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Domino Cross Dehydrogenative Coupling of 2-Aryl Acetals with Ketones Using DDQ as Oxidant and Reactant Precursor

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A novel domino cross dehydrogenative coupling of 2-aryl acetals with unmodified ketones has been developed, using DDQ as both the oxidant and reactant precursor.

Keywords acetals, C—H activation, DDQ, cross dehydrogenative coupling, ketones

Introduction

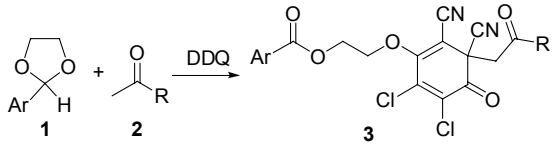
Cross-coupling reactions involving C—H activation have emerged as robust alternatives to conventional transformations for the construction of new C—C and C-hetero bonds.[1] Among these cross-coupling reactions, considerable attention has been paid to cross-dehydrogenative-coupling (CDC) reactions.[2] Owing to avoiding the use of functionalized substrates, they have been a more atom-economic and environmentally friendly method and a very promising tool for the creation of new bonds.

The CDC reactions of various sp^3 C—H bonds, such as α-C—H bonds of tertiary amines,[3] ethers[1c] and π-systems including arenes,[4] alkenes[5] and alkynes,[6] with a variety of electrophiles have been successfully developed.[2]

Acetals are important compounds, and widely used as protective groups for 1,2-/1,3-diols, and carbonyl group.[7] In fact, acetals are geminal diethers and somewhat similar to ethers, but are more susceptible to oxidation than ethers. To the best of our knowledge, however, no examples of CDC reactions of acetals are available. The similarity to ethers and susceptibility to oxidation inspired us to embark on an investigation of CDC reactions of acetals with unmodified ketones, with the aim of seeking procedures for oriented synthesis of monoprotected β-dicarbonyl compounds.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a well-known oxidant in organic synthesis[8] and has been utilized in efficient CDC reactions involving sp^3 C—H activation.[5,6,9] In these transformations, DDQ usually serves only as dehydrogenating reagent and is not incorporated into the final product.[10]

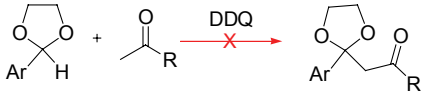
Herein, we report for the first time a novel domino CDC reaction of acetals with methyl ketones by sp^3 C—H activation using DDQ as the oxidant and reactant precursor. It allows the incorporation of DDQ as molecular moiety into the final product (Eq. 1).



(1)

Results and Discussion

Initially, we attempted to perform the coupling reaction of 2-phenyl-1,3-dioxolane (**1a**) and acetophenone (**2a**) using DDQ as oxidant under N_2 atmosphere at 100 ℃, hopefully achieving the coupled product by sp^3 C—H activation and subsequent C—C bond formation (Eq. 2, Ar＝R＝Ph). We were delighted to find that the reaction gave one new main spot by TLC analysis. However, ^{1}H NMR spectrum suggested that it was not the coupled product as expected. Based on further ^{13}C NMR, IR and MS analysis, we postulated that this was probably derived from DDQ as well as acetal and ketone and possessed the structure **3** as shown in Eq. 1 (Ar＝R＝Ph).



(2)

To further identify the product structure, we attempted to grow single crystals of adducts by natural evaporation from a mixture of different solvents. Luck-

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ily, the colorless block crystal of **3b** was achieved from Et_2O/petroleum ether and its X-ray crystal analysis (see SI section 3) confirmed the structure as postulated above (Figure 1).

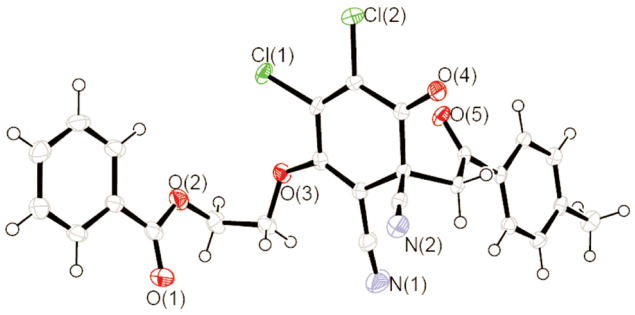

Figure 1 X-ray structure of the benzoate **3b**.

