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Propargylation of 1,3-Dicarbonyl Compounds with 1,3-Diarylpropynes via Oxidative Cross-Coupling between sp^3 C−H and sp^3 C−H

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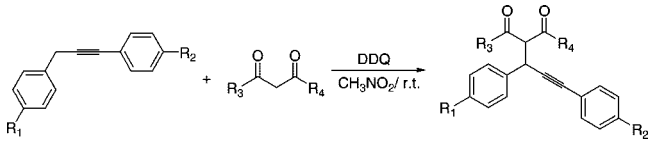

A highly efficient oxidative-coupling reaction between diarylpropargylic sp^3 C−H and active methylenic sp^3 C−H was achieved with DDQ as oxidant. The reaction afforded a direct method for the propargylation of 1,3-dicarbonyl compounds, thus providing a concise synthesis of the corresponding products.

C−C bond formation by direct oxidative cross-coupling of two unfunctionalized substrates has attracted great interest recently. In such transformation, starting materials could be used directly in C−H form without prefunctionalization and thus the synthetic procedure could be shorter, simpler, and atom economical. A number of excellent achivements have been made.[1,2] The developed C−C bond formation by oxidative cross-coupling included the following types: (1) sp^3 C−H and sp^3 C−H; (2) sp^2 C−H with sp^2 C−H; (3) sp^3 C−H with sp^2 C−H; and (4) sp^3 C−H with sp C−H. However, the sp^3 C−H bonds that undergo the cross-coupling reaction usually locate at the α-position of a heteroatom such as nitrogen, oxygen, or sulfur atom.[2] The reason may lie in that the heteroatom activates the adjacent sp^3 C−H bond and further stabilizes the *in situ* formed intermediate. In contrast, the activation of the C−H bond adjacent to the carbon atom has scarcely been explored. Only a few reactions were reported. For example, the allylic sp^3 C−H bond of cyclohexene was coupled with the methylenic sp^3 C−H bond with copper(I) bromide and cobalt(II) chloride as the catalyst.[2e] The coupling of cyclohexane or diarylmethane with methylene compounds catalyzed by the system of $FeCl_2$/(t-$Bu)_2O_2$ was reported.[2b,c] In these cases, one or two metal catalysts were usually coordinated with an oxidative reagent to activate the C−H bond. Li's group has also reported a highly efficient coupling reaction between benzyl ethers and simple ketones mediated by DDQ without using any metal catalyst.[2f] With the interest in activation of the C−H bond,[3] we herein wish to report a highly efficient and concise oxidative cross-coupling reaction between diarylpropargylic sp^3 C−H and active methylenic sp^3 C−H mediated by DDQ.

The alkylation of 1,3-dicarbonyl compounds represents one of the most common C−C bond formation methodologies in organic synthesis. An efficient and atom economical approach to the alkylation of 1,3-dicarbonyl compounds is to use alcohols as electrophiles with such catalysts as transition metals, Brønsted acids, or Lewis acids.[4] However, such a strategy has been applied mostly to the synthesis of allyl- and benzyl-substituted 1,3-dicarbonyl compounds, and little attention has been paid to the propargylation of 1,3-dicarbonyl compound, although the corresponding products are useful synthetic intermediates. Very recently, three examples concerning the propargylation of 1,3-dicarbonyl compounds with propargylic alcohols were reported.[5] However, the propargylation with use of the propargylic C−H bond directly still remains a challenge.

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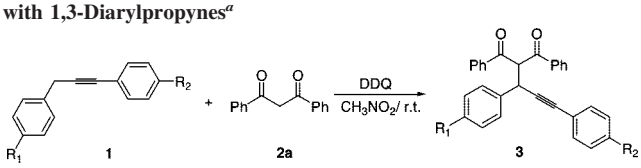
TABLE 1. Study of DDQ-Promoted C−C Bond-Forming Reaction with 1,3-Diarylpropynes[a]



entry	R_1, R_2	time (h)	yield (%)[b]	product
1[c]	H, H (**1a**)	10	49	**3a**
2	H, H (**1a**)	10	56	**3a**
3	CH_3, H (**1b**)	6	75	**3b**
4	CH_3O, H (**1c**)	3	91	**3c**
5	Cl, H (**1d**)	12	44	**3d**
6	H, CH_3O (**1e**)	10	52	**3e**

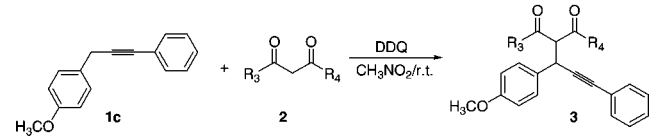
[a] Conditions: 0.5 mmol of **2a**, 0.6 mmol of **1**, 1.5 mL of $MeNO_2$, 0.6 mmol of DDQ. [b] Isolated yield. [c] 1.5 mL of CH_2Cl_2 was used as solvent.

