# 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as a Highly Efficient and Mild Catalyst for Diethyl Acetalization of Carbonyl Compounds

Babak Karimi* and Ashraf Miri Ashtiani†

*Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), P.O. Box 45195-159, Gaveh-Zang, Zanjan, Iran*

†*Department of Chemistry, Iranian Research Organization for Science and Technology, Tehran 15819, Iran*

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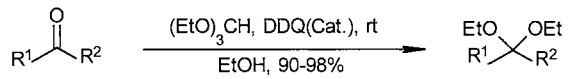
Various types of structurally different carbonyl compounds in the presence of ethyl orthoformate $(EtO)_3CH$ could be efficiently converted to their diethyl acetals by using a catalytic amount (1-3 mol%) of DDQ under mild reaction conditions.

Acetals are one of the most important and widely used protecting groups for carbonyl compounds.[1] Due to the synthetic importance of the formation of acetals, the development of new, improved methods for their preparation continues to attract attention.[2] In spite of the Noyori's and its related procedures[2b,3] which work under mild and aprotic conditions, most of the available methods for the preparation of acetals were accomplished in an acidic medium. Among this, literature survey shows that a few methods are available for the conversion of carbonyl groups in aldehydes and ketones to their corresponding diethyl acetals such as $(EtO)_3CH/HCl$,[4] $(EtO)_3CH/FeCl_3$ in refluxing EtOH,[5] $(EtO)_3CH$/Amberlyst-15,[6] charchol bisulfate,[1] and $(EtO)_3CH/ZrCl_4$.[7] The harsh and acidic conditions, and low yield of the desired acetals specially in the case of aromatic and cyclic ketones are drawbacks of the previously introduced methods for the preparation of diethyl acetals. Although, DDQ has been found to be effective catalyst for the conversion of acetals to their carbonyl compounds under mild reaction conditions,[8,9] to our knowledge there is no report for catalytic effect of this reagent in opposite manner.[10] In this report we wish to disclose a new efficient method for the preparation of diethyl acetals by using a catalytic amount of DDQ under mild and neutral reaction conditions (Scheme 1).[11]

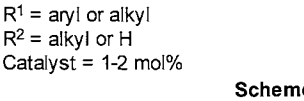
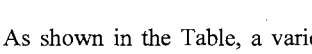
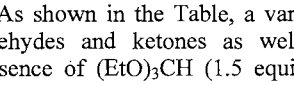



$R^1$ = aryl or alkyl
$R^2$ = alkyl or H
Catalyst = 1-2 mol%

**Scheme 1.**

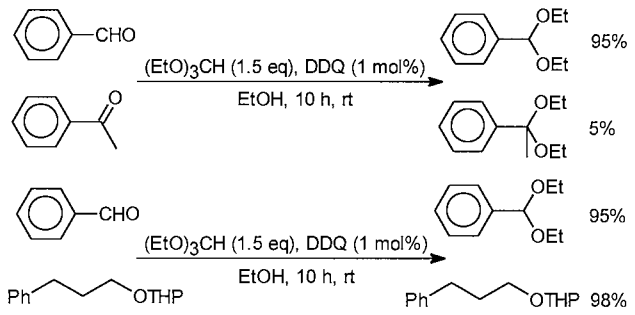
As shown in the Table, a variety of aromatic and aliphatic aldehydes and ketones as well as cinnamaldehyde in the presence of $(EtO)_3CH$ (1.5 equiv.) and DDQ (1-2 mol%) in absolute ethanol were smoothly converted to their corresponding diethyl acetals in good to excellent yields (entries 1, 3-14). It is worthy to mention that lower quantities of DDQ (i.e. 0.1 mol%) also gave satisfactory result at longer reaction time (entry 2). The preparation of diethyl acetals of cyclic ketones are usually accompanied by the considerable formation of the corresponding ethyl vinyl ethers in the presence of acidic reagents.[6,7] Efficient formation of these types of acetals in the presence of DDQ is an interesting feature of the presented method (Table, entries 13, 14). On the other hand, the preparation of open-chain acetals from their corresponding diaryl ketones such as benzophenone generally requires forceful conditions.[12] In this regard, we found that diethyl-acetalization of relatively hindered ketones such as (-)-camphor and benzophenone as well as 3-β-acetoxyandrost-5-ene-17-one was achieved in moderate to good yields in the presence of 3 mol% of DDQ (Table, entries 12, 15, 16). It is worthy to mention that acid sensitive substrates such as 1,3-dioxanes, TBDMS and THP ethers survive under these conditions even after prolonged reaction time (Table, entries 17-19).

