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A Concise, Metal-Free Approach to the Synthesis of Oxime Ethers from Cross-Dehydrogenative-Coupling of sp^3 C–H Bonds with Oximes

Jun Jin,[a] Yan Li,[a] Zhi-jing Wang,[a] Wei-xing Qian,*[a] and Wei-liang Bao*[a]

Keywords: Oxime ethers / C-H activation / Allylic compounds / Cross-coupling / Dehydrogenation

A concise oxime ether synthesis by a metal-free dehydrogenative cross-coupling reaction between allylic sp^3 C–H bonds and oximes promoted by 2,3-dichloro-5,6-dicyanoquinone (DDQ) is reported. The corresponding oxime ethers are obtained in good yields.

Introduction

The formation of carbon–heteroatom bonds from a common intermediate is of great significance to the drug discovery process.[1] In particular, the oxime ether motif is a highly effective pharmacophore and is widely applied in pesticide and drug molecular design.[2] For example, oxime ether **A** (Figure 1), which can be used to screen for possible antibacterial and antifungal activities, was found to be a potential anticonvulsant compound.[2h] A series of novel benzoylphenylureas containing oxime ether group **B** (Figure 1) exhibits excellent larvicidal activities against oriental armyworm and mosquito.[2d] Furthermore, oxime ethers have also attracted a lot of attention in organic synthesis, as they can be used as an efficient substrate in 1,2-addition reactions with organometallic[3] or radical species.[4] The conventional method for oxime ether synthesis is the condensation of *O*-alkylhydroxylamines with carbonyl compounds.[5,6] The direct preparation of oxime ethers is commonly limited to base-catalyzed reactions of oximes with alkyl or aryl halides.[7–9] Recently, several new methods have been developed. Takemoto synthesized allylated oxime ethers by using a transition-metal-catalyzed reaction.[10] Copper iodide mediated cross-coupling of aryl halides with oximes was achieved by Wailes.[11] Meyer recently found a copper(II)-mediated cross-coupling of oximes with phenylboronic acid.[12] Direct synthesis of oxime ethers from unactivated alkenes catalyzed by cobalt was reported by Carreira.[13] Although these methods are efficient, they have the drawback of using a metal catalyst, which generates metal-ion-containing waste.[14]

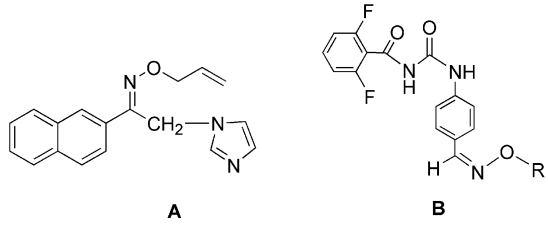

Figure 1. Valuable structures containing an oxime ether motif.

Recently, groups have focused on constructing C–O bonds by the direct utilization of C–H bonds, because the substrates do not need to be prefunctionalized and the reaction is atom economic.[15] Allylic sp^3 C–H bonds were employed for the construction of C–X (X = C/O) bonds.[16] We have developed an oxidative coupling reaction between diarylallylic sp^3 C–H and activated methylenic sp^3 C–H bonds mediated by DDQ.[16b] A concise metal-free oxidative cross-coupling reaction between 1,3-diarylallylic sp^3 C–H bonds and alcohols/thiols to form C–O/C–S bonds has also been uncovered by our group.[16c] It is worthy to note that generation of oxime ethers directly from allylic sp^3 C–H bonds and oxime without a metal catalyst has been studied rarely.

Encouraged by the progress in the activation of diarylallylic sp^3 C–H bonds, we hope to form oxime ethers by similar methodology. Herein, we report a concise metal-free oxidative coupling reaction promoted by 2,3-dichloro-5,6-dicyanoquinone (DDQ) between allylic sp^3 C–H bonds and oximes.

