Advanced Synthesis & Catalysis

Title: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-Mediated C(sp2)-C(sp3) Cross-Dehydrogenative Coupling Reaction: α-Alkylation of Push-Pull Enamines and α-Oxo Ketene Dithioacetals

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2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-Mediated C(sp^2)-C(sp^3) Cross-Dehydrogenative Coupling Reaction: α-Alkylation of Push-Pull Enamines and α-Oxo Ketene Dithioacetals

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Abstract. A novel metal-free cross-dehydrogenative coupling (CDC) reaction of C(sp^2)-H of enamines and α-oxo ketene dithioacetals with C(sp^3)-H of 1,3-diarylpropenes mediated by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone is reported. The α-alkylation products are obtained with moderate to good yields. The method provides an efficient and alternative strategy for the synthesis of the corresponding products.

Keywords: C-H activation; Cross-coupling; Dehydrogenation; Metal-free; DDQ

Introduction

The construction of carbon-carbon bond is a fundamental strategy in organic chemistry, which provides the key process for the synthesis of complex molecules[1]. The pioneer work of oxidative coupling of C-C bond from unfunctionalized C-H bonds has been demonstrated by Li[2], which has the advantages as shorter route and more efficient atom economy. In general, metal catalyst is required to combine with the oxidant to furnish the transformation. It is well-known that utilizing metal catalyst brings the drawbacks of metal residual in processing. To avoid the problem, some groups have developed the metal-free oxidative coupling most recently[3]. DDQ has been already proven as an efficient metal-free oxidant in CDC reaction[4]. However, by the detailed survey on reports of the coupling of olefinic C(sp^2) with C(sp^3), it shows still scare among them. For example, Floreancig[4f-g] and co-workers reported intramolecular cyclizations of benzylic or allylic ethers.

Push-pull enamine is an important organic intermediate which usually contains an electron-withdrawing group (EWG), such as carbonyl group or nitrile at α-position, and electron-donating amino group at β-position (**Figure 1**). With α-position nucleophilic core, β-position and EWG dielectrophilic cores, push-pull enamines have diverse applications especially in the synthesis of *N*-heterocycles[5]. Several α-arylation reactions via C-H bond activation have been reported[6]. For example, Georg[6d] group reported an arylation of cyclic enaminones with arylboronic acids via a dual catalytic system of palladium and copper catalysts. To the best of our knowledge, α-alkylation reaction of push-pull enamines via C-H bond activation has not been reported up to now. In continue of our interests in DDQ-mediated metal-free CDC reaction[4a-c,7], the coupling between C(sp^2) of push-pull enamines and C(sp^3) of 1,3-diarylpropenes was developed.

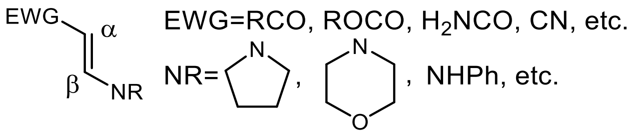
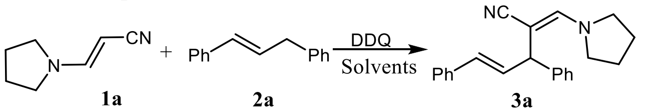


Figure 1 The Structure of Push-pull Enamine

Results and Discussion

Initially, (*E*)-3-(1-pyrrolidinyl)-acrylonitrile **1a** and 1,3-diphenylpropene **2a** were chosen as model substrates for optimization. The reaction was conducted in 1,2-dichloroethane (DCE) with 1.2 equivalent of DDQ (**Table 1**). In consideration of the stability of enamine in the presence of oxidant, **1a** was added to the reaction solution at last. Delightfully, the desired product **3a** was obtained with 66% yield after 3 hours (entry 1). The yield increased to 70% when the reaction time was prolonged to 6 hours. (entry 2). Increasing reaction temperature to 40 °C or decreasing to 0 °C could not improve the yield (entries 4-6). During detecting the ratio of **1a** and **2a**, the yield rose to 78% when the ratio was 1:2 (entries 7-8). The further screening of the solvents could not promote the yield, such as CH_3NO_2, CH_2Cl_2, $CHCl_3$ and 1,4-dioxane (entries 11-14).

