Tetrahedron Letters 56 (2015) 1641–1644

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The oxidative coupling of benzylic compounds catalyzed by 2,3-dichloro-5,6-dicyano-benzoquinone and sodium nitrite using molecular oxygen as a co-oxidant

Dongping Cheng[a], Kun Yuan[a], Xiaoliang Xu[b], Jizhong Yan[a,*]

[a] College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China
[b] College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China

ARTICLE INFO

Article history:
Received 27 November 2014
Revised 30 January 2015
Accepted 6 February 2015
Available online 12 February 2015

Keywords:
C–C coupling
DDQ
Oxidation
Molecular oxygen

ABSTRACT

Catalyzed by DDQ and $NaNO_2$, the oxidative coupling between benzylic compounds and 1,3-dicarbonyls in the presence of molecular oxygen and HCOOH was developed. The 1% catalytic amount of DDQ is enough to complete the reaction. This system shows high efficiency and the coupling products are obtained in good to excellent yields within half an hour.

The construction of C–C bond is one of the most fundamental and important reactions in organic synthesis because it provides key step in the synthesis of complex molecules. In the past decade, the construction of C–C bond via C–H oxidative activation is a hot topic owing to avoiding the use of pre-functionalized precursors and improving the atom-economy.[1,2] Oxidants such as di-*tert*-butyl peroxide, *tert*-butyl-hydroperoxide, hydrogen peroxide, molecular oxygen have been already proved to be efficient in the oxidative coupling reaction. From the point of green chemistry,[3] use of molecular oxygen as the terminal oxidant is the most ideal way because of its great abundance in nature and water as the only by-product. It is well-known that molecular oxygen is almost inert under mild conditions due to the energy barrier between substrate and molecular oxygen. To accomplish the oxidation, transition metals or transition-metal complexes have been usually required to active molecular oxygen.[4–6] However, transition metals are generally expensive and potentially toxic and especially some transition-metal complexes are not easily available. Thus, transition-metal-free coupling reaction which simultaneously employs molecular oxygen as oxidizing reagent has attracted increasing interest in recent years.

2,3-Dichloro-5,6-dicyano-benzoquinone (DDQ), being a well-known oxidant, has been widely applied in oxidative coupling reactions.[7–31] Unfortunately, a stoichiometric or excess amount of DDQ is usually required in order to make the reaction to fully complete and the by-product DDQ-H_2 causes the purification difficulty. A practical way to solve this problem is to develop a method in which only a catalytic amount of DDQ is needed.[32–41] In 2010, Floreancig reported that several oxidative reactions including the coupling of acetophenone with isochroman, were catalyzed by 15–20 mol % of DDQ with up to 6 equiv of MnO_2 as a co-oxidant.[36] The amount of DDQ is greatly decreased, but the use of excess amounts of co-oxidant generates larger amounts of unwanted by-product. Molecular oxygen is a terminal oxidant and it is ideal if molecular oxygen can be employed as co-oxidant in DDQ-mediated reactions. However, molecular oxygen cannot directly transform the in situ formed DDQ-H_2 to DDQ under mild conditions, which means that an additional compound should act as the bridge between molecular oxygen and the cycle of DDQ-H_2 and DDQ. Very recently, Prabhu published the first report of regenerating DDQ by using catalytic amount of azobisisobutyronitrile and molecular oxygen.[39] In order to complete the coupling reaction of *N*-aryltetrahydroisoquinoline, the catalytic amount of DDQ is up to 10 mol %. With the interest of applying of catalytic DDQ in the oxidative reaction, herein, we wish to report an efficient coupling reaction of benzylic compounds and 1,3-dicarbonyls catalyzed by DDQ (1 mol %) and $NaNO_2$ in the atmosphere of molecular oxygen.

