α-Vinylation of Haloquinones with Methyl Acrylate and MVK under Baylis-Hillman Reaction Conditions

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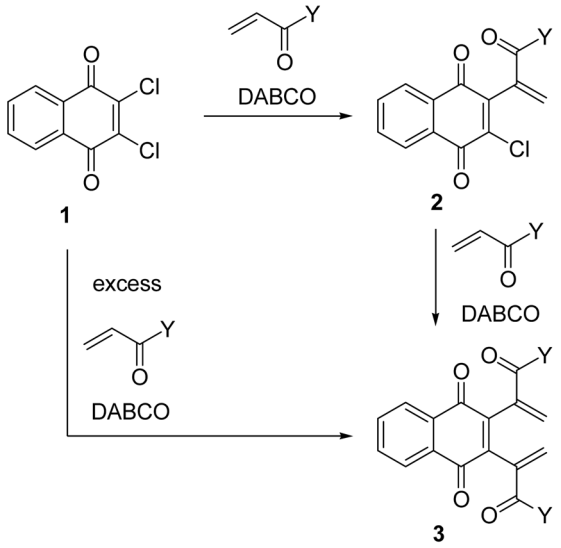
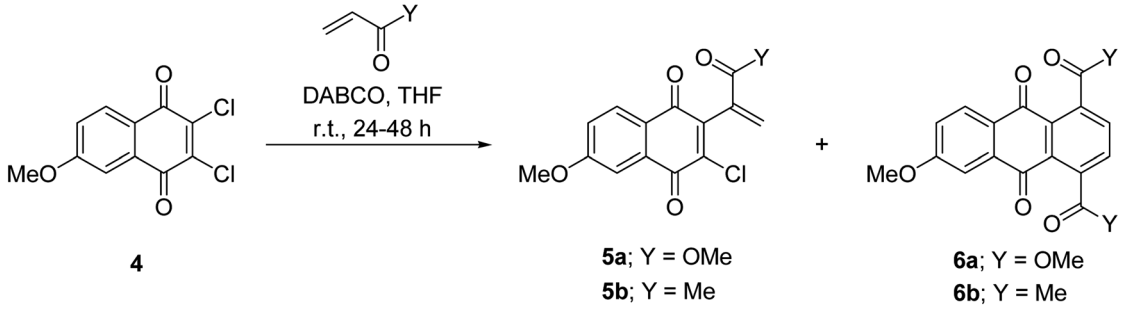
The Baylis-Hillman reaction has been one of the most intensively studied carbon-carbon bond-forming reactions in organic synthesis.[1] In our earlier paper,[2] we demonstrated that DABCO-attached enolate anion of activated olefins were useful in substitution reaction of 2,3-dihalo-1,4-naphthoquinone leading to the formation of the α-vinyl-naphthoquinones under the Baylis-Hillman reaction conditions as shown in Scheme 1. We desired to extend this method to other haloquinone derivatives. General methods for introducing α-vinyl unit into substrates involve palladium-catalyzed cross-coupling reactions of α-stannyl acrylate with aryl iodides or triflates,[3] ethyl 2-bromoacrylate with arylboronic acids[4] and ethyl 2-bromoarylate with aryl halides using electro-generated reactive zinc metal.[5]



Scheme 1

First, we investigated the effect of an resonance electron-donating methoxy group on the regiochemistry of the vinylation reaction using 2,3-dichloro-6-methoxy-1,4-naphthoquinone (**4**) as a substrate. Reaction of **4** with methyl acrylate (6 equiv) in the presence of 1.2 equiv of DABCO in THF at room temperature provided 3-chloro-6-methoxy-2-vinyl-1,4-naphthoquinone **5a** (71%) and unexpected 1,4-dicarbomethoxy-6-methoxyanthraquinone **6a** (4%). When the reaction was carried out using excess methyl acrylate (10 equiv) and DABCO (2.5 equiv), vinylnaphthoquinone **5a** (35%) and anthraquinone **6a** (21%) were produced. Also, treatment of **4** with methyl vinyl ketone (MVK) (6 equiv) and DABCO (1.2 equiv) in THF at 10-15 °C gave the corresponding vinylnaphthoquinone **5b** (53%) and anthraquinone **6b** (9%). Use of excess MVK (10 equiv) and DABCO (2.5 equiv), no increase of yields was observed (Scheme 2 and Table 1). We assumed that the major compounds **5** were formed by addition of the DABCO-attached enolate anion to the more electrophilic C-2 carbon on the quinone core of **4** by the influence of methoxy substituent.[6] The minor compounds **6** were presumably produced through the second vinylation, 6π-electrocyclization and oxidation reaction under the reaction conditions.[2]

