Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201401038

A Dehydrogenative Diels–Alder Reaction of Prenyl Derivatives with 2,3-Dichloro-5,6-dicyanobenzoquinone

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Received: October 31, 2014; Revised: January 19, 2015; Published online: ■■ ▮▮, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201401038.

Abstract: An efficient dehydrogenative Diels–Alder (DHDA) reaction of prenyl derivatives with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) has been developed under mild conditions, leading to a series of cyclohexene derivatives with good to excellent yields and excellent diastereoselectivity.

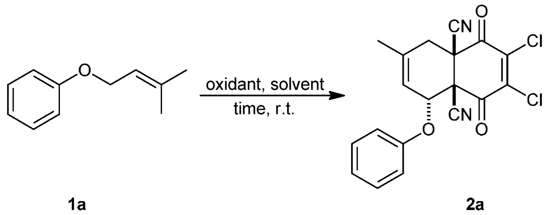
Keywords: C–H activation; cycloaddition; dehydrogenation; diastereoselectivity; oxidation

The Diels–Alder (DA) reaction is one of the most fundamental and synthetically useful reactions in organic chemistry. In which a diene is combined with a dienophile to form a cyclohexene derivatives, and two new C–C bonds and several new stereocenters may be generated in a single step.[1] Studies on the DA reaction have a long history, many remarkable endeavors have been made to develop various DA reactions.[2] However, one limitation of the reaction is that the diene component is usually unavailable and needs to be prepared. As a consequence, a dehydrogenative Diels–Alder (DHDA) reaction strategy has been emerged.[3] This contains two variations: one is that a DA reaction takes place followed by a dehydrogenation (usually aromatization);[4] the other is that a dehydrogenative reaction takes place prior to a DA reaction.[5] The latter one is more challenging and potential useful, because a C–H bond oxidation reaction is involved to prepare a diene in situ, and the newly generated stereocenters of the DA reaction product are remained. Recently, the White group developed an efficient Pd-catalyzed DHDA reaction with terminal alkenes.[5a] As this is an efficient method to realize DA reactions, it is high desirable to discover new variants of this type reaction. Here we report an efficient, metal-free DHDA reaction of prenyl derivatives with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

As a powerful oxidizing reagent in organic chemistry, DDQ has been proven to be useful for a wide range of reactions,[6] such as oxidation of hydroaromatic compounds,[7a] steroid derivatives (ketones, pyrrazoles, lactones, etc.),[7b] alcohols,[7c] phenols,[7d] allylic and benzylic ethers,[7e] and heterocyclic compounds.[7f] Additionally, 1,4-benzoquinones are good dienophiles for the DA reaction.[8] Inspired by allylic oxidation reactions with DDQ,[7e, 9] we envisage that the oxidation of a prenyl motif by DDQ would generate an allylic carbocation intermediate, then elimination of a proton and rearrangement would form an isoprene motif.[10] Finally, a DA reaction of the isoprene derivative and DDQ would yield a DHDA reaction product.

To test this hypothesis, we examined the reaction using prenyl ether **1a** and DDQ in a ratio of 1:1.1 in DCM at room temperature, to our delight, the desired DHDA reaction product **2a** was obtained in 40% yield as a single diastereomer (Table 1, entry 1). Increasing the amount of DDQ gave a significant increase in yield, and **2a** was obtained in 94% yield when a slightly excess of DDQ was employed (Table 1, entry 3). However, other 1,4-benzoquinones (BQ) such as 2,6-Me_2BQ, BQ, or 2,3,5,6-Cl_4BQ all returned no desired products; the starting materials were recovered (Table 1, entries 7-9), indicating that the dehydrogenative step didn't occur under these conditions. When an excess amount of other strong dienophiles, such as maleic anhydride, *N*-phenylmaleimide, and tetracyanoethylene, were employed together with DDQ for this reaction, unfortunately, no cross DHDA reaction products, resulting from the reaction with these dienophiles, were detected. **2a**, resulting from the reaction with DDQ was the only product obtained.[11] The reason may be due to DDQ is the strongest dienophile among them. Indeed, the successful DA reaction of these dienophiles with isoprene, without DDQ, confirm this point.[11] With solvents other than DCM, the yields clearly diminished (Table 1, entries 4-6).