Firstly, catalyzed by 10 mol % DDQ and 10 mol % $NaNO_2$, 1,3-diphenyl 1,3-propanedione **1a**, and 1,3-diphenyl propene **2a** were chosen as model substrates at room temperature in the

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[*] Corresponding author. Fax: +86 571 8832 0913.
E-mail address: yjz@zjut.edu.cn (J. Yan).

http://dx.doi.org/10.1016/j.tetlet.2015.02.018
0040-4039/

presence of O_2. To our delight, the coupling product could be obtained although the yield was only 15% (Table 1, entry 1). The yield was increased to 28% when acetic acid was added to the system. The reason may be that the acid could promote the decomposition of $NaNO_2$ to NO which rapidly reacted with O_2 to form NO_2.[42,43] Other acids were surveyed and similar results were observed (Table 1, entries 2–6). The yield was up to 78% when a mixture of $HCOOH/CH_2Cl_2$ was used. Then a number of solvents were examined (Table 1, entries 7–10). The reaction could proceed in DCE, $CHCl_3$, and CH_3CN, but the yield was low. CH_3NO_2 was a relatively suitable solvent for the reaction. No product was obtained when the reaction was performed in the absence of DDQ (Table 1, entry 11). In the absence of HCOOH, $NaNO_2$, or molecular oxygen, the catalytic system showed poor reactivity (Table 1, entries 12–14). To decrease the amount of DDQ, 1 mol % of DDQ was examined and the product was obtained in 76% yield (Table 1, entry 15). When the reaction was carried out at 40 °C, the yield was improved to 98% (Table 1, entry 16). However, the yield was decreased if the temperature was increased to 60 or 80 °C (Table 1, entries 17–18). The reason might be that $NaNO_2$ decomposed rapidly under high temperatures.

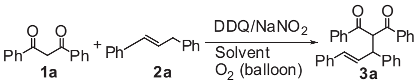
With the best reaction conditions in hand, various substrates were subjected to the coupling reaction (Table 2). It was shown that the catalytic system exhibits high reactivity toward the examined compounds. As far as the active compounds **1** were concerned, obvious electron effect was observed. The benzene ring with electron-donating group such as methyl, methoxyl gave the corresponding products in 82–99% yields (Table 2, entries 2–3, 5–6). In comparison, a moderate yield was obtained when benzene ring had fluorine substituent (Table 2, entry 7). In the reaction, it was found that 1,3-diphenyl propene was converted to allyl alcohol which was further oxidized to the corresponding ketone. When substrate **1g** reacted with 1,3-diphenyl propene **2a**, the by-product 1,3-diphenyl propen-3-one was given in 44% yield. Heteroaryl species were acted as well and afforded the coupling products in excellent yields (Table 2, entries 8–9). β-Keto esters such as ethyl benzoylacetate, ethyl acetoacetate were compatible with the catalytic system (Table 2, entries 12–13). It should be pointed out that the products **3b**–**3m** were mixtures of diastereoisomers when nonsymmetrical β-diketones or β-ketoesters were used as substrates. To expand the scope of the substrate, different 1,3-diaryl propenes were investigated (Table 2, entries 14–18). As for the asymmetrical substituted substrates **2b**, **2d**, **2e**, and **2f**, both α- and γ-products were obtained. The ratios of α- and γ-products were 3:2, 7:3, 2:3, and 9:11 for **3n**, **3p**, **3q**, and **3r** according to NMR, respectively.

Finally, the gram-scale application of this catalytic system is investigated.[44] A reaction of 5 mmol (1.12 g) 1,3-diphenyl 1,3-propanedione **1a** and 6 mmol (1.16 g) 1,3-diphenyl propene **2a** was carried out with 1 mol % DDQ, 10 mol % $NaNO_2$ in CH_3NO_2 (15 mL) and HCOOH (7.5 mL) under oxygen balloon at 40 °C. The coupling product was obtained in 88% yield, which indicated that our catalytic system was an efficient and practical process for the oxidative coupling reaction of benzylic compounds with 1,3-dicarbonyls.