Secondly, we studied α-vinylation of 2-bromo-1,4-naphthoquinone (**7**) with methyl acrylate or MVK. Interestingly, we observed that vinylation with methyl acrylate proceeded exclusively at the carbon bearing hydrogen to provide the 2-bromo-3-vinylnaphthoquinone **8** in 58% yield. But, vinylation with MVK proceeded at the carbon bearing bromine to afford the 2-vinylnaphthoquinone **10** and



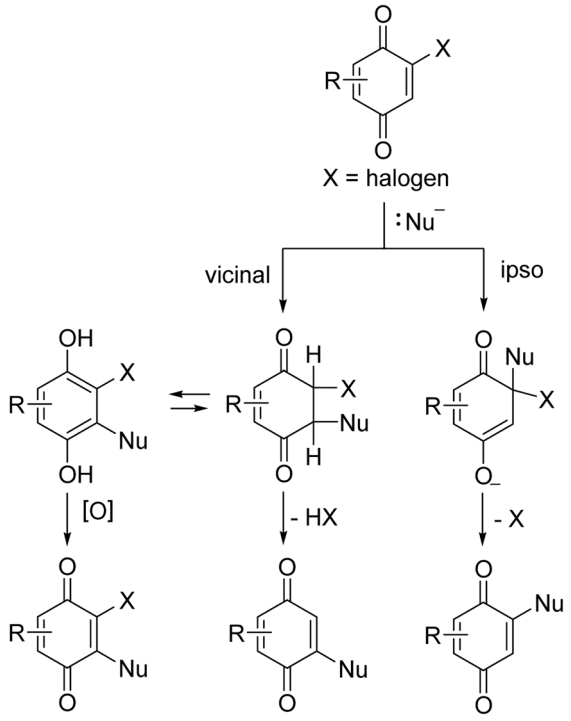
Scheme 2

Table 1. Reaction of 2,3-Dichloro-6-methoxy-1,4-naphthoquinone (**4**) with MA and MVK

Method	Reaction Condition[a]	Time (h)	Product (% yield)
A	**4**/MA/DABCO (1/6/1.2)	24[b]	**5a** (71) **6a** (4)
B	**4**/MA/DABCO (1/10/2.5)	48[b]	**5a** (35) **6a** (21)
A	**4**/MVK/DABCO (1/6/1.2)	24[c]	**5b** (53) **6b** (9)
B	**4**/MVK/DABCO (1/10/2.5)	48[c]	**5b** (41) **6b** (5)

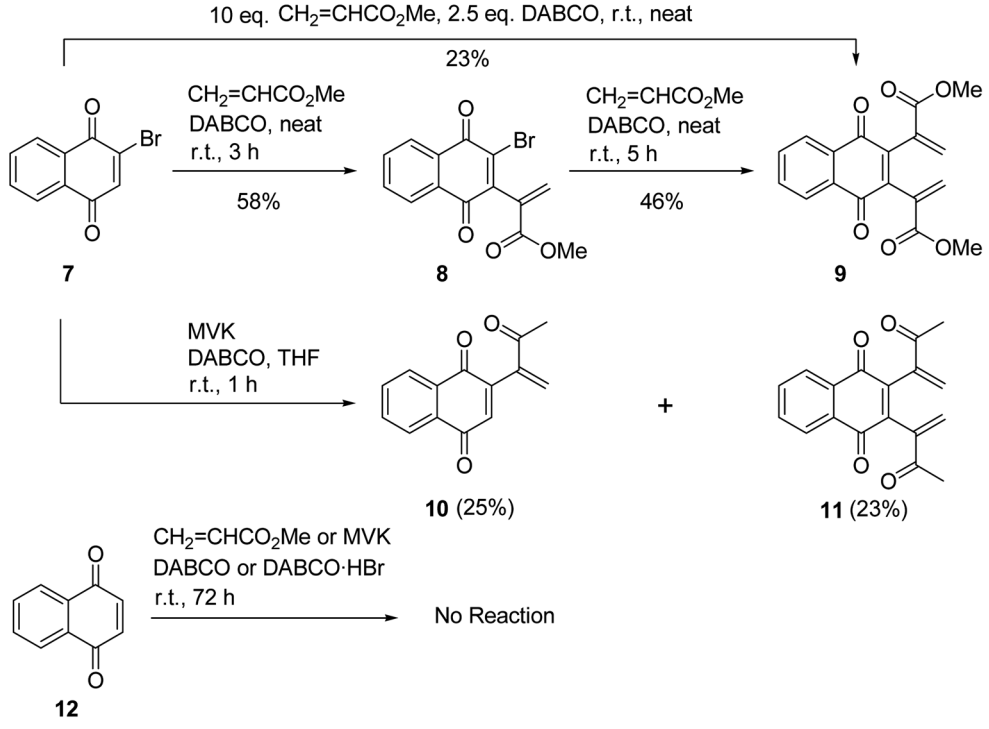
[a]MA = methyl acrylate; MVK = methyl vinyl ketone. Parentheses values are the number of equivalent. [b]Room temperature. [c]10-15 °C.