Table 1: Optimization Conditions[a]



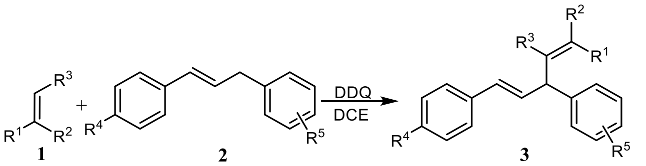
1a **2a** **3a**

entry	**1a**:**2a**	solvent	t (hr)	yield (%)[b]
1	1:1.5	DCE	3	66
2	1:1.5	DCE	6	70
3	1:1.5	DCE	9	69
4[c]	1:1.5	DCE	6	71
5[d]	1:1.5	DCE	6	67
6[d]	1:1.5	DCE	12	70
7	**1:2**	DCE	**6**	**78**
8	1:2.5	DCE	6	78
9[e]	1:2	DCE	6	75
10[f]	1:2	DCE	6	71
11	1:2	CH_3NO_2	6	59
12	1:2	1,4-dioxane	6	56
13	1:2	CH_2Cl_2	6	56
14	1:2	$CHCl_3$	6	70

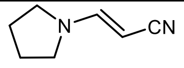
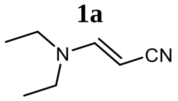
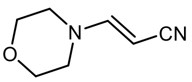
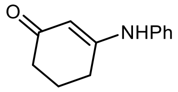
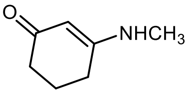
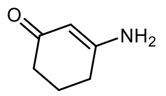
[a] **2a**, DDQ (1.2 equiv.), 2 mL of solvent stirred for 5 mins, then **1a** (0.5 mmol) was added at r.t. [b] Isolated yield. [c] 40 °C. [d] 0 °C. [e] DDQ (1.1 equiv.). [f] DDQ (1.3 equiv.).

With the optimization conditions in hand, the scope of reaction was examined (**Table 2**). Various 1,3-diarylpropenes were subjected to the reaction. The substrate bearing the substitution of *para*-chloro on the aromatic ring, the desired product was obtained with 81% yield (entry 2). While bearing an electron-donating group on the aromatic ring, including methyl and methoxyl, the yields of corresponding products ranged from 64% to 75% (entries 3-6). The yield decreased to 60% when the chloro group was substituted on the *ortho*-position (entry 7), which showed that the reaction had a slight steric effect. It should be noted that a mixture of α-and γ-position isomer products were obtained when the asymmetric 1,3-diarylpropenes were used (entries 2-8). (*E*)-3-Diethylaminoacrylonitrile **1b** and (*E*)-3-(1-morpholino)-acrylonitrile **1c** were suitable for the reaction and the corresponding products were given in good yields (entries 9-10). Except for 3-aminoacrylonitriles, β-amino-ketenes were available push-pull enamines. The desired products were obtained with 66-85% yields when the cyclic β-amino-ketenes were used as substitutes (entries 11-13). However, the coupling products of chain enaminones **1i** and **1j** with 1,3-diphenylpropene **2a** were unstable, and only the hydrolyzed products were obtained in moderate yields (**Scheme 1**). (*E*)-*N*,*N*-dimethyl-2-nitroethen-1-amine **1k** reacted with **2a** to generate the further hydrolyzed product (**Scheme 1**). Neither the coupling product nor hydrolyzed product was obtained when ethyl (*E*)-3-morpholinoacrylate was surveyed. Additionally, *Z*-enamines **1l-1n** were detected. No desired coupling products were given, but only the hydrolyzed products (**Scheme 1**).

Table 2: The Coupling Reaction of 1,3-Diarylpropenes with Push-pull Enamines[a]