Table 1. Optimization of the reaction conditions.[a]



Entry	oxidant (equiv)	Solvent	Time [h]	Yield [%][b]
1	DDQ (1.1)	DCM	48	40
2	DDQ (2.5)	DCM	48	82
3	DDQ (2.1)	DCM	48	94
4	DDQ (2.1)	ACN	48	15
5	DDQ (2.1)	toluene	48	32
6	DDQ (2.1)	THF	60	5
7[c]	2,6-Me$_2$BQ (2.1)	DCM	60	NR
8	BQ (2.1)	DCM	60	NR
9	2,3,5,6-Cl$_4$BQ (2.1)	DCM	60	NR
10[d]	2,3,5,6-Cl$_4$BQ (2.1)	DCE	60	NR

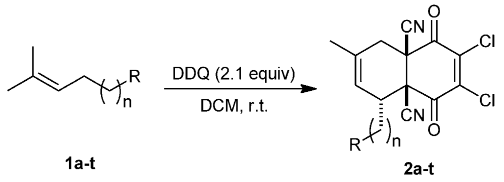
[a] Reactions were carried out with compound **1a** (0.2 mmol) and oxidant (equiv) in solvent (2.0 mL) at r.t.

[b] Isolated yield.

[c] BQ = 1,4-benzoquinone.

[d] The reaction temperature is 90 °C.

Table 2. DHDA reaction of DDQ with prenyl derivatives.[a]



Entry	Substrate	R	n	Time [h]	Yield [%][b]
1	**1a**	C$_6$H$_5$O	0	48	95[c]
2	**1b**	4-CH$_3$-C$_6$H$_4$O	0	48	90
3	**1c**	4-CH$_3$O-C$_6$H$_4$O	0	36	92
4	**1d**	4-Cl-C$_6$H$_4$O	0	48	81
5	**1e**	4-Br-C$_6$H$_4$O	0	48	72
6	**1f**	4-NO$_2$-C$_6$H$_4$O	0	60	NR
7	**1g**	3-CH$_3$-C$_6$H$_4$O	0	48	85
8	**1h**	3-Cl-C$_6$H$_4$O	0	60	60
9	**1i**	3-Br-C$_6$H$_4$O	0	60	70
10	**1j**	2-CH$_3$-C$_6$H$_4$O	0	48	88
11	**1k**	2-Cl-C$_6$H$_4$O	0	60	61
12	**1l**	2-Br-C$_6$H$_4$O	0	60	77
13	**1m**	C$_6$H$_5$	0	48	80
14	**1n**	C$_6$H$_5$O	1	48	84
15	**1o**	4-CH$_3$O-C$_6$H$_4$O	1	60	67
16	**1p**	4-NO$_2$-C$_6$H$_4$O	1	60	NR
17	**1q**	4-NO$_2$-C$_6$H$_4$O	2	60	96
18	**1r**	TsO	2	48	56[d]
19	**1s**	BnO	0	48	53
20	**1t**	2,3-dimethyl-2-butene		48	58

[a] Reactions were carried out with compound **1a-t** (0.20 mmol) and DDQ (0.42 mmol) in DCM (2.0 mL) at r.t.

[b] Isolated yield.

[c] 2.0 mmol scale.

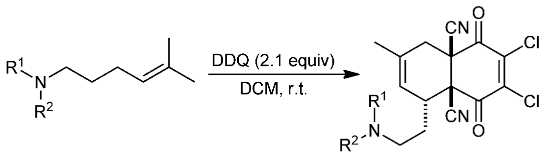
[d] *trans*:*cis* = 8.5:1, determined by ^{1}H NMR analysis.

Having established the optimal reaction conditions, we then first carried out the reaction between DDQ and a variety of prenyl ethers to test the scalability and generality. A 10-fold increase in scale resulted in little change in the yield (Table 2, entry 1 vs Table 1, entry 3). Substrates with electron-rich substituents at the *para*-position of the phenyl ring gave the corresponding products in good yields (Table 2, entries 2 and 3). However, substrates with electron-deficient substituents at the *para* position returned clearly decreased yields (Table 2, entries 4, 5), and the strong electron-deficient 4-nitro substituted **1f** resulted in no reaction (Table 2, entry 6). The negative effects of the electron-deficient substrates on the yields could result from the electron-deficient allylic protons being less reactive toward oxidation. Similar phenomena were observed when the reactions were conducted with substrates containing various substituents at the 3- or 2-position of the phenyl ring (Table 2, entries 7–12).