**Table.** Acetalization of carbonyl compounds in the presence of $(EtO)_3CH$ and DDQ in absolute ethanol.

| Run | $R^1$ | $R^2$ | Substrate /$(EtO)_3CH$ / DDQ | Time / h | Yield[a] / % |
|---|---|---|---|---|---|
| 1 | Ph | H | 1 : 1.5 : 0.01 | 10 | 95 |
| 2 | Ph | H | 1 : 1.5 : 0.001 | 24 | 94 |
| 3 | 4-$(CH_3)C_6H_4$ | H | 1 : 1.5 : 0.01 | 6 | 98 |
| 4 | 4-$(Cl)C_6H_4$ | H | 1 : 1.5 : 0.01 | 8 | 96 |
| 5 | 4-$(NO_2)C_6H_4$ | H | 1 : 2 : 0.01 | 24 | 98 |
| 6 | 4-$(MeO)C_6H_4$ | H | 1 : 1.5 : 0.01 | 10 | 94 |
| 7 | Citronellal | | 1 : 1.5 : 0.01 | 10 | 90[b] |
| 8 | PhCH=CH | H | 1 : 1.5 : 0.01 | 5 | 89 |
| 9 | $PhCH_2CH_2$ | $CH_3$ | 1 : 2 : 0.02 | 10 | 92 |
| 10 | Ph | $CH_3$ | 1 : 2 : 0.02 | 18 | 98 |
| 11 | 4-$(Cl)C_6H_4$ | $CH_3$ | 1 : 2 : 0.01 | 27 | 94 |
| 12 | Ph | Ph | 1 : 3 : 0.03 | 72 | 85 |
| 13 | 4-Phenylcyclohexanone | | 1 : 1.5 : 0.01 | 16 | 90 |
| 14 | cyclopentanone | | 1 : 1.5 : 0.02 | 20 | 85 |
| 15 | (-)-camphore | | 1 : 3 : 0.03 | 72 | 65[b] |
| 16 | 3-β-acetoxyandrost-5-ene-17-one | | 1 : 3 : 0.03 | 50 | 79[b] |
| 17 |  | | 1: 1.5 : 0.01 | 24 | -[c] |
| 18 |  | | 1 : 1.5 : 0.01 | 24 | -[d] |
| 19 |  | | 1 : 1.5 : 0.01 | 24 | -[e] |

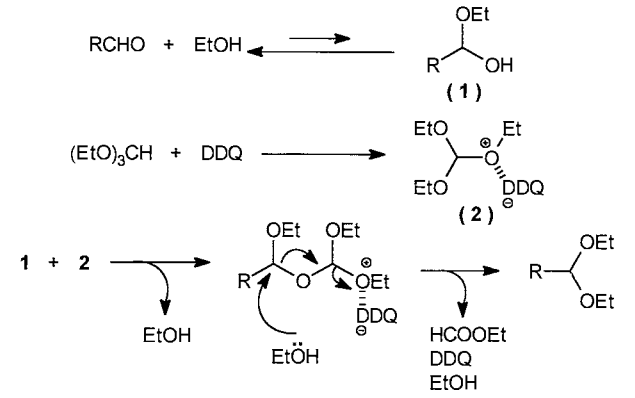
[a]Isolated yields. [b]NMR yield. [c]The starting material remains intact. [d]A trace amount of the corresponding alcohol (≈ 10-12%) was detected by GC and NMR spectroscopy. [e] ≈ 18 % of the corresponding alcohols was detected by GC.

We have also monitored competitive acetalization of benzaldehyde in the presence of acetophenone and 2-(3-phenyl-1-propyloxy) tetrahydropyran and the product ratios were determined by NMR spectroscopy.The results are demonstrated in Scheme 2. This observation clearly shows that the method is potentially applicable for the selective acetalization of aldehydes in the presence of ketones and acid sensitive substrates.




**Scheme 2.**

The exact role of DDQ is not clear at this stage and needs to be further studied in detail. Oku *et al.* have discussed different possible mechanism for the deprotection of acetals by DDQ in wet organic solvents.[8] Although for the reaction of DDQ in aqueous media they provided some evidences for *in-situ* proton production, but due to anhydrous conditions in our experiments no proton generation is detected so far. Among this, they have proposed the possibility that DDQ could function as a Lewis acid. On the other hand, we have found at the present time no experimental evidence regarding a charge transfer reaction pathway proposed by Iranpoor and his coworkers.[13,14] During our studies, we found that solvent plays an important role in the acetalization of carbonyl compounds in the presence of DDQ. When benzaldehyde was allowed to react with $(EtO)_3CH$ (1.5 equiv.) and DDQ (1 mol%) in $CH_2Cl_2$ in stead of absolute ethanol, after 10 h only a small amount (20%) of the corresponding diethyl acetal was formed. This may be due to the fact that ethanol accelerates the formation hemiacetal **1** (Scheme 3). In light of these observations, therefore, at the present time we also believed that DDQ probably could act as a mild Lewis acid under anhydrous conditions to produce oxonium species **2**, which in turn reacts with intermediate hemiacetal **1** to give the acetals as shown in Scheme 3.




**Scheme 3.**

At the present time, however, this method can be considered as an efficient method for the preparation of various types of structurally different diethyl acetals of acid sensitive substrates under very mild reaction conditions. Further applications of DDQ in organic synthesis are ongoing in our laboratories.

