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Multicomponent reactions involving *p*-benzoquinones, diazo esters, titanium(IV) isopropoxide and alcohol in the presence of rhodium(II) acetate as catalyst

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Abstract—A Rh$_2$(OAc)$_4$ catalyst derived oxonium ylide intermediate underwent nucleophilic addition with the C=C or C=O bond of *p*-benzoquinones. The syntheses of 2-substituted hydroquinones and 1-hydroxy-4-oxocyclohexa-2,5-dienyls have been demonstrated.
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α-Diazocarbonyl compounds have found wide application in organic synthesis as a result of their diverse reactivities.[1,2] Research in this area has been mostly concentrated on transition metal complex catalyzed diazo decompositions, which generate metallo-carbenoid intermediates. Metallo-carbenoids derived from α-diazocarbonyl compounds using rhodium catalysts were mainly employed for carbonyl ylide or onium ylide generation.[1–3] Recently, onium ylides derived from oxygen,[1–3b,4] sulfur,[5] phosphorus[6] and nitrogen[7] have also received attention as surrogates for diazocarbonyl compounds in metallo-carbenoid mediated processes. The chemistry of oxonium ylides has been very successful in syntheses based on their rearrangement, nucleophilic addition reactions and aldol-condensations. A similar process has also been studied via the rhodium(II)-generated oxonium ylide intermediate from α-diazocarbonyl compounds in the presence of a Lewis acid.[4,8,9] Interestingly, several molecules having a 2-substituted hydroquinone core unit with a terpenoid portion ranging in size from one to nine isoprene units exist in Nature. For example, fornicins[10] A–C (**1a**–**c**) and methoxyconidiol[11] (**2**) are novel prenylated phenolic systems (Fig. 1). These compounds exhibited a moderate cytotoxic activity in Hep-2 cells. Based on our continuing interest in oxonium ylide[9] chemistry, we herein report multicomponent reac-
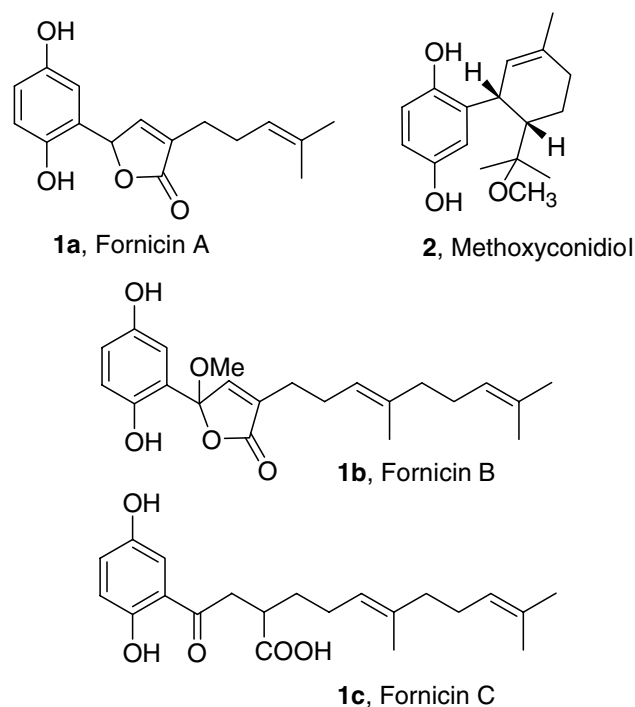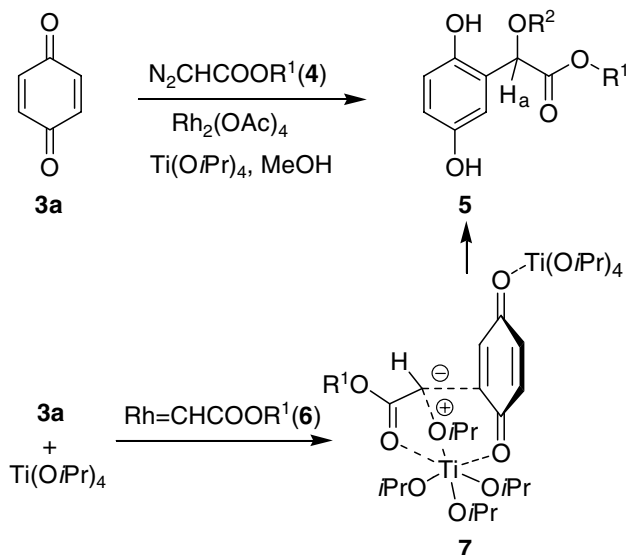