Results and Discussion

We chose 1,3-diphenylpropene (**1a**) and benzaldehyde oxime (**2a**) as the standard substrates to search for the optimized reaction conditions (Table 1). Initially, we examined

[a] Department of Chemistry, Xixi Campus, Zhejiang University, Hangzhou 310028, P. R. China
Fax: +86-571-8827-3814
E-mail: wlbao@css.zju.edu.cn

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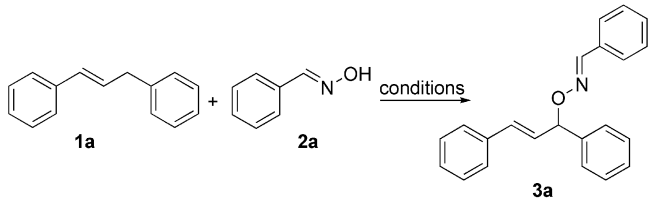
the cross-coupling reaction in CH_2Cl_2. To our delight, desired product **3a** was obtained in 65% yield at room temperature in the presence of DDQ as the oxidant (Table 1, Entry 2). No product was observed in the presence of $PhI(OAc)_2$ and *tert*-butyl peroxide oxidants (Table 1, Entries 12 and 13). To improve the reaction yield, we examined the ratios of 1,3-diphenylpropene to DDQ. It was found that when 1,3-diphenylpropene/DDQ = 1:1.2, the result was better (Table 1, Entry 1). Decreasing the amount of DDQ resulted in reduced yields. If the amount of DDQ was increased to more than 1.5 equivalents, the yield was not improved (Table 1, Entries 10 and 11). No product was detected in the absence of DDQ (Table 1, Entry 14). Various solvents were tested to find the best one. When CH_3NO_2 was used as the solvent, the reaction was slower and the yield was lower (Table 1, Entry 5). The reaction could proceed in 1,4-dioxane, CH_3CN, THF, and $CHCl_3$, but the results were not so good (Table 1, Entries 3, 4, 6, and 7). A drastic decrease in yield occurred when the reaction was warmed (Table 1, Entry 9). Setting the reaction temperature to 0 °C, the oxime ether formed sluggishly and led to 63% product yield after 5 h (Table 1, Entry 8). Therefore, the optimized reaction conditions are: 1,3-diphenylpropene (0.5 mmol)/oxime (0.6 mmol)/DDQ (0.6 mmol)/CH_2Cl_2 (2 mL) at room temperature.

With the optimized conditions in hand, various substrates were subjected to the reaction, and the corresponding results are listed in Table 2. Both aliphatic and aromatic oximes were compatible in the current cross-coupling reaction. In addition, the electronic effect of the substituent on the aromatic oximes was also investigated. Substrates with an electron-donating group on the aromatic ring (Table 2, Entries 2, 3 and 8) reacted rapidly, whereas those with electron-withdrawing groups (Table 2, Entries 4–7) reacted

Table 1. Screening of reaction conditions.[a]

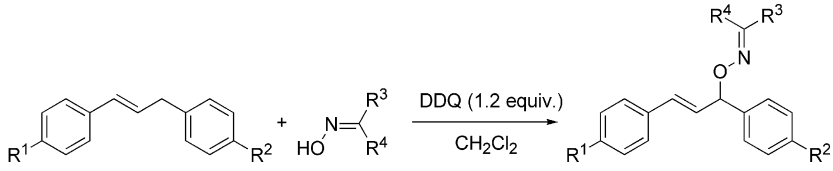


1a 2a 3a

Entry	Oxidant	Solvent	*T* [°C]	Yield[b] [%]
1	DDQ	CH_2Cl_2	r.t.	71[a]
2	DDQ	CH_2Cl_2	r.t.	65[c]
3	DDQ	1,4-dioxane	r.t.	45
4	DDQ	CH_3CN	r.t.	48
5	DDQ	CH_3NO_2	r.t.	40
6	DDQ	THF	r.t.	55
7	DDQ	$CHCl_3$	r.t.	63
8	DDQ	CH_2Cl_2	0	63
9	DDQ	CH_2Cl_2	35	57
10	DDQ	CH_2Cl_2	r.t.	65[d]
11	DDQ	CH_2Cl_2	r.t.	74[e]
12	$PhI(OAc)_2$	CH_2Cl_2	r.t.	0
13	2-(*tert*-butylperoxy)-2-methypropane	CH_2Cl_2	r.t.	0
14	–	CH_2Cl_2	r.t.	0

[a] **1a** (0.5 mmol), **2a** (0.6 mmol), solvent (2 mL), DDQ (0.6 mmol), r.t. (22–27 °C), 1 h. [b] Isolated yield. [c] **1a** (0.6 mmol), DDQ (0.6 mmol). [d] DDQ (0.45 mmol). [e] DDQ (0.75 mmol).