This result encouraged us to further investigate this novel CDC reaction. To begin with, we screened the reaction parameters to improve the yield of the coupling product on this model system. Various reaction temperatures, solvents and molar ratios were examined (Table 1). When 1.8 equiv. DDQ was used, the product was obtained in 40% yield (Entry 1). Decrease in the amount of DDQ to 1.2 equiv. reduced the yield to only 18% (Entry 2). Evidently, the ratio of DDQ to acetal made a great difference to the yield. Thus, 2.4 and 3.0 equiv. DDQ were also tested. The use of 2.4 equiv. DDQ gave 61% yield. With 3.0 equiv. DDQ being used, the reaction mixture became too thick for efficient stirring, leading to a slight decrease in yield (Entry 4, 58%). Decrease in the equivalent of acetophenone led to a decline in yield (Entry 3 vs. 5). Both increasing and lowering the reaction temperature resulted in a considerable decrease in yield (Entries 6 and 7). The use of $MeNO_2$ and DCE as solvents led to relatively low yields (Entries 8 and 9). From the results above, the optimal conditions are using acetal/ketone/DDQ ratio 1∶5∶2.4 (molar ratio) at 100 ℃ under N_2 in neat condition, under which the desired product was afforded in 61% yield.

With the optimized reaction conditions in hand, a variety of substrates including cyclic acetals and ketones were subjected to this transformation and the corresponding results were listed in Table 2. In general, there is little difference in yield for the three dioxolanes studied. Aryl methyl ketones were found to be excellent substrates, providing the desired products in synthetically useful yields. Aliphatic ketones, however, yielded no desired products. For example, when acetone or cyclohexanone reacted with 2-phenyl-1,3-dioxolane (**1a**), no desired product was detected. It is interesting to note that alkyl groups and ethers sensitive to DDQ, including methyl, ethyl, and ethoxyl groups, well survived this reaction condition. Additionally, as for ketones bearing electron-rich substituents (Entries 5 and 6), prolonging reaction time resulted in a dramatic decrease in the yield.

Table 1 Optimization of the reaction conditions[a]

Entry	**1a**/**2a**/DDQ	Temp.[b]/℃	Solvent[c]	Yield[d]/%
1	1∶5∶1.8	100	Neat	40
2	1∶5∶1.2	100	Neat	18
3	1∶5∶2.4	100	Neat	61
4[e]	1∶5∶3.0	100	Neat	58
5	1∶3∶2.4	100	Neat	52
6	1∶5∶2.4	130	Neat	23
7	1∶5∶2.4	50	Neat	25
8	1∶5∶2.4	100	$MeNO_2$	53
9	1∶5∶2.4	100	DCE	36

[a] 2-Phenyl-1,3-dioxolane (2 mmol) and acetophenone used as the substrates. [b] Oil bath. [c] Not dried. [d] Isolated yield. [e] Difficult to stir.

Table 2 CDC reactions of 2-aryl acetals with simple ketones[a]

Entry	Acetal (Ar)	Ketone (R)	Product	Yield[b]/%
1	Ph (**1a**)	Ph (**2a**)	**3a**	61
2	Ph (**1a**)	4-MePh (**2b**)	**3b**	64
3	Ph (**1a**)	4-EtPh (**2c**)	**3c**	63
4	Ph (**1a**)	2,4-$(Et)_2$Ph (**2d**)	**3d**	58
5[c]	Ph (**1a**)	1-naphthyl (**2f**)	**3e**	43
6[c]	Ph (**1a**)	2,4-$(EtO)_2$Ph (**2g**)	**3f**	40
7	4-MePh (**1b**)	Ph (**2a**)	**3g**	60
8	4-MePh (**1b**)	4-MePh (**2b**)	**3h**	62
9	4-MePh (**1b**)	4-ClPh (**2h**)	**3i**	37
10	4-ClPh (**1c**)	Ph (**2a**)	**3j**	59
11	4-ClPh (**1c**)	4-MePh (**2b**)	**3k**	60

[a] Reaction conditions: acetals (2 mmol), ketones (10 mmol), DDQ (4.8 mmol), N_2, 100 ℃, 1 h. [b] Isolated yield. [c] Stirred for 30 min.

