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γ-Carbonyl Quinones: Radical Strategy for the Synthesis of Evelynin and Its Analogues by C–H Activation of Quinones Using Cyclopropanols

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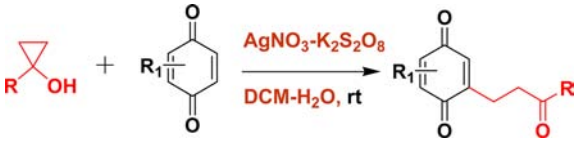
ABSTRACT



Cyclopropanols, on oxidative ring opening with $AgNO_3$–$K_2S_2O_8$ in DCM–H_2O at room temperature and under open flask conditions, produced β-keto radicals which were successfully added to quinones to furnish γ-carbonyl quinones. This mild method has been applied to the synthesis of cytotoxic natural products, 4,6-dimethoxy-2,5-quinodihydrochalcone and evelynin.

Quinone motifs are prevalent in a number of naturally occurring biologically active compounds.[1] As a result of their unique structure, quinones carry out important biological functions such as oxidative phosporylation and bioenergetic transport.[2] Interest in synthetic variations of quinones has been steadily increasing as the naturally occurring quinones reveal a wide variety of biological activities such as antibiotic,[3a] anticancer,[3b] antimalarial,[3c] antitumor,[3d] and antidiabetic,[3e] besides playing a vital role in cellular metabolism. Since quinones possess redox properties, their efficacy has been exploited in the industry as dyes and pigments.[4] In synthetic organic chemistry, quinones found their use as dienophiles in Diels–Alder reactions,[5] oxidations,[6] and as ligands in coordination chemistry.[7]

Even though quinones have captured human attention for a long time, there are only limited methods available for the functionalization of quinones. For example, demethylasterriquinone B1 was prepared by Lewis acid catalysis followed by reoxidation with DDQ.[8a] Similarly, aryl-substituted 1,4-quinones have been synthesized from electron-rich arenes by conjugate addition followed by in situ dehydrogenation strategy.[8b] The other well-known method for C–C bond formation, such as Heck coupling, faced hardship as a result of competing complex formation by palladium as well as poor accessibility of haloquinones.[9]

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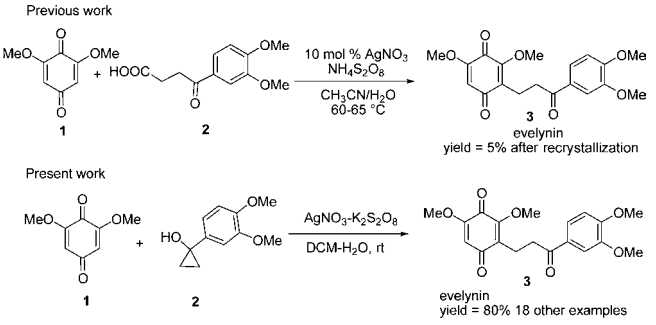
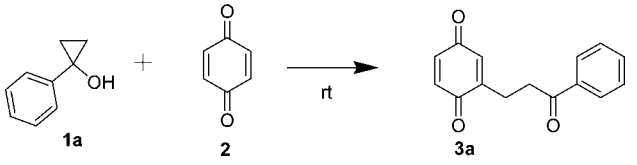
These drawbacks make an alternate approach, radical coupling, an attractive protocol for making substituted quinones by C−H functionalization of quinones. The major advantages of radical chemistry such as excellent reactivity, mild conditions, functional group tolerance, and more atom economy make the metal-mediated radical strategy attractive for an ideal chemical synthesis. The radical strategy was utilized in the preparation of arylated and alkylated quinones from boronic acids[10a,b] and diazonium species.[10c] Oxidative decarboxylation approach by Kochi[11a] and Minisci[11b] was followed for the generation of radicals, which was used for the functionalization of naphthaquinones with amino acids.[11c] The major problems associated with the Minisci reaction are the modest yields and lack of selectivity.



Cyclopropanols are versatile compounds which can be a repertoire for various classes of synthetic molecules such as azaheterocycles,[12a] β-substituted ketones,[12b] allyl chlorides,[12c] and other products by virtue of the strain energy associated with the three-membered ring. After Kulinkovich discovered that the reaction between esters and Grignard reagents in the presence of $Ti(OPr^i)_4$ produced cyclopropanols,[15] a plethora of reactions have started emerging on these synthetically useful intermediates. The ring opening of cyclopropanols by the one-electron oxidants such as Mn salts,[12a] CAN,[12b] Ag(I) with persulfate,[13] etc. under mild conditions delivers reactive radical species, β-keto radicals. Though it is possible to generate such radicals from β-keto acids by oxidative decarboxylation, harsh conditions (high temperature and acidic) are required to get the desired reaction. Considering the intrinsic reactivity of these radicals, a milder method is essential to limit the formation of other potential side products and also to have a broad substrate scope. On the basis of the above facts, we envisioned that a mild method can be developed from cyclopropanols. Even though the reaction of cyclopropanols with electron-deficient alkenes was studied as a multicomponent reaction,[13] their reactivity with quinones has not been explored until now.