Table 2. Formation of oxime ether with 1,3-diphenylpropene (**1**) and oxime **2**.[a]



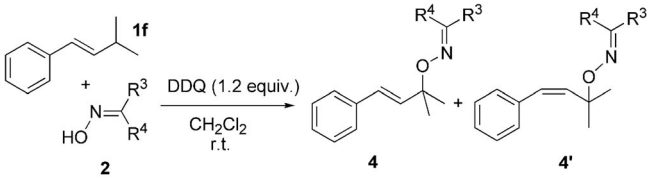
Entry	R^1, R^2	R^3, R^4	Time [min]	Product	Yield[b] [%]
1	H, H: **1a**	C_6H_5, H: **2a**	60	**3a**	71
2	**1a**	4-$CH_3C_6H_4$, H: **2b**	50	**3b**	77
3	**1a**	4-$CH_3OC_6H_4$, H: **2c**	40	**3c**	85
4	**1a**	4-ClC_6H_4, H: **2d**	65	**3d**	67
5	**1a**	3-$NO_2C_6H_4$, H: **2e**	90	**3e**	52
6	**1a**	3-ClC_6H_4, H: **2f**	80	**3f**	61
7	**1a**	2-BrC_6H_4, H: **2g**	65	**3g**	57
8	**1a**	2-$CH_3OC_6H_4$, H: **2h**	50	**3h**	82
9	**1a**	C_6H_5, CH_3: **2i**	65	**3i**	68
10	**1a**	C_6H_5, C_6H_5: **2j**	70	**3j**	63
11	**1a**	2-furanyl, H: **2k**	70	**3k**	55
12	**1a**	1-naphthyl, H: **2l**	60	**3l**	68
13	**1a**	styryl, H: **2m**	70	**3m**	65
14	**1a**	$CH_2(CH_2)_3CH_2$: **2n**	75	**3n**	61
15	Cl, Cl: **1b**	4-$CH_3C_6H_4$, H: **2b**	55	**3o**	65
16	CH_3O, CH_3O: **1c**	4-$CH_3C_6H_4$, H: **2b**	50	**3p**	83
17	H, CH_3: **1d**	4-$CH_3C_6H_4$, H: **2b**	70	**3q**	77[c]
18	H, Cl: **1e**	4-$CH_3C_6H_4$, H: **2b**	80	**3r**	67[c]

[a] **1** (0.5 mmol), **2** (0.6 mmol), CH_2Cl_2 (2 mL), DDQ (0.6 mmol, unless noted), at r.t. [b] Isolated yield. [c] For these two substrates both α- and γ-ethers were formed. For **3q** and **3r** the ratio of the α- and γ-oxime ethers was 2:1 and 3:5, respectively.

slowly and usually resulted in a lower yield. Interestingly, the keto oxime also gave the desired products in good yield (Table 2, Entries 9 and 10). To expand the scope of substrates, we further examined substituted 1,3-diphenylpropenes. The corresponding products were obtained in good yield (Table 2, Entries 15–18). 1,3-Diphenylpropene bearing a methyl group on the aromatic ring could react better than the one with an electron-withdrawing group. However, as for the asymmetrically substituted substrates **1d** and **1e**, both α- and γ-oxime ethers were formed. According to our previous research,[16c] the ratio of α- and γ-oxime ethers was 2:1 and 3:5, respectively (Table 2, Entries 17 and 18).