divinylnaphthoquinone **11** in 25 and 23% yields, respectively. The second vinylation of **8** and one-pot divinylation of **7** using excess DABCO (2.5 equiv) and methyl acrylate (10 equiv) gave the same known symmetrical divinylnaphthoquinone **9** in 46 and 23% yields[2] (Scheme 3). Since the conversion of **7** to a divinylnaphthoquinone **9** was successful, we next examined the reaction of 1,4-naphthoquinone (**12**) with methyl acrylate or MVK in the presence of DABCO or DABCO·HBr salt, however, no reactions occurred. In general, attack of the nucleophile could reasonably occur either at the *ipso* carbon or at the carbon *vicinal* to it, and then extrusion of HX or a subsequent proton migration by keto-enol tautomerization followed by oxidation, leading respectively to a 2- or 3-vinyl substituted product as shown in Scheme 4.[7] But, no good explanation for this divergent behavior between methyl acrylate and MVK is available this moment.

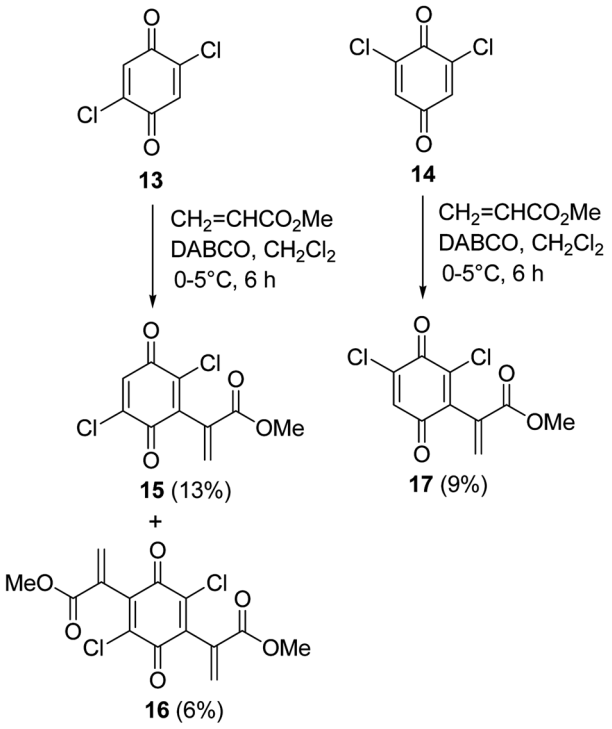


Scheme 4

Finally, we examined these vinylation reaction of monocyclic 2,5-dichloro-1,4-benzoquinone (**13**) and 2,6-dichloro-1,4-benzoquinone (**14**) with methyl acrylate. Quinone **13** furnished 2,5-dichloro-3-vinyl-1,4-benzoquinone **15** (13%) and 2,5-dichloro-3,4-divinyl-1,4-benzoquinone **16** (6%), and quinone **14** afforded 2,6-dichloro-3-vinyl-1,4-benzoquinone **17** (9%) in a very disappointing yield (Scheme 5). Vinylations of **13** and **14** with MVK were unsuccessful. Although the yields are very low, the vinylation proceeded at the carbon bearing hydrogen again. The reason for the low yields might be attributed to the side reactions that dichloro-



Scheme 3



Scheme 5

benzoquinones could react with the DABCO without methyl acrylate presumably to give unidentified complex DABCO salt very rapidly which was indicated by TLC.

