the expected quinone, in 78% yield (Scheme 1).[15]

**Scheme 1.** Pyridine-Mediated Reaction of 3,4-Diphenylcyclobutene-1,2-dione and Dimethyl Acetylenedicarboxylate



The structure of the product **3a** was assigned on the basis of spectroscopic data. In the IR spectrum, a peak at 3500 $cm^{-1}$ corresponding to the −OH absorption and a peak at 1728 $cm^{-1}$ corresponding to the ester carbonyl functionality were observed. A sharp singlet at δ 3.94 corresponding to the carbomethoxy groups was seen in the $^1H$ NMR spectrum. The $^{13}C$ resonance signal for the carbomethoxy carbonyl group was seen at δ 169.2 and that of the carbon bearing hydroxyl group at δ 149.3. The compound gave satisfactory mass analysis also. On treatment with iodomethane and potassium carbonate **3a** afforded the dimethylated product in 92% yield. The reaction appears to be general with other derivatives of cyclobutenedione and the results are presented in Table 1.

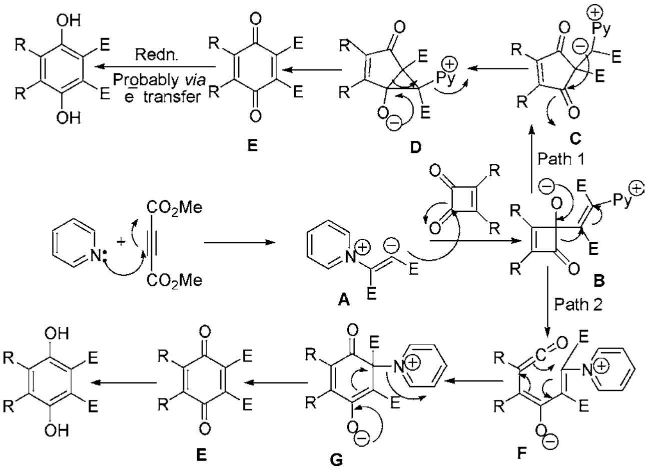
**Table 1.** Reaction with Various Cyclobutene-1,2-diones



| entry | R | product (%) |
|---|---|---|
| 1 | 4-methylphenyl, **1b** | **3b** (72) |
| 2 | 3,4-dimethylphenyl, **1c** | **3c** (70) |
| 3 | 4-chlorophenyl, **1d** | **3d** (65) |
| 4 | 4-bromophenyl, **1e** | **3e** (67) |
| 5 | 2-thienyl, **1f** | **3f** (65) |

To rationalize the formation of the product **3a**, two possible mechanistic postulates are outlined in Scheme 2. The zwitterion **A**, formed from pyridine and the acetylene, adds to one of the carbonyls of the dione to form a new zwitterion **B**, which can conceivably be stabilized by two different mechanistic pathways. In the series of events designated as

**Scheme 2.** Proposed Mechanistic Pathway for the Reaction in Scheme 1



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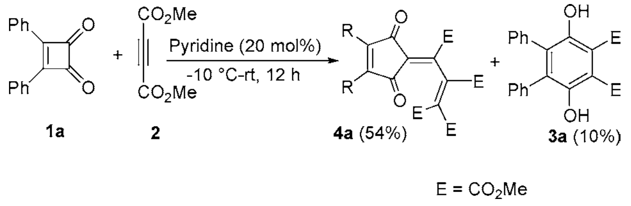
(15) The reaction also works when pyridine is used in catalytic amounts (20 mol %) and anhydrous dimethoxyethane (DME) as solvent but the reaction occurs at a much slower rate and the product is obtained in low yield.

path 1, the cyclobutene ring expands to a five-membered pyridinium ylide **C**.[16] The latter then suffers an intramolecular nucleophilic attack to form the cyclopropane intermediate **D**, which can eliminate pyridine to furnish the quinone **E**. The latter is not isolated—presumably it undergoes a reduction mediated by electron transfer from pyridine to afford the hydroquinone **3a**.

In the designated path 2, an electrocyclic ring opening of **B** is conceived to generate a ketene-zwitterion **F**, which can undergo a 6$\pi$ cyclization–pyridine elimination sequence to form quinone **E**. Similar ketene intermediates, however, are known to arise from cyclobutenes under elevated temperatures only. Therefore this mechanistic possibility may be discounted on the basis of the mild reaction conditions employed in the present reaction.

Controlled experiments with varying stoichiometry of reactants revealed an interesting reactivity pattern, leading to an entirely different product as well as lending indirect support for the mechanistic rationale in path 1. Thus, 3,4-diphenylcyclobutene-1,2-dione (1 equiv) and excess DMAD (2.4 equiv) were taken in anhydrous DME and a catalytic amount of pyridine (20 mol %) was added to it and the experiment was conducted as before (vide supra). To our surprise, this reaction afforded the cyclopentenedione derivative **4a** as the major product (54%) along with the hydroquinone in very low yield (10%) as depicted in Scheme 3.