Encouraged by the above results, we further investigated the reactions between 3-methyl-1-phenylbut-1-ene and oxime. To our delight, the corresponding oxime ether could be successfully formed in moderate to good yield. As indicated in Table 3, the reaction was highly selective, as the *E*-oxime ether was dominant. Oximes containing an electron-rich group on the aromatic ring (Table 3, Entries 1, 4, and 6) reacted rapidly with better stereoselectivity. As for cyclohexanone oxime, no *Z*-oxime ether was produced.

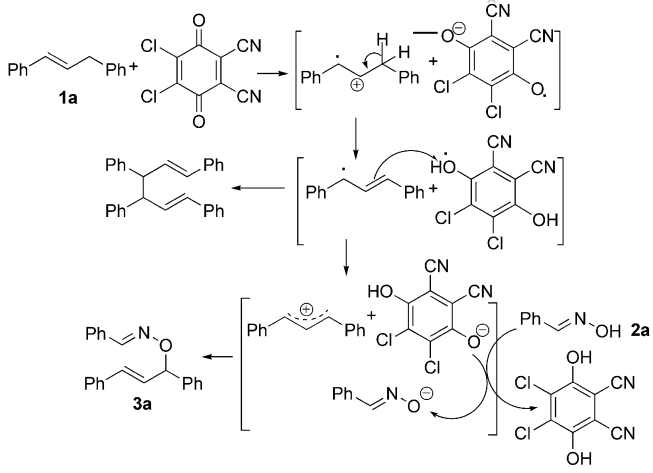
Table 3. Formation of oxime ether with 3-methyl-1-phenylbut-1-ene (**1f**) and oxime **2**.[a]



Entry	R^3, R^4	Time [min]	Product (*E*/*Z*)	Yield[b] [%]
1	4-$CH_3C_6H_4$, H: **2b**	60	**4a/4a′** (10:1)	75
2	3-$NO_2C_6H_4$, H: **2e**	140	**4b/4b′** (4:1)	55
3	2-BrC_6H_4, H: **2g**	130	**4c/4c′** (4:1)	59
4	2-$CH_3OC_6H_4$, H: **2h**	50	**4d/4d′** (50:3)	80
5	C_6H_5, CH_3: **2i**	120	**4e/4e′** (3:1)	65
6	$CH_2(CH_2)_3CH_2$: **2n**	70	**4f/4f′** (>99:1)	67

[a] **1** (0.5 mmol), **2** (0.6 mmol), CH_2Cl_2 (2 mL), DDQ (0.6 mmol, unless noted). [b] Isolated yield.

On the basis of the experimental observations and the literature,[17] a tentative mechanism was thus proposed (Scheme 1). The formation of oxime ethers may follow two pathways: hydride transferred directly from the allylic position to DDQ and/or proton abstraction after an electron was abstracted from the allylic double bond by DDQ. In our experiments, when 2-bromobenzaldehyde oxime was treated with 1,3-diphenylpropene, the self-coupling product of 1,3-diphenylpropene was observed, which implied the coupling reaction may proceed through a single-electron-transfer process. A rearranged product from **1d** or **1e** was also obtained in the experiments. Therefore, an allylic cation may also be involved in the reaction. The incoming nucleophile can attack at the original allylic or γ-position to form the isomerized products.



Scheme 1.

Conclusions

In summary, a novel direct cross-dehydrogenative-coupling (CDC) between allylic compounds and oximes was developed by using DDQ as a promoter. This method provides a highly efficient, fast, and convenient approach to synthesize oxime ethers.

Experimental Section

General Procedure: To a 25-mL round-bottom flask charged with 1,3-diarylpropene (0.5 mmol) and benzaldehyde oxime (0.6 mmol) in CH_2Cl_2 (2 mL) was added DDQ (0.6 mmol). The mixture was stirred at room temperature and monitored by TLC. After the starting material was completely consumed, the reaction mixture was directly passed through Celite and rinsed with ethyl ether (3×10 mL). Then, the combined extracts were washed with brine, dried with $MgSO_4$, and concentrated. Purification was done by column chromatography on silica gel (200–300 mesh; petroleum ether/ethyl acetate, 20:1) to give the pure product.

Supporting Information (see footnote on the first page of this article): Full characterization details and copies of the ^1H and ^{13}C NMR spectra of the prepared compounds.

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