In conclusion, additional examples of the use of DABCO-attached enolate anion of methyl acrylate and MVK in substitution reactions of haloquinones to form α-vinylquinone bonds avoiding the use of organometallic reagents have been described.

Experimental Section

All reagents and solvents were reagent grade or were purified by standard methods before use. Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin layer chromatography (tlc) was carried out on Merck silica gel 60 F254 tlc plates. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Microanalyses were obtained using a Carlo Erba EA 1180 element analyzer. Infrared spectra were recorded on a Nicolet Magna 550 FTIR spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Gemini 300 spectrometer. All chemical shifts are reported in ppm relative to TMS and coupling constants (J) are expressed in Hz.

The 2,3-dichloro-6-methoxy-1,4-naphthoquinone (**4**) was prepared following the literature procedure.[6] 2-Bromo-1,4-naphthoquinone (**7**), 2,5-dichloro-1,4-benzoquinone (**13**) and 2,6-dichloro-1,4-benzoquinone (**14**) were purchased from Aldrich.

Methyl 2-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)propenoate (5a) and 1,4-Dicarbomethoxy-7-methoxyanthraquinone (6a).

Method A: A mixture of 2,3-dichloro-6-methoxy-1,4-naphthoquinone (**4**, 0.51 g, 2 mmol), methyl acrylate (1.1 mL, 12 mmol) and DABCO (0.27 g, 2.4 mmol) in THF (5 mL) was stirred for 24 h at r.t. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/EtOAC (10 : 1) to afford **5a** (0.43 g, 71%) and **6a** (0.03 g, 4%) as solids.

5a; mp 136-137 °C; IR (KBr) 1720, 1674, 1649, 1591, 1496, 1434, 1286 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 3.71 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.10 (s, 1H, CH), 6.74 (s, 1H, CH), 7.44 (dd, J = 8.5 and 2.4 Hz, 1H, aromatic), 7.52 (d, J = 2.4 Hz, 1H, aromatic), 8.00 (d, J = 8.5 Hz, 1H, aromatic); ^{13}C NMR (DMSO-d$_6$) δ 52.5, 56.3, 111.0, 120.7, 120.8, 124.3, 129.3, 129.4, 132.9, 142.2, 142.7, 164.0, 164.3, 177.3, 180.0.

Anal. Calcd for $C_{15}H_{11}ClO_5$: C, 58.74; H, 3.62. Found: C, 58.59; H, 3.51.

6a; mp 202 °C; IR (KBr) 1731, 1675, 1591, 1324, 1273 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.45 (dd, J = 8.5 and 2.7 Hz, 1H, aromatic), 7.56 (d, J = 2.7 Hz, 1H, aromatic), 7.94 (s, 2H, aromatic), 8.11 (d, J =8.5 Hz, 1H, aromatic); ^{13}C NMR (DMSO-d$_6$) δ 52.8, 53.0, 56.2, 110.2, 121.5, 125.9, 129.7, 130.6, 130.7, 132.3, 132.6, 134.6, 135.1, 135.2, 164.4, 168.7, 168.8, 180.1, 181.3.

Anal. Calcd for $C_{19}H_{14}O_7$: C, 64.41; H, 3.98. Found: C, 64.20; H, 3.83.

Method B: A mixture of **4** (0.51 g, 2 mmol), methyl acrylate (1.8 mL, 20 mmol) and DABCO (0.56 g, 5 mmol) in THF (5 mL) was stirred for 48 h at r.t. The work-up procedure was the same as described above to afford **5a** (0.21 g, 35%) and **6a** (0.15 g, 21%).

3-(3-Chloro-6-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-3-buten-2-one (5b) and 1,4-Diacetyl-7-methoxyanthraquinone (6b).