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10 The use of DDQ has been demonstrated as a reagent of choice for the preparation of THP ethers: K. Tanemura, T. Horaguchi, and T. Suzuki, *Bull. Chem. Soc. Jpn.*, **65**, 304 (1992) and also for isopropylidenation of acid sensitive carbohydrates: O. Kjolberg and K. Neumann, *Acta Chem. Scand.* **47**, 843 (1993); O. Kjolberg and K. Neumann, *Acta Chem. Scand.*, **48**, 80 (1994).

11 Typical procedure for diethyl-acetalization of carbonyl compounds with DDQ: To a solution of benzaldehyde (1.06 g, 10 mmol), and $(EtO)_3CH$ (1.95 g, 15 mmol) in absolute EtOH (25 mL) was added DDQ (22.7 mg, 0.1 mmol) and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion (10 h), a saturated cold aqueous solution of $K_2CO_3$ (40 mL) was added and the mixture was extracted with $CH_2Cl_2$ (4 × 40 mL). The organic extracts were separated and dried over anhydrous $Na_2SO_4$. Evaporation of the solvent under reduced pressure gave almost pure product(s). Further purification was achieved by vacuum distillation to afford pure benzaldehyde diethyl acetal in 95% yield.

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14 When the acetalization reaction of benzaldehyde was monitored as an example under argon atmosphere, the rate acceleration was not observed.

15 Most of the products are known and all of the isolated products gave satisfactory IR spectra; typical spectral data are as following: a) benzaldehyde diethyl acetal: $^1$H-NMR ($CDCl_3$/TMS, 250 MHz): δ = 7.40-7.44 (m, 2H), 7.25-7.33 (m, 3H), 5.48 (s, 1H), 3.44-3.55 (m, 4H), 1.19-1.27 (m, 6H); $^{13}$C-NMR($CDCl_3$/TMS, 63 MHz): δ = 138.99, 128.01, 127.91, 126.66, 100.95, 60.28, 15.24. b) 4-chlorobenzaldehyde diethyl acetal: $^1$H-NMR ($CDCl_3$/TMS, 250 MHz): δ = 7.26-7.40 (m, 4H), 5.45 (s, 1H), 3.42-3.79 (m, 4H), 1.15-1.24 (m, 6H); $^{13}$C-NMR($CDCl_3$/TMS, 63 MHz): δ = 137.59, 133.95, 128.21, 128.01, 100.63, 60.84, 15.06. c) 4-nitrobenzaldehyde diethyl acetal: $^1$H-NMR ($CDCl_3$/TMS, 250 MHz): δ = 8.17-8.20 (m, 2H) , 7.63-7.67 (m, 2H), 5.57 (s, 1H), 3.49-3.67 (m, 4H), 1.21-1.26 (m, 6H). d) acetophenone diethyl acetal: $^1$H-NMR ($CDCl_3$/TMS, 250 MHz): δ= 7.60-7.61(m, 2H), 7.25-7.57 (m, 3H), 3.38-3.56 (m, 4H), 1.59 (s, 1H), 1.21-1.28 (m, 6H); $^{13}$C-NMR($CDCl_3$/TMS, 63 MHz): δ = 151.56, 135.62, 135.01, 133.81, 108.87, 64.29, 34.82, 22.66. e) 4-chloroacetophenone diethyl acetal: $^1$H-NMR ($CDCl_3$/TMS, 250 MHz): δ = 7.43-7.46 (m, 2H), 7.25-7.28 (m, 2H), 3.26-3.51 (m, 4H), 1.50 (s, 3H), 1.16-1.22 (m, 6H); $^{13}$C-NMR($CDCl_3$/TMS, 63 MHz): δ = 150.12, 140.88, 135.72, 135.34, 108.42, 64.25, 34.66, 22.95. f) 4-phenylcyclohexanone diethyl acetal: $^1$H-NMR ($CDCl_3$/TMS, 250 MHz): δ= 7.11-7.31 (m, 5H), 3.40-3.54 (m, 4H), 2.50-2.59 (m, 1H), 2.18-2.23 (m, 2H), 1.74-1.83 (m, 4H), 1.56-1.61 (m, 2H), 1.24-1.30 (m, 6H); $^{13}$C-NMR($CDCl_3$/TMS, 63 MHz): δ = 125.92, 126.52, 126.76, 127.01, 108.51, 54.81(two peaks), 43.71, 42.78, 33.93(two peaks), 29.76. g) 2,2-diethoxy-4-phenylbutane: $^1$H-NMR ($CDCl_3$/TMS, 250 MHz): δ = 7.23-7.37 (m, 5H), 3.52-3.64 (m, 4H), 2.69-2.76 (m, 2H), 1.99-2.06 (m, 2H), 1.51 (s, 3H), 1.23-1.33 (m, 6H); $^{13}$C-NMR($CDCl_3$/TMS, 63 MHz): δ = 142.62, 128.77, 128.65, 126.17, 101.59, 55.99, 39.56, 31.13, 22.56, 15.94.