On the base of our results and literatures[35,40] an additional experiment was tested. 0.5 mmol DDQ-H_2 and 0.05 mmol $NaNO_2$ were mixed and stirred in CH_3NO_2/HCOOH under oxygen balloon. DDQ-H_2 was completely oxidized to DDQ in ten minutes. It shows that NO can be oxidized to NO_2 in the presence of O_2 and NO_2 can readily oxidize DDQ-H_2 to DDQ.

A possible mechanism for the coupling reaction was proposed in Scheme 1. The reaction may proceed through three pathways. One is a one-step hydride transfer to DDQ; the other two are hydrogen atom abstraction or proton abstraction followed by a second electron transfer after an initial electron transfer.[16] In the experiment, we obtained the 1,3-diphenyl propen-3-one which should be in situ formed by further oxidation of 1,3-diphenyl propene. The diastereoisomer products were given in the reaction of 1,3-diphenylpropene with nonsymmetrical β-diketones or β-ketoesters. The asymmetrical 1,3-diarylpropene **2b**, **2d**, **2e**, and **2f** coupled with 1,3-diphenyl 1,3-propanedione to generate a mixture of the corresponding α- and γ-products. The above results indicated the allylic cation with itself being rearranged between α- and γ-positions involved in the coupling reaction. The attack of the nucleophile to α- or γ-position gave the isomerized products. The α-products were more stable than the γ-products when **2b** and **2d** were chosen as the substrates. As for **2e** and **2f**, the

Table 1
Optimization of the oxidative coupling[a]

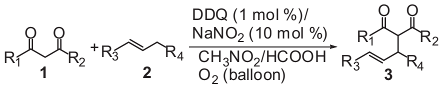


Entry	DDQ (mol %)	$NaNO_2$ (mol %)	Acid/solvent	Temp (°C)	Yield[b] (%)
1	10	10	CH_2Cl_2	rt	15
2	10	10	CH_3COOH/CH_2Cl_2	rt	28
3	10	10	$(COOH)_2/CH_2Cl_2$	rt	21
4	10	10	HCl/CH_2Cl_2	rt	22
5	10	10	$C_6H_5CO_2H/CH_2Cl_2$	rt	29
6	10	10	$HCOOH/CH_2Cl_2$	rt	78
7	10	10	HCOOH/DCE	rt	53
8	10	10	$HCOOH/CHCl_3$	rt	25
9	10	10	$HCOOH/CH_3CN$	rt	26
10	10	10	$HCOOH/CH_3NO_2$	rt	86
11	0	10	$HCOOH/CH_3NO_2$	rt	0
12	10	10	CH_3NO_2	rt	16
13	10	0	$HCOOH/CH_3NO_2$	rt	9
14[c]	10	10	$HCOOH/CH_3NO_2$	rt	10
15	1	10	$HCOOH/CH_3NO_2$	rt	76
16	1	10	$HCOOH/CH_3NO_2$	40	98
17	1	10	$HCOOH/CH_3NO_2$	60	91
18	1	10	$HCOOH/CH_3NO_2$	80	80

[a] **1a** (0.5 mmol, 0.112 g), **2a** (0.6 mmol, 0.128 g), solvent (2.5 mL), acid (0.25 mL), O_2 balloon, 0.5 h.
[b] Isolation yield.
[c] In the absence of molecular oxygen.

Table 2

The oxidative coupling of 1,3-diarylpropenes[a]