Figure 1. 2-Substituted hydroquinone units present in naturally existing systems.

tions involving *p*-benzoquinones, diazo esters, titanium(IV) isopropoxide and alcohol in the presence of Rh$_2$(OAc)$_4$ as catalyst affording 2-substituted hydroquinones or 1-hydroxy-4-oxocyclohexa-2,5-dienyls.

Scheme 1.

Table 1. Synthesis of 2-substituted hydroquinones **5**

Entry	R[1]	R[2]	Product	Yield[a] (%)
1	Ethyl	Isopropyl	**5a**	82
2	Ethyl	Methyl	**5b**	63
3	*n*-Butyl	Isopropyl	**5c**	68
4	*n*-Butyl	Methyl	**5d**	52
5	*n*-Hexyl	Isopropyl	**5e**	50
6	Benzyl	Isopropyl	**5f**	73
7	Benzyl	Methyl	**5g**	45[b]

[a] Yields are unoptimized and refer to isolated pure compound **5**.
[b] The corresponding isopropoxy group substituted product of **5** (5%) was also isolated.

Initially, the treatment of *p*-benzoquinone (**3a**), 1.1 equiv of titanium(IV) isopropoxide and ethyl diazoacetate **4a** in the presence of rhodium(II) acetate catalyst in dichloromethane afforded product **5a** in 82% yield (Scheme 1, Table 1), which was characterized based on spectral data.[12] The ^{1}H NMR spectrum of ester **5a** exhibited a characteristic multiplet around 1.18 ppm for the methyl protons of the isopropyl group, two broad singlets at 2.51 and 6.22 ppm for the two hydroxyl groups and a singlet at 5.02 ppm for proton-H_a. The ^{13}C NMR and DEPT-135 spectra of **5a** showed resonances for two CH_3 carbons, one CH_2 carbon, two CH carbons and four quaternary carbons including a carbonyl carbon. In addition, the absence of the two quaternary carbonyl carbon resonance signals of *p*-benzoquinone clearly indicated that the product was the 2-substituted hydroquinone **5a** formed via a three-component reaction. Further, the three-component reaction of mono-substituted diazo ester **4a** was performed in the presence of methanol to afford **5b** in moderate yield. Ester **5b** showed the presence of a methoxy group instead of an isopropyl group based on the ^{1}H NMR spectrum.[12]

Mechanistically, it is clear that the transition state **7** could be generated successfully by nucleophilic attack of one of the isopropoxy oxygens of titanium(IV) iso-

propoxide on the electron deficient rhodium-carbenoid carbon atom present in intermediate **6** (Scheme 1). Subsequent nucleophilic addition at the C=C bond of benzoquinone could be accomplished by the transient oxonium ylide dipole of transition state **7**. Consequently, titanium(IV) isopropoxide activation of the carbonyl groups of *p*-benzoquinone leads to aromatization to afford **5a**. The above three-component reaction furnished methoxy substituted product **5b** when methanol was used as an external nucleophile. The more nucleophilic methoxy group might replace the isopropoxy group to form the corresponding oxonium ylide in transition state **7** (Scheme 1).

The reaction was extended to various mono-substituted diazo esters such as butyldiazo acetate (**4b**), hexyldiazo acetate (**4c**) and benzyldiazo acetate (**4d**) to furnish 2-substituted hydroquinones **5c**–**g**, either in the presence or absence of methanol. It is interesting to note that our earlier study indicated that the aldol-type addition reaction of the tricyclooxonium ylide intermediate c involves only the C=O group of *p*-benzoquinone.[9] In contrast, in these reactions nucleophilic addition occurred at the C=C group of benzoquinone only to furnish 2-substituted hydroquinones **5c**–**g** chemoselectively.