The reaction between 1-phenylcyclopropanol and 1,4-benzoquinone was explored to find the optimal reaction conditions, and the results are summarized in Table 1.

Table 1. Screening Experiments

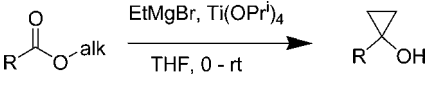


entry	reagent(s)	solvent	time (min)	isolated yield (%)
1	$Mn(OAc)_3$ (2.2 equiv)	AcOH	90	52
2	$Mn(OAc)_3$ (2.2 equiv)	MeOH−AcOH (9:1)	95	48
3	$AgNO_3$ (0.2 equiv)/ $K_2S_2O_8$ (3 equiv)	$CH_2Cl_2-H_2O$ (1:1)	60	65
4	$FeSO_4$ (0.5 equiv)/ $K_2S_2O_8$ (3 equiv)	$CH_2Cl_2-H_2O$ (1:1)	70	61
5	CAN (2.2 equiv)	MeOH	60	traces
6	$FeSO_4$ (0.5 equiv)/ TBHP (3 equiv)	MeOH−H_2O	60	traces
7	$AgNO_3$ (0.2 equiv)/ MnO_2 (3 equiv)	ACN	60	30

Although $Mn(OAc)_3$ was successful in bringing the desired conversion, its success is marred with a slower reaction and considerable amounts of disubstitution. $K_2S_2O_8$ reacted rapidly to produce the monosubstituted product in the presence of catalytic amounts of $AgNO_3$ as well as $FeSO_4$, but $AgNO_3$ looked superior because of short reaction time and better yield. The other oxidants, CAN and TBHP, produced a mixture of side products along with traces of desired product. MnO_2 delivered a lower yield and was found to be less efficient for this reaction. After the study of the results from the screening experiments, $AgNO_3$ (20 mol %) and $K_2S_2O_8$ (3 equiv) in DCM−H_2O (1:1, v/v) was found to be the best condition to investigate the further scope of the reaction.

The required cyclopropanols were prepared in good yields by the Kulinkovich reaction,[15] as per Scheme 1.

Scheme 1. Preparation of Cyclopropanols



A wide range of cyclopropanols were reacted with 1,4-benzoquinone under the optimized conditions, and the results are shown in Figure 1.

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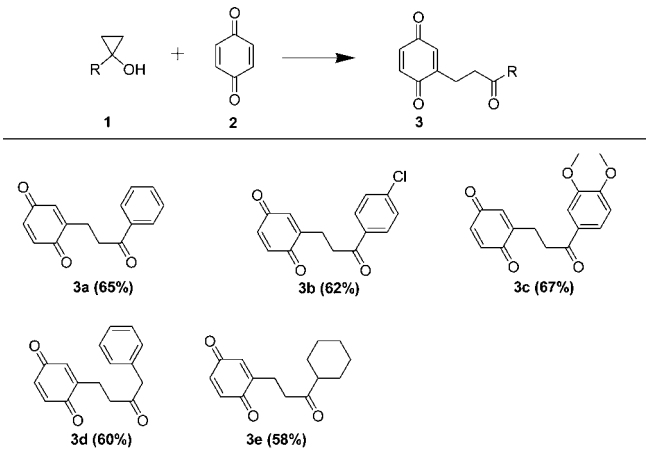


Figure 1. Scope of the reaction between 1,4-benzoquinone and cyclopropanols. Reaction conditions: **1** (0.55 mmol), **2** (0.5 mmol), $AgNO_3$ (0.1 mmol), $K_2S_2O_8$ (1.5 mmol), 4 mL of $CH_2Cl_2-H_2O$ (1:1, v/v), 25 °C, 60 min. Yields of isolated products.