Next, we examined an all-carbon containing substrate **1m** for this DHDA reaction; as expected, the desired cycloaddition product **2m** was obtained as a single isomer in 80% yield (Table 2, entry 13). Additionally, substrates with one more carbon in the chain lead to similar results as above mentioned (Table 2, entries 14–16). There is no longer an electron withdrawing effect for the allylic proton when a longer carbon chain is employed (Table 2, entry 17). Notably, all these products were obtained with excellent *trans* selectivity. Prenyl tosylate is also a suitable substrate for this DHDA reaction (Table 2, entry 18), offering excellent handle for further synthetic manipulations. Prenyl benzyl ether returned the desired product **3s** in 53% yield, indicating the encouraging level of chemoselectivity (Table 2, entry 19). Surprisingly, simple alkene substrate 2,3-dimethyl-2-butene also gave in the desired DHDA product with moderate yield (Table 2, entry 20).

Encouraged by these results, prenyl derivatives containing nitrogen functional groups were also examined. A substrate containing *N*-benzyl and *N*-tosyl groups resulted in the desired DHDA product in 93% yield with exclusive *trans* selectivity (Table 3, entry 1). A similar result was observed when the benzyl group was substituted by a *p*-methoxybenzyl (PMB) group (Table 3, entry 2).[12] Other sulfonyl groups containing several functional groups such as nitro, alkoxy, and halo could be well tolerated, and the desired DHDA products were obtained with excellent yields (Table 3, entries 3-5). The structures and stereoselectivity were confirmed by NMR and X-ray

Table 3. Selective DHDA reaction of DDQ with prenyl derivatives.[a]



3a-g **4a-g**

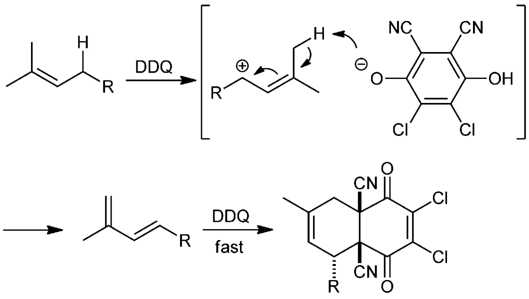
Entry	Substrate	R^1	R^2	Time [h]	Yield [%][b]
1	**3a**	4-CH_3-$C_6H_4SO_2$	Bn	20	96
2	**3b**	4-CH_3-$C_6H_4SO_2$	PMB	20	93
3	**3c**	4-NO_2-$C_6H_4SO_2$	PMB	20	87
4	**3d**	4-CH_3O-$C_6H_4SO_2$	PMB	20	92
5	**3e**	4-Br-$C_6H_4SO_2$	PMB	20	96
6	**3f**	4-NO_2-$C_6H_4SO_2$	C_6H_5	20	95
7	**3g**	C_6H_5	PMB	10	0[c]

[a] Reactions were carried out with compound **3a-g** (0.20 mmol) and DDQ (0.42 mmol) in DCM (2.0 mL) at r.t.

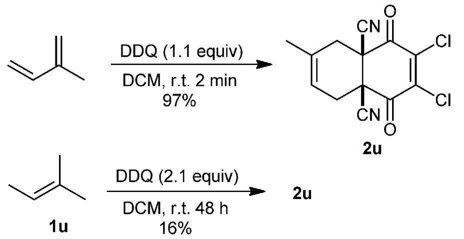
[b] Isolated yield.

[c] 4-Methoxybenzaldehyde was obtained in 81% yield.

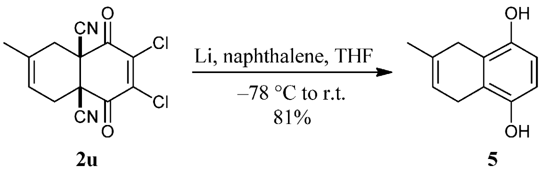
crystal analysis (**4c**, Figure 1).[13] A substrate with *N*-sulfonyl and *N*-phenyl groups also gave excellent results (Table 3, entry 6). However, a substrate with *N*-phenyl and *N*-PMB groups returned no desired DHDA product; in contrast, 4-methoxybenzaldehyde was formed by deprotection of the PMB group (Table 3, entry 7).[12]



Scheme 1. Proposed mechanism.