To extend the oxonium ylide mediated nucleophilic addition to benzoquinones, a range of di-substituted diazo esters and substituted *p*-benzoquinones were investigated. Reaction of *p*-benzoquinone **3a**, 1.1 equiv of titanium(IV) isopropoxide and ethyl phenyldiazoacetate (**8a**) in the presence of rhodium(II) acetate catalyst afforded **9a** in 72% yield (Scheme 2, Table 2).[12] The
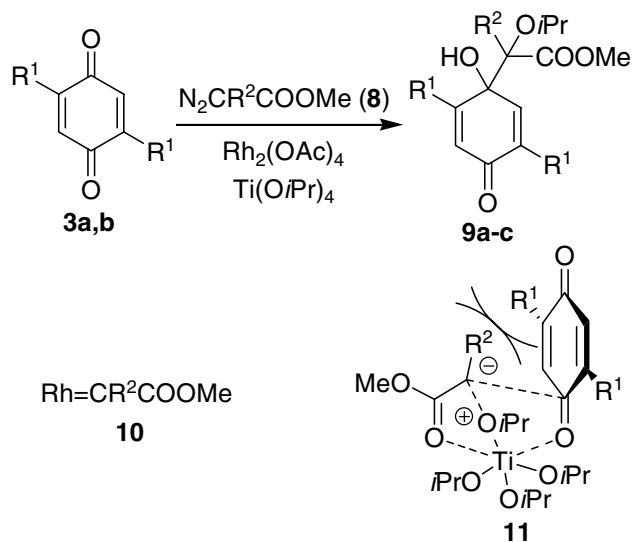
Scheme 2.

Table 2. Synthesis of 1-hydroxy-4-oxocyclohexa-2,5-dienyls **9**

Entry	R[1]	R[2]	Product	Yield[a] (%)
1	H	C_6H_5	**9a**	72
2	H	COOMe	**9b**	64
3	CH_3	COOMe	**9c**	76

[a] Yields are unoptimized and refer to isolated pure compound **9**.

FT-IR spectrum of **9a** exhibited characteristic peaks at 1736, 1776, and 3443 cm^{-1} due to the carbonyl, ester and hydroxyl groups, respectively. The ^{1}H NMR spectrum of product **9a** exhibited a singlet at 3.54 ppm for the methyl protons of the ester group, two doublets at 1.06 ppm and 1.14 ppm for the two non-equivalent methyls of the isopropyl group. The ^{13}C NMR and DEPT-135 spectra of **9a** showed peaks for two CH$_3$ carbons, one OCH$_3$ carbon and five quaternary carbons including two carbonyl carbons thereby confirming the structure of **9a**.

Mechanistically, the chemoselectivity may be explained based on the formation of transition state **11** by nucleophilic attack of one of the isopropoxy O-atoms on the electron deficient rhodium-carbenoid carbon in intermediate **10** (Scheme 2). Subsequent nucleophilic addition to the C=O group of *p*-benzoquinone could be accomplished through the transient oxonium ylide dipole of transition state **11**. The reason for this may be due to steric hindrance arising from the proximity between the R^2-group of the diazo ketone and the H or CH$_3$ of quinone in transition state **11**. The reaction was performed with other disubstituted α-diazo esters such as dimethyl diazomalonate (**8b**) to furnish product **9b** in moderate yield. Further, the oxonium ylide mediated three-component reaction of 2,6-dimethyl-1,4-benzoquinone (**3b**), titanium(IV) isopropoxide and dimethyl diazomalonoate furnished ester **9c** in good yield. All these reactions were carried out by the slow addition of diazo esters to the reaction mixture containing *p*-benzoquinone, titanium(IV) isopropoxide and rhodium(II) acetate at reflux. Purification was carried out using silica gel column chromatography. Interestingly, no product was isolated when the reaction was performed either in the absence of rhodium(II) acetate or in the absence of titanium(IV) isopropoxide.