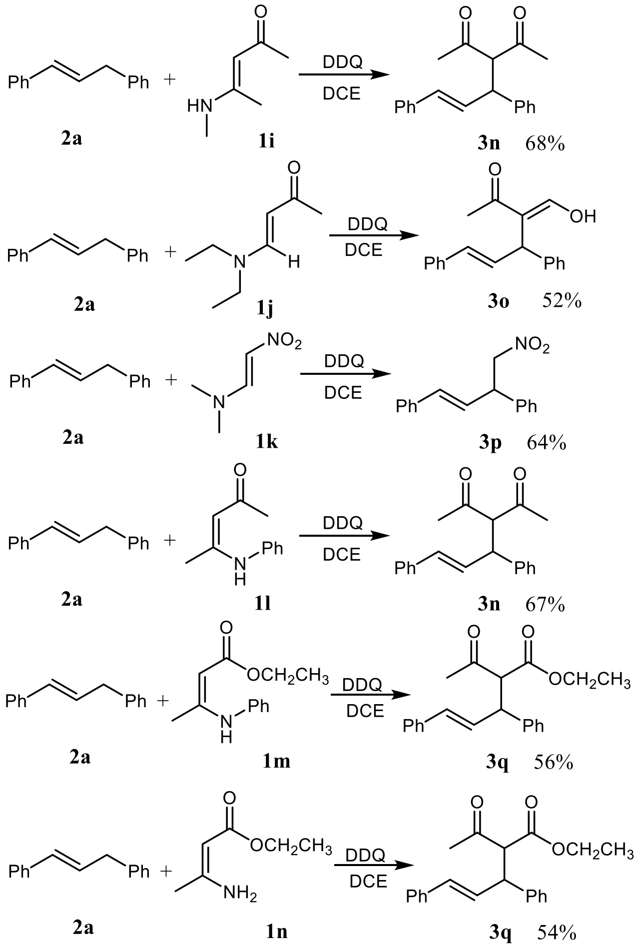
1 **2** **3**

entry	**1**	R⁴, R⁵ **2**	**3**	yield (%)[b]
1	 **1a**	H, H **2a**	**3a**	78
2[c]	**1a**	H, 4-Cl **2b**	**3b**	81
3[c]	**1a**	H, 4-CH_3 **2c**	**3c**	71
4[c]	**1a**	H, 4-OCH_3 **2d**	**3d**	64
5[c]	**1a**	CH_3, H **2e**	**3e**	75
6[c]	**1a**	H, 3-CH_3 **2f**	**3f**	72
7[c]	**1a**	H, 2-Cl **2g**	**3g**	60
8[d]	**1a**	Br, 4-Cl **2h**	**3h**	75
9	 **1b**	H, H **2a**	**3i**	81
10	 **1c**	H, H **2a**	**3j**	73
11	 **1d**	H, H **2a**	**3k**	85
12	 **1e**	H, H **2a**	**3l**	71
13	 **1f**	H, H **2a**	**3m**	66

[a] **2** (1.0 mmol), DDQ (0.6 mmol), 2 mL of DCE, stirred for 5 mins, then **1** (0.5 mmol) was added at r.t., 6 hrs. [b] Isolated yield. [c] α- and γ-position isomer products were obtained and the ratio of **3b**, **3c**, **3d**, **3e**, **3f**, **3g** is 44:56, 60:40, 60:40, 40:60, 50:50, 40:60, respectively. [d] The α- and γ- isomers could not be determined by NMR due to the inherent similarity of chloro and bromo atom.

α-Oxo ketene dithioacetal is another available push-pull structure in organic chemistry[8]. Much efforts has been dedicated to apply it in the synthesis of heterocycle compounds and odorless thiol equivalents[9]. Due to the push-pull effect, the olefinic linkage is polarized and the α-C-H bond is liable to be activated. Liu[10] group reported the α-alkylation of α-oxo ketene dithioacetals with diarylmethane mediated by DDQ. Inspired by this report and our current experiment results, the coupling reaction of α-oxo ketene dithioacetals **4** with 1,3-diphenylpropene **2a** was investigated.

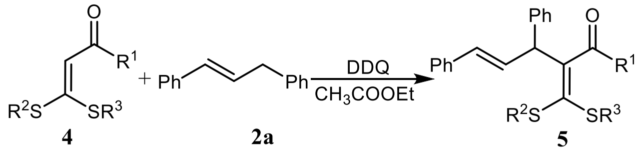
After optimizing the coupling reaction conditions, the desired product **5a** was obtained with 92% yield after one hour, when the reaction of **4a** with **2a** was performed in ethyl acetate in the presence of DDQ (**Table 3**). Several α-aroyl ketene dithioacetals were subjected to the coupling reaction. The corresponding products were obtained in good to excellent yields (entries 1-11). 2-Furoyl- and 2-thienoylketene dithioacetals were applicative for the coupling. Other ketene dithioacetals **4l**–**m** with functional groups at the α-position, including acetyl, carbamoyl, and ethoxycarbonyl, were successfully applied to the coupling reaction (entries 12–14).



Scheme 1 The Reaction of Chain Enamines **1i-1n** with 1,3-Diphenylpropene

In order to reveal the mechanism of reaction, some control experiments were conducted. Radical scavenger TEMPO was added into the reaction mixture of **1a** and **2a**, and as well as in mixture of **4a** and **2a**. The corresponding products of **3a** and **5a** was decreased to 39% and 70%, respectively (**Scheme 2**). It indicated the radical intermediate was generated in the reaction process. Based on the literatures[4h,6a] and our above results, a possible mechanism was depicted in **Scheme 3**. Initially, 1,3-diphenylpropene **2a** reacted with DDQ to generate the radical ion pair **I** by a single electron transfer (SET) process. Then, the ion pair **II** was formed through the hydrogen atom transfer (HAT). Finally, the allylic cation was attacked by the nucleophilic reagent enamine **1a** to give the coupling product **3a**. Due to the occurrence of allylic cation, a mixture of α- and γ-isomer products were obtained when the substrates 1,3-diarylpropenes **2** were unsymmetric.