Method A: A mixture of **4** (0.51 g, 2 mmol), MVK (0.84 g, 12 mmol) and DABCO (0.27 g, 2.4 mmol) in THF (5 mL) was stirred for 24 h at 10-15 °C. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/EtOAC (6 : 1) to afford **5b** (0.31 g, 53%) and **6b** (0.06 g, 9%) as solids.

5b; mp 104-106 °C; IR (KBr) 1678, 1655, 1594, 1579, 1494, 1321 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 2.43 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 6.21 (s, 1H, CH), 6.76 (s, 1H, CH), 7.42-7.52 (m, 2H, aromatic) 7.97 (d, J = 8.5 Hz, 1H, aromatic); ^{13}C NMR (DMSO-d$_6$) δ 26.0, 56.2, 110.9, 120.6, 124.4, 129.4, 132.0, 133.0, 141.5, 142.1, 144.5, 163.9, 177.2, 180.0, 196.9.

Anal. Calcd for $C_{15}H_{11}ClO_4$: C, 61.98; H, 3.81. Found: C, 61.85; H, 3.75.

6b; mp 207 °C; IR (KBr) 1704, 1670, 1594, 1496, 1431, 1288 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ 2.50 (s, 6H, CH_3), 3.98 (s, 3H, OCH_3), 7.48 (d, J = 9.8 Hz, 1H, aromatic), 7.59 (s,

1H, aromatic), 7.75 (s, 2H, aromatic), 8.13 (d, J = 9.8 Hz, 1H, aromatic); ^{13}C NMR (DMSO-d_6) δ 26.0, 58.5, 110.2, 124.5, 129.4, 133.2, 136.2, 142.8, 142.9, 144.2, 144.7, 145.2, 151.6, 152.5, 163.9, 181.9, 183.0, 204.9, 205.0.

Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.80; H, 4.38. Found: C, 70.62; H, 4.19.

Method B: A mixture of **4** (0.51 g, 2 mmol), MVK (1.40 g, 20 mmol) and DABCO (0.56 g, 5 mmol) in THF (5 mL) was stirred for 48 h at 10-15 °C. The work-up procedure was the same as described above to afford **5b** (0.24 g, 41%) and **6b** (0.03 g, 5%).

Methyl 2-(3-Bromo-1,4-dioxo-1,4-dihydronaphthalen-2-yl)propenoate (8). A mixture of 2-bromo-1,4-naphthoquinone (**7**, 1.19 g, 5 mmol), methyl acrylate (4.5 mL, 50 mmol) and DABCO (0.67 g, 6 mmol) was stirred for 10 minutes at r.t. The work-up procedure was the same as described above to afford **8** (0.93 g, 58%) as a yellow solid; mp 106-107 °C (lit.[2] 106-107); IR (KBr) 1723, 1676, 1660, 1590, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H, OCH_3), 5.93 (s, 1H, CH), 6.82 (s, 1H, CH), 7.76-7.83 (m, 2H, aromatic), 8.12-8.23 (m, 2H, aromatic); ^{13}C NMR ($CDCl_3$) δ 52.6, 127.4, 130.9, 131.2, 132.2, 132.3, 134.1, 134.4, 134.9, 139.5, 146.6, 164.2, 177.5, 180.6.

3-(1,4-Dioxo-1,4-dihydronaphthalen-2-yl)-3-buten-2-one (10) and 2,3-Di-(3-buten-2-on-3-yl)-1,4-naphthoquinone (11). A mixture of **7** (1.19 g, 5 mmol), MVK (0.9 mL, 15 mmol) and DABCO (0.67 g, 6 mmol) in THF (10 mL) was stirred for 1 h at 10-15 °C. The work-up procedure was the same as described above to afford **10** (0.28 g, 25%) and **11** (0.34 g, 23%) as yellow solids.

10; mp 121-123 °C; IR (KBr) 1680, 1657, 1594, 1415 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H, CH_3), 6.11 (s, 1H, CH), 6.30 (s, 1H, CH), 6.93 (s, 1H, CH), 7.75-7.78 (m, 2H, aromatic), 8.07-8.10 (m, 2H, aromatic); ^{13}C NMR ($CDCl_3$) δ 26.5, 126.2, 126.8, 128.0, 131.8, 131.9, 133.9, 136.1, 136.2, 144.8, 147.9, 183.6, 184.7, 197.7; MS m/z (%) 226 (M^+, 23), 225 (41), 198 (75), 184 (100), 155 (24), 128 (90).

Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.51; H, 4.28.

11: mp 162-164 °C (lit.[2] 162-164); IR (KBr) 1692, 1664, 1596, 1432 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 6H, CH_3), 5.88 (s, 2H, CH), 6.23 (s, 2H, CH), 7.34-7.77 (m, 2H, aromatic), 8.06-8.09 (m, 2 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 25.8, 126.5, 128.1, 131.6, 133.9, 143.8, 145.4, 183.3, 197.9.

Preparation of 2,3-Di-(1-carbomethoxyethen-1-yl)-1.4-naphthoquinone (9) from 8. A mixture of **8** (1.61 g, 5 mmol), methyl acrylate (4.5 mL, 50 mmol) and DABCO (0.67 g, 6 mmol) was stirred for 5 h at r.t. The work-up procedure was the same as described above to afford **9** (0.76 g, 46%) as a solid; mp 101-102 °C (lit.[2] 101-102).

One-pot Preparation of 9 from 2-Bromo-1,4-naphthoquinone (7). A mixture of **7** (1.19 g, 5 mmol), methyl acrylate (4.5 mL, 50 mmol) and DABCO (1.40 g, 12.5 mmol) was stirred for 5 h at r.t. The work-up procedure was the same as described above to afford **9** (0.38 g, 23%) as a solid; mp 101-102 °C.

Methyl 2-(2,5-Dichloro-1,4-benzoquinone-3-yl)propenoate (15) and 2,5-Dichloro-3,6-di-(1-carbomethoxyethen-1-yl)-1,4-benzoquinone (16). A mixture of 2,5-dichloro-1,4-benzoquinone (**13**, 0.50 g, 2.83 mmol), methyl acrylate (0.73 mL, 8.49 mmol) and DABCO (0.32 g, 2.83 mmol) in CH_2Cl_2 (20 mL) was stirred for 6 h at 0-5 °C. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/EtOAc (10 : 1) to afford **15** (0.10 g, 13%) as an oil and **16** (0.06 g, 6%) as a solid.

15; IR (KBr) 1727, 1679, 1587, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H, OCH_3), 5.93 (s, 1H, CH), 6.82 (s, 1H, CH), 7.19 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 53.0, 132.3, 133.3, 133.7, 140.9, 142.1, 144.7, 164.3, 176.4, 177.2.

Anal. Calcd for $C_{10}H_6Cl_2O_4$; C, 46.01; H, 2.32. Found: C, 45.84; H, 2.26.

16; mp 177-179 °C; IR (KBr) 1727, 1677, 1592, 1438, 1306 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 6H, OCH_3), 5.97 (s, 2H, CH), 6.83 (s, 2H, CH); ^{13}C NMR ($CDCl_3$) δ 52.7, 132.0, 133.5, 140.6, 141.8, 164.1, 175.9.

Anal. Calcd for $C_{14}H_{10}Cl_2O_6$: C, 48.72; H, 2.92. Found: C, 48.60; H, 2.78.

Methyl 2-(2,6-Dichloro-1,4-benzoquinone-3-yl)propenoate (17). A mixture of 2,6-dichloro-1,4-benzoquinone (**14**, 0.50 g, 2.83 mmol), methyl acrylate (0.73 mL, 8.49 mmol) and DABCO (0.32 g, 2.83 mmol) in CH_2Cl_2 (20 mL) was stirred for 6 h at 0-5 °C. The work-up procedure was the same as described above to afford **17** (0.06 g, 9%) as a solid; mp 175-176 °C; IR (KBr) 1731, 1693, 1659, 1550, 1434 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H, OCH_3), 5.93 (s, 1H, CH), 6.82 (s, 1H, CH), 7.10 (s, 1H, CH); ^{13}C NMR ($CDCl_3$) δ 52.6, 111.7, 131.7, 133.5, 140.9, 143.4, 152.8, 164.0, 172.7, 181.0.

Anal. Calcd for $C_{10}H_6Cl_2O_4$: C, 46.01; H, 2.32. Found: C, 45.87; H, 2.25.

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