Reaction of 1,4-cyclohexanedione with ethyl diazoacetate gave **12**. Reaction of ethyl diazoacetate (**4a**), 2,6-dimethyl-1,4-benzoquinone (**3b**) and titanium(IV)-isopropoxide in the presence of rhodium(II) acetate dimer catalyst furnished **13** as an inseparable diastereomeric mixture in the ratio of 2:1 (Fig. 2) via nucleophilic addition at the C=O group instead of the C=C group. A similar reaction with cyclohexenone furnished an inseparable diastereomeric mixture of **14** in the ratio of 2:1. All the above reactions gave only the C=O addition products in a chemoselective manner.

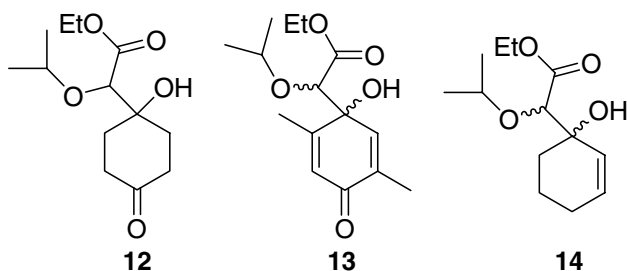In conclusion, the oxonium ylide derived from mono-substituted diazo esters underwent only C=C nucleophilic addition of *p*-benzoquinone to furnish various 2-substituted hydroquinones with complete chemoselectivity. In contrast, oxonium ylides derived from mono- or disubstituted diazo esters with substituted or unsubstituted *p*-benzoquinones afforded only the C=O nucleophilic products, 1-hydroxy-4-oxocyclohexa-2,5-dienyls.

Acknowledgments

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12. *General procedure for the three-component reaction of diazo esters, titanium(IV) isopropoxide and p-benzoquinones:* To a CH$_2$Cl$_2$ (8 mL) solution of Rh$_2$(OAc)$_4$ catalyst (0.01 mmol), titanium isopropoxide (1.1 mmol) and *p*-benzoquinone (1.1 mmol) was added the diazo ester (1.0 mmol) in CH$_2$Cl$_2$ (4 mL) via a syringe pump over 30 min at reflux (for compounds **9**) or room temperature (for compounds **5**, **12–14**). The reaction mixture was cooled to room temperature and the solvent was removed.

Figure 2.

Ethyl acetate (30 mL) was added and the reaction mixture was washed with 20 mL saturated aqueous NH_4Cl and the aqueous phase was extracted with EtOAc (2×20 mL). The combined organic phase was washed with water, saturated brine and then dried over anhydrous Na_2SO_4. After filtration, the solvent was removed and a portion of the crude product was subjected to ^{1}H NMR analysis for the determination of the product ratio. The crude product was purified by flash chromatography on silica gel using hexane:EtOAc as eluent to afford products **5** or **9** or **12–14**. Spectral data for selected compounds: Compound **5a**, 82% yield. Semi-solid; v_{max} (KBr)/cm^{-1} 3486, 2978, 2965, 1776, 1468, 1269, 1114, 736. ^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.26–1.18 (m, 9H, CH_3), 2.51 (br s, 1H, OH), 3.81–3.72 (m, 1H, CH), 4.27–4.12 (m, 2H, CH_2), 5.02 (s, 1H, CH), 6.22 (br s, 1H, OH), 6.72 (s, 2H, ArH), 7.33 (s, 1H, ArH). ^{13}C NMR (CDCl$_3$, 50.3 MHz) δ 13.8 (CH_3), 21.7 (CH_3), 61.9 (OCH_2), 71.7 (CH), 77.8 (CH), 115.3 (=CH), 117.0 (=CH), 118.0 (=CH), 121.5 (*quat-C*), 148.9 (*quat-C*), 149.1 (*quat-C*), 171.3 (C=O). HRMS (ESI, LCMS) for C$_{13}$H$_{18}$O$_5$ [(M+Na)$^+$] calcd 277.1054. Found: 277.1048. Compound **5b**, 63% yield. Semi-solid; v_{max}(KBr)/cm^{-1}

3486, 2978, 2965, 1780, 1466, 1270, 1244, 1114, 731. ^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.23 (t, 3H, $J = 7.0$ Hz, CH_3), 2.41 (br s, 1H, OH), 3.