Scheme 2. Reaction of DDQ with isoprene and **1u**.



Scheme 3. Synthesis of **5**.

A proposed mechanism for this DHDA reaction is depicted in Scheme 1. Initially, a transfer of hydride ion to DDQ occurs, resulting in the formation of an allylic carbocation intermediate and DDHQ. Subsequent deprotonation and rearrangement to an isoprene intermediate, which undergoes a DA reaction with DDQ leads to the cycloaddition product. Notably, most of the reactions need a long reaction time, and the desired isoprene intermediates were not separated during the process. The reason may be because the DA reaction of DDQ with the isoprene intermediates is too faster to be trapped. Indeed, treatment of 1.1 equiv of DDQ with isoprene in DCM at room temperature for 2 min, the desired DA reaction product was obtained in quantitative yield (Scheme 2). Meanwhile, reaction of isoprene precursor **1u** with 2.1 equiv of DDQ for 48 h gave **2u** only in 16% yield. These results indicate the first dehydrogenation step is the rate determine step in this DHDA reaction.

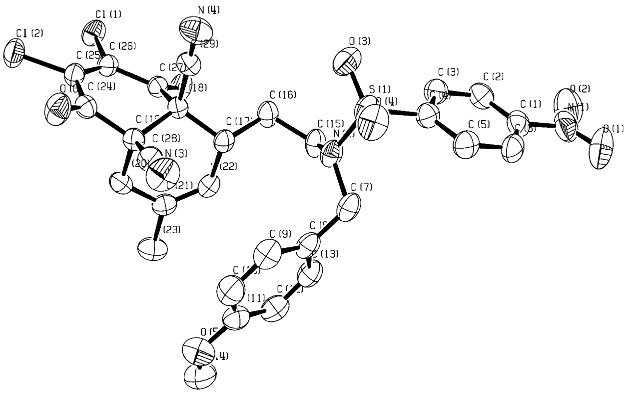


Figure 1. X-ray structure of **4c**.

In summary, we have developed an efficient DHDA reaction of prenyl derivatives with DDQ. A series of DDQ adduct cyclic product were prepared with good to excellent yields and excellent diastereoselectivity. Which are potential building blocks for further transformations (e. g. Scheme 3).[14] The scope of the protocol is large, and the substrates can be flexibly varied. Control experiments indicate that the dehydrogenation step is the rate determine step of this reaction. Further investigations to better understanding the mechanism and to extend the scope and application of this DHDA reaction are underway.

Experimental Section

General Procedure for the DHDA Reaction of DDQ with Prenyl Derivatives (Table 2)

A solution of prenyl substrate (0.20 mmol, 1.0 equiv) and DDQ (94 mg, 0.42 mmol, 2.1 equiv) in DCM (2.0 mL) was stirred at room temperature for 48–60 h. TLC revealed the absence of starting material. The reaction mixture was quenched by saturated $NaHCO_3$ solution (2.0 mL) and extracted with EtOAc (3×5.0 mL). The combined extracts were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether, EtOAc) to yield the corresponding product.

Acknowledgements

We thank the National Natural Science Foundation of China (NSFC-21203148, 21302151), Science and Technology Department of Shaanxi Province (2013 JQ2012), Education Department of Shaanxi Province (2013 JK0644), the New Teachers' Fund for Doctor Stations (20126101120010), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, Ministry of Education, and the Northwest University for financial support.

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[13] A single crystal of compound **4c** was obtained from slow evaporation of the solvent from a solution of **4c** in a mixture of dichloromethane and hexane (1:1) at r. t. All of the hydrogens were omitted for the sake of clarity. CCDC 1027148 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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6 A Dehydrogenative Diels–Alder Reaction of Prenyl Derivatives with 2,3-Dichloro-5,6-dicyanobenzoquinone

Adv. Synth. Catal. **2015**, *357*, 1 – 6

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