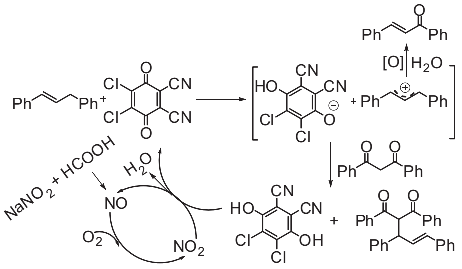
Entry	R_1, R_2 **1**	R_3, R_4 **2**	Product **3**	Yield[b] (%)
1	C_6H_5, C_6H_5 (**1a**)	C_6H_5, C_6H_5 (**2a**)	**3a**	98
2	C_6H_5, 2-$CH_3C_6H_4$ (**1b**)	**2a**	**3b**	99
3	C_6H_5, 3-$CH_3OC_6H_4$ (**1c**)	**2a**	**3c**	82
4	C_6H_5, 3-BrC_6H_4 (**1d**)	**2a**	**3d**	91
5	C_6H_5, 4-$CH_3OC_6H_4$ (**1e**)	**2a**	**3e**	99
6	C_6H_5, 4-$CH_3C_6H_4$ (**1f**)	**2a**	**3f**	88
7	C_6H_5, 4-FC_6H_4 (**1g**)	**2a**	**3g**	48
8	C_6H_5, Thienyl (**1h**)	**2a**	**3h**	99
9	C_6H_5, Furanyl (**1i**)	**2a**	**3i**	99
10	C_6H_5, CH_3 (**1j**)	**2a**	**3j**	94
11	CH_3, CH_3 (**1k**)	**2a**	**3k**	80
12	C_6H_5, OCH_2CH_3 (**1l**)	**2a**	**3l**	91
13[c]	CH_3, OCH_2CH_3 (**1m**)	**2a**	**3m**	83
14	**1a**	C_6H_5, 4-$CH_3OC_6H_4$ (**2b**)	**3n**[d]	84
15	**1a**	4-$CH_3OC_6H_4$, 4-$CH_3OC_6H_4$ (**2c**)	**3o**	41
16	**1a**	C_6H_5, 4-$CH_3C_6H_4$ (**2d**)	**3p**[d]	86
17	**1a**	C_6H_5, 4-BrC_6H_4 (**2e**)	**3q**[d]	86
18	**1a**	4-$CH_3OC_6H_4$, C_6H_5 (**2f**)	**3r**[d]	72

[a] **1** (0.5 mmol), **2** (0.6 mmol), DDQ (0.005 mmol), $NaNO_2$ (0.05 mmol), CH_3NO_2 (2.5 mL), HCOOH (0.25 mL), 40 °C, O_2 balloon, 0.5 h.

[b] Isolation yield.

[c] **1** (0.6 mmol), **2** (0.5 mmol).

[d] For all of these substrates both α- and γ-products were formed. For **3n**, **3p**, **3q**, and **3r**, the ratios of the α- and γ-products were separately 3:2, 7:3, 2:3, and 9:11 determined by NMR.



Scheme 1. Possible mechanism for the coupling reaction.

γ-products were the main products. It tended to support the intermediacy of an allylic cation that preferred to couple on the allylic carbon where the positive charge was stabilized to the greatest extent by an electron-donating group. As far as the regeneration of DDQ was concerned, at first, NO released from $NaNO_2$ in the presence of HCOOH was oxidized to NO_2 by dioxygen. Then the by-product DDQ-H_2 was oxidized to regenerate DDQ by NO_2. Finally, the reduced NO was reoxidized to NO_2 by O_2.

We have developed an efficient and mild catalytic system of DDQ/$NaNO_2$/O_2 for the oxidative coupling reaction of benzylic compounds with 1,3-dicarbonyls. It was worth mentioning that the catalytic amount of DDQ was the least up to now and only one percent was necessary.

Acknowledgment

The authors are grateful to Zhejiang Provincial Natural Science Foundation of China (No. LY12B02017).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.02.018.

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44. First, a reaction of 5 mmol (1.12 g) 1,3-diphenyl 1,3-propanedione **1a** and 6 mmol (1.16 g) 1,3-diphenyl propene **2a** was carried out under the optimized reaction. The coupling product was obtained in 55% yield. This poor result might be owing to the small amount of HCOOH in the solvent. Then, the amounts of CH_3NO_2 and HCOOH were changed to 15 mL and 7.5 mL respectively. To our delight, the reaction was completed after half an hour and the coupling product was obtained in 88% yield.