Table 3: The Coupling Reaction of 1,3-Diphenylpropene with Ketene Dithioacetals[a]



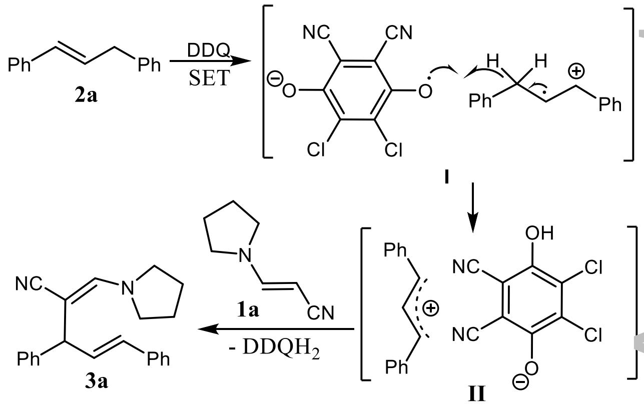
entry	R^1, R^2, R^3 **4**	**5**	yield (%)[b]
1	C_6H_5, -CH_2CH_2- **4a**	**5a**	92
2	4-MeC_6H_4, -CH_2CH_2- **4b**	**5b**	95
3	4-MeOC_6H_4, -CH_2CH_2- **4c**	**5c**	85
4	4-BrC_6H_4, -CH_2CH_2- **4d**	**5d**	98
5	3-MeC_6H_4, -CH_2CH_2- **4e**	**5e**	90
6	2-MeC_6H_4, -CH_2CH_2- **4f**	**5f**	92
7	3-BrC_6H_4, -CH_2CH_2-**4g**	**5g**	91
8	2-ClC_6H_4, -CH_2CH_2- **4h**	**5h**	91
9	2-naphthyl, -CH_2CH_2- **4i**	**5i**	85
10	2-thienyl, -CH_2CH_2- **4j**	**5j**	91
11	2-furyl, -CH_2CH_2- **4k**	**5k**	66
12	NH_2, -CH_2CH_2- **4l**	**5l**	88
13[c]	CH_3, CH_2CH_3, CH_2CH_3 **4m**	**5m**	89
14[c]	CH_3CH_2O, CH_2CH_3, CH_2CH_3 **4n**	**5n**	31

[a] 0.5 mmol of **4**, 1.0 mmol of **2a**, 0.6 mmol of DDQ, 2 mL of ethyl acetate, r.t. 1 hr. [b] Isolated yield. [c] 6 hrs.

$$\mathbf{1a} + \mathbf{2a} \xrightarrow[\text{TEMPO (2.0 equiv)}]{\text{DDQ}} \mathbf{3a}\ \text{(39\% yield)}$$

$$\mathbf{4a} + \mathbf{2a} \xrightarrow[\text{TEMPO (2.0 equiv)}]{\text{DDQ}} \mathbf{5a}\ \text{(70\% yield)}$$

Scheme 2 The Control Experiments



Scheme 3 Possible Mechanism

Conclusion

In summary, we developed a novel DDQ mediated metal-free CDC reaction of push-pull enamines and α-oxo ketene dithioacetals with 1,3-diarylpropenes which gave the C(sp^3)-H and C(sp^2)-H coupling products with moderate to excellent yields. It provides a convenient method for the synthesis of the corresponding product.

Experimental Section

General information. Column chromatography was carried out on silica gel (200-300 mesh). ^{1}H NMR spectra were recorded on a 500 or 600 MHz spectrometer. ^{13}C NMR spectra were recorded on a 125 or 150 MHz spectrometer. Chemical shifts were reported in parts per million (δ) relative to the internal standard TMS (0 ppm) for $CDCl_3$. The coupling constants, *J*, were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded on ESI-TOF. The reagents were purchased from commercial chemical reagent companies and used without further purification unless otherwise stated.

1. General procedure for the synthesis of 3: A solution of 1,3-diarylpropene **2** (1.0 mmol) and DDQ (0.6 mmol, 0.136 g) in CH_2ClCH_2Cl (2 mL) was stirred for 5 minutes, then enamine **1** (0.5 mmol) was added. The resulting mixture was stirred for 6 hrs at room temperature. After completion of the reaction, the solvent was concentrated under reduced pressure. Purification was done by column chromatography on silica gel (200-300 mesh) with petroleum ether and ethyl acetate (8:1) as the eluent to give the pure product **3**.

2. General procedure for the synthesis of 5: To a solution of α-oxo ketene dithioacetal **4** (0.5 mmol) and 1,3-diphenylpropene **2a** (1.0 mmol) in ethyl acetate (2 mL), DDQ (0.6 mmol, 0.136 g) was added. The resulting mixture was stirred for 1 hr at room temperature. After completion of the reaction, the solvent was concentrated under reduced pressure. Purification was done by column chromatography on silica gel (200-300 mesh) with petroleum ether and ethyl acetate (8:1) as the eluent to give the pure product **5**.

Supporting information

Characterization data and copies of ^{1}H and ^{13}C NMR spectra for all isolated compounds **3** and **5**.

Acknowledgements

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FULL PAPER

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