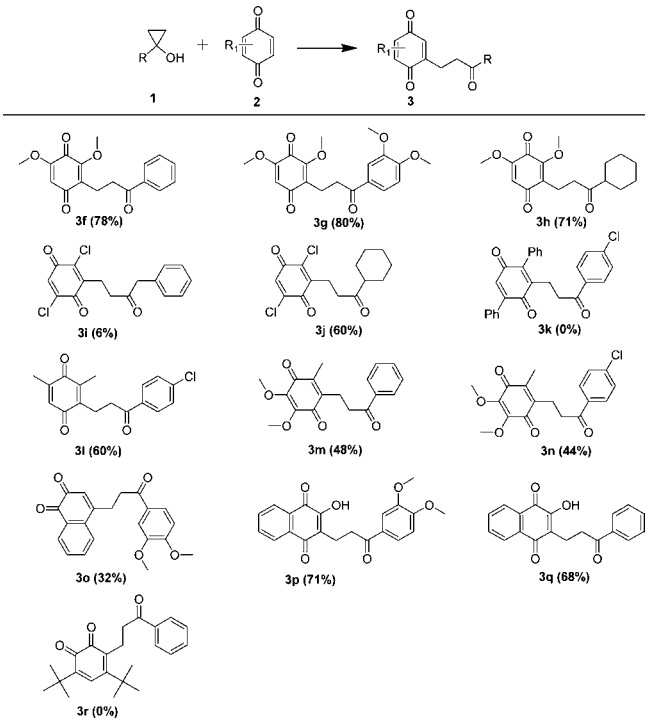


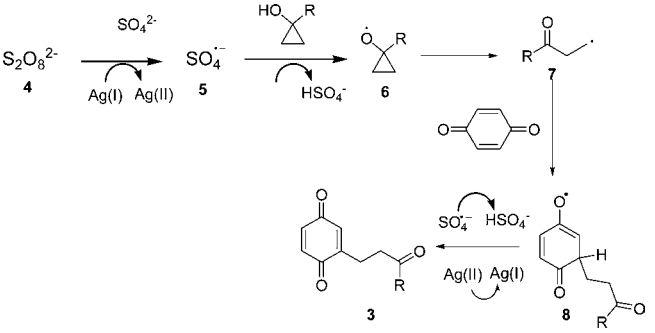
Figure 2. Scope of the reaction between 1,4-benzoquinone and cyclopropanols. Reaction conditions: **1** (0.55 mmol), **2** (0.5 mmol), $AgNO_3$ (0.1 mmol), $K_2S_2O_8$ (1.5 mmol), 4 mL of $CH_2Cl_2-H_2O$ (1:1, v/v), 25 °C, 60 min. Yields of isolated products.

All the reactions underwent a clean reaction to deliver the desired product in good yields. The reaction conditions are well-tolerated by chloro (**3b**) and methoxy (**3c**) substituents. Aromatic cyclopropanols gave marginally higher yields than the aliphatic ones.

To have a further understanding of the scope of quinones, the reaction was performed with a variety of substituted quinones (Figure 2). Sterically hindered substrates (**3k** and **3r**) failed to react under these circumstances, whereas the trisubstituted quinone (**3m** and **3n**) reacted slowly and furnished lower yields. Electron-donating methoxy group (**3f** and **3g**) helped the reaction by producing higher amounts of the desired product. Due to a probable steric influence, only a lesser amount of the product was isolated from 1,2-naphthaquinone. To our surprise, a free hydroxyl group survived the oxidative reaction conditions and also generated good yields. To add to the fruitfulness of the method, the cytotoxic natural products 4,6-dimethoxy-2,5-quinodihydrochalcone[14a] (**3f**) and evelynin (**3g**)[14b] were prepared with over 70% yield, thus outperforming the earlier method with β-ketoacid where only ~5% of evelynin was isolated.

The mechanistic pathway is portrayed in Scheme 2, which is in consistent with the general method of oxidative ring opening of cyclopropanols and a radical addition to quinones. Sulfate radical ion **5**, produced by the action of Ag(I) on persulfate **4**, reacts with cyclopropanols to form an cyclopropoxy radical **6** which opens up to form β-keto radical **7**. This radical adds to quinones by providing a radical intermediate **8** which undergoes reoxidation with Ag(II) to hand over the final product **3** as well as regenerate Ag(I).

Scheme 2. Plausible Mechanism



In conclusion, a convenient method for the preparation of diverse γ-carbonyl quinones has been developed by C−H activation of quinones using cyclopropanols and a $AgNO_3/K_2S_2O_8$ oxidant system. The reactivity of β-keto radicals is rapid, and hence a protection and deprotection strategy is not generally required. This new method has also been successful for the preparation of cytotoxic natural products, 4,6-dimethoxy-2,5-quinodihydrochalcone (**3f**) and evelynin (**3g**), and a series of highly substituted γ-carbonyl quinones in high yield. The reaction conditions are mild and tolerable to several sensitive functional groups, flexible to extend to different substrates, and

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employ cheap and readily available reagents. We trust that this method looks attractive and that the new chemical entities made by this strategy might be useful scaffolds in various scientific applications.

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Supporting Information Available. Detailed experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.