On the basis of the above experiment results together with the related reports,[10] a plausible mechanism is proposed for the formation of the unusual coupling product (Figure 2). Firstly, single electron transfer followed by H-atom abstraction or direct hydride abstraction may generate an acetal cation, on which subsequent nucleophilic attack at the C-4 rather than C-2 position by a DDQH counterion provides DDQH ether. This may be due to the steric hindrance of the cation and thermodynamic stability of the intermediate ether. Then, the DDQH ether coupling with ketone may be involved in a free radical process, mediated by another DDQ molecule.

Conclusions

In summary, for the first time we present a novel domino CDC reaction of acetals with simple aryl ketones by using DDQ as a sole oxidant and a reactant precursor. In this transformation, new C—O and C—C bonds are successively formed. The scope and mechanism of this method as well as the application of these

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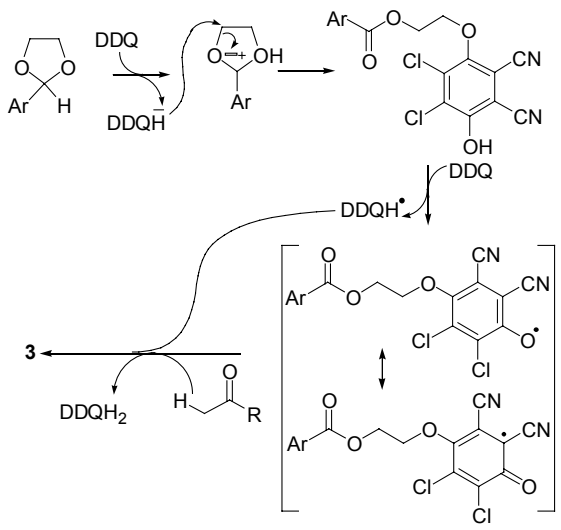

Figure 2 Proposed mechanism for this domino CDC reaction.

coupled products are under further investigation.

Experimental

To a mixture of DDQ (4.8 mmol) and ketone (10 mmol), acetal (2.0 mm) was added dropwise under nitrogen at room temperature. Then the reaction mixture was stirred at 100 ℃ (oil bath) immediately. After 1 h, the resulting mixture was diluted with ethyl acetate, to which little silica gel was added. The solvent was removed under the reduced pressure and the resulting powder was added to the top of a short silica-gel column and purified using petroleum ether/ethyl acetate in a 10∶1 ratio (volume ratio) as the eluent to afford the desired product. The data for selected compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (dd, J=8.4, 1.2 Hz, 2H), 7.88 (dd, J=8.4, 1.2 Hz, 2H), 7.66 (t, J=7.6 Hz, 1H), 7.58 (tt, J=7.6, 1.2 Hz, 1H), 7.50 (t, J=8.0 Hz, 2H), 7.45 (t, J=8.0 Hz, 2H), 4.85—4.76 (m, 2H), 4.69 (t, J=4.4 Hz, 2H), 4.50 (d, J=18.0 Hz, 1H), 4.36 (d, J=18.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.18, 178.68, 166.10, 158.06, 144.61, 136.55, 135.04, 133.86, 133.41, 129.73 (2C), 129.63, 129.27, 129.12 (2C), 128.49 (4C), 113.56, 113.06, 93.29, 73.39, 62.42, 48.22, 45.02; IR (KBr) ν_{max}: 2238.87 (CN), 2215.65 (CN), 1722.88 (ester C=O), 1708.69 (ketone C=O), 1680.31 (C=O), 1272.04 (ester C—O) cm^{-1}; MS (APCI) m/z: 512.0 $[M+NH_4]^+$. Anal. calcd for $C_{25}H_{16}Cl_2N_2O_5$: C 60.62, H 3.26, N 5.66; found C 60.74, H 3.45, N 5.53.

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