**Scheme 3.** Pyridine-Catalyzed Reaction of 3,4-Diphenylcyclobutene-1,2-dione and Dimethyl Acetylenedicarboxylate



The product **4a** was characterized on the basis of spectroscopic data. The IR spectrum showed characteristic absorptions at 1741 cm$^{-1}$ corresponding to the ester carbonyl moiety and at 1697 cm$^{-1}$ due to the enone functionality. The $^{1}$H NMR showed four singlets at $\delta$ 3.93, 3.92, 3.80, and 3.78 corresponding to the four carbomethoxy groups. The $^{13}$C resonance signals of the four carbomethoxy carbonyl groups were seen at $\delta$ 164.0, 163.7, 162.5, and 162.3 whereas the enedione carbonyl signals were seen at $\delta$ 189.6 and 187.4. Unambiguous evidence for the structure of **4a** was obtained by single-crystal X-ray analysis (Figure 2).[17]

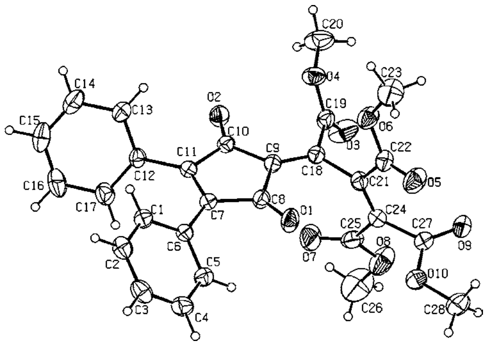
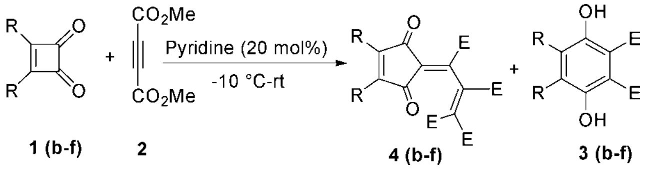


**Figure 2.** X-ray crystal structure of **4a**.

This reaction also appears to be general and the results are summarized in Table 2.

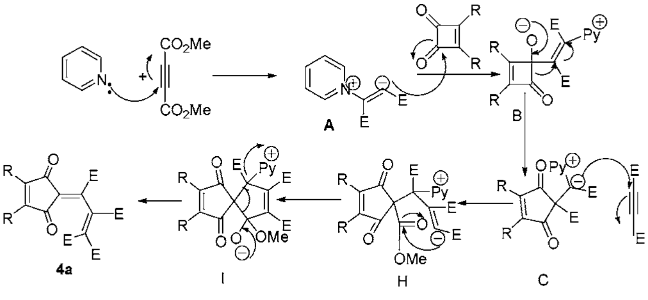
**Table 2.** Reaction with Various Cyclobutene-1,2-diones



| entry | R | **4** (%) | **3** (%) |
|---|---|---|---|
| 1 | 4-methylphenyl, **1b** | **4b** (48) | **3b** (11) |
| 2 | 3,4-dimethylphenyl, **1c** | **4c** (43) | **3c** (13) |
| 3 | 4-chlorophenyl, **1d** | **4d** (52) | **3d** (10) |
| 4 | 4-bromophenyl, **1e** | **4e** (48) | **3e** (11) |
| 5 | 2-thienyl, **1f** | **4f** (55) | **3f** (15) |

A possible mechanistic pathway for the formation of **4a** is shown in Scheme 4. Conceivably, the pyridinium ylide **C** adds to another molecule of DMAD to give **H**. The latter then undergoes an acyl migration via a spirocyclic intermediate **I** followed by the elimination of pyridine to yield the final product **4a**.

**Scheme 4.** Proposed Mechanistic Pathway for the Reaction in Scheme 3



The mechanistic divergence of this reaction may be rationalized as follows: after the ring enlargement of the

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[16] For ring expansion of a cyclobutenedione ring after the addition of a nucleophile see refs 9b and 9e.

[17] CCDC file no. 275458 contains the supplementary crystallographic data for this paper. See Supporting Information for details.

cyclobutenone intermediate **B** to the cyclopentenedione derivative **C**, the latter has the option of undergoing further rearrangement as in the case of the first reaction (Scheme 2) or to undergo Michael addition to DMAD, which is present in excess. The latter path would lead to the new zwitterion **H**, which is set up for the acyl transfer and consequent ejection of pyridine to deliver the dienyl cyclopentenedione **4a**. The reason for **C** to react with DMAD in preference to intramolecular addition to the carbonyl may be attributed to steric hindrance imparted by the substituents at the anionic center. Evidently in the experiment in which pyridine is used as the solvent, there is hardly any DMAD available for reaction with **C**, thus necessitating the latter to proceed on the reaction pathway leading to the hydroquinone derivative.

In conclusion, we have encountered a novel reaction of the pyridine-DMAD zwitterion with cyclobutene-1,2-dione leading to two different ring expanded products under different conditions. In one case, the four-membered ring is converted to a six-membered ring, which is a hexasubstituted benzene. In the other case, this four-membered ring is converted to a novel cyclopentenedione derivative. The mild experimental conditions used in these reactions are especially noteworthy. As there are well-established procedures to convert hydroquinones to quinones, the reaction described herein offers a convenient and simple route to the synthesis of fully substituted *p*-benzoquinones.

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**Supporting Information Available:** Experimental procedure and spectroscopic data, including crystallographic data (CIF file), for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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