Montevecchi has reported that phenylalkylacetylenes were oxidized to conjugated (*Z*)-enynes by DDQ.[6] The first step of the reaction was described as a single-electron-transfer process between the alkyne triple bond and DDQ, which generates the radical ion pair. Then it transforms into its ion pair through hydrogen atom transfer from the alkyne radical cation to $DDQ^{\bullet-}$. In light of the mechanism and our recent findings, we explored the coupling between 1,3-diphenylpropyne **1a** and dicarbonyl compound **2a**. The reaction was carried out with DDQ in CH_2Cl_2 at room temperature. A color change from colorless to deep blue was observed, which may indicate the formation of a complex.[7] The desired product **3a** was obtained in 49% yield in 10 h (Table 1, entry 1). Then a number of solvents were screened to optimize the reaction conditions. No coupling product was obtained when the reaction was carried out in THF or dioxane. The reaction could proceed in DMSO, DMF, $CHCl_3$, CH_2Cl_2, DCE, $MeNO_2$, and NMP. The highest yield (56%) resulted from the reaction in $MeNO_2$ (Table 1, entry 2). The yield did not improve markedly when the temperature was raised to 90 °C in $MeNO_2$. It seemed that the reaction was insensitive to temperature. As for the influence of DDQ dosage on the reaction, it was found that decreasing the amount of the DDQ resulted in reduced yield, while increasing the amount to 1.5 equiv did not make the reaction system complex and the yield was just a little lower.

The scope of the coupling reaction was explored. Thus the electronic effect of the benzylic ring was first examined. Compounds **1b** and **1c** possessing an electron-donating group on the benzylic ring coupled with dicarbonyl compound **2a** efficiently and products **3b** and **3c** were obtained in 75% and 91% yield, respectively (Table 1, entries 3 and 4). In comparison, the reaction of **1d** possessing a *p*-chloro group on the benzylic ring proceeded slowly and gave product **3d** in 44% yield only (Table 1, entry 5). Electron-donating substituents such as methyl and methoxyl group can efficiently stabilize the benzylic cationic species and hence promote the desired C−C bond-forming process. On the other hand, treatment of 1-(4-methoxylphenyl)-3-phenylpropyne **1e** with **2a** at room temperature afforded 52% yield (Table 1, entry 6). The "R_2" substituent on the benzene ring exerts little influence on the coupling reaction.

Various substrates were subjected to this cross-coupling reaction (Table 2). It could be concluded from the table that

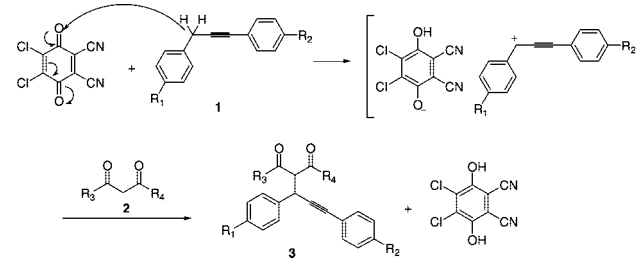
TABLE 2. DDQ-Promoted C−C Bond-Forming Reaction with 3-(4-Methoxylphenyl)-1-phenylpropyne 1c and Active Methylenic Compounds[a]



entry	R_3, R_4	time (h)	yield (%)[b]	product
1	4-$CH_3C_6H_4$, C_6H_5 (**2b**)	1	92	**3f**
2	4-$CH_3OC_6H_4$, C_6H_5 (**2c**)	1	83	**3g**
3	4-ClC_6H_4, C_6H_5 (**2d**)	4	64	**3h**
4	4-BrC_6H_4, C_6H_5 (**2e**)	4	70	**3i**
5	3-ClC_6H_4, C_6H_5 (**2f**)	5	76	**3j**
6	3-$CH_3OC_6H_4$, C_6H_5 (**2g**)	2	80	**3k**
7	2-$CH_3C_6H_4$, C_6H_5 (**2h**)	0.5	82	***3l***
8	thienyl, C_6H_5 (**2i**)	0.5	81	**3m**
9	furanyl, C_6H_5 (**2j**)	1.5	74	**3n**
10	C_6H_5, CH_3 (**2k**)	1.0	92	**3o**
11[c]	C_6H_5, OEt (***2l***)	7	48	**3p**
12[c]	CH_3, CH_3 (**2m**)	10	47	**3q**

[a] Conditions: 0.5 mmol of **2**, 0.6 mmol of **1c**, 1.5 mL of $MeNO_2$, 0.6 mmol of DDQ. [b] Isolated yield. [c] 0.5 mmol of **2l** or **2m**, 0.6 mmol of **1c**, 0.6 mmol of DDQ, 90 °C.

SCHEME 1. A Possible Mechanism



electron-donating substituents on the aromatic ring of substrates **2** also exhibited a positive effect. For example, dicarbonyl compounds **2b**, **2c**, **2g**, and **2h**, which bear electron-donating substituents on the aromatic ring, reacted rapidly with propargylic compound **3c** and satisfactory yields were obtained (Table 2, entries 1, 2, 6, and 7). For substrates **2d**, **2e**, and **2f**, which bear electron-withdrawing groups, longer time was required for the reaction to be completed and relatively lower yields (64−76%) were afforded (Table 2, entries 3−5). Heterocyclic aryl groups such as furanyl and thienyl were compatible with the present procedure (Table 2, entries 8 and 9). Benzoylacetone was a suitable candidate here (Table 2, entry 10). Acetylacetone and ethyl benzoylacetate could also be used as the substrates despite the lower rate and yields. Again, raising the reaction temperature to 90 °C did not result in considerable yield improvement (Table 2, entries 11 and 12).

According to literature[7] and based on our experiments, a possible mechanism was proposed in Scheme 1. The formation of product may have two pathways, hydride transferred directly from propargylic position and/or hydrogen abstraction after an electron was transferred from the propargylic triple bond to DDQ. However, compounds **1c** and **1e** reacted with dicarbonyl compound **2a** to give the sole products **3c** and **3e**, respectively. The incoming nucleophile attacks mainly at the original benzylic cation position. This means the mechanism of hydride abstraction may be more possible.

In summary, we have developed an efficient coupling reaction between diarylpropargylic compounds and active methylenes using DDQ as a promoter. It is the first C−C bond-formation

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example by activating the diarylpropargylic sp^3 C−H bond directly. It avoids prefunctionalization of the starting materials and thus provides a concise synthesis of propargyl-substituted carbonyl compounds.

Experimental Section

To a 10 mL two-necked round-bottomed flask containing methylenic compound **2a** (0.5 mmol, 0.112 g), 1,3-diarylpropyne **1c** (0.6 mmol, 0.133 g), and $MeNO_2$ (1.5 mL) was added DDQ (0.6 mmol, 0.136 g). The resulting mixture was stirred for 3 h at room temperature. Purification was done by column chromatography on silica gel (200−300 mesh) with petroleum ether and ethyl acetate (10:1) as the eluent to give the pure product **3c** (0.203 g, 91%). Mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 8.13 (d, J = 7.6 Hz, 2H), 7.78 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.51−7.44 (m, 5H), 7.31 (t, J = 7.6 Hz, 2H), 7.26−7.13 (m, 3H), 7.01 (d, J = 6.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 5.88 (d, J = 10.4 Hz, 1H), 5.14 (d, J = 9.6 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 193.4, 192.6, 158.8, 137.0, 136.5, 133.5, 133.4, 131.4, 131.2, 129.6, 129.1, 128.8, 128.6, 128.5, 127.9, 127.88, 122.9, 114.0, 89.7, 85.0, 63.3, 55.2, 38.0; ESI-MS m/z 467.2 [M + Na]. Anal. Calcd for $C_{31}H_{24}O_3$: C, 83.76; H, 5.44. Found: C, 83.54; H, 5.61. For more details, see the Supporting Information.

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Supporting Information Available: Experimental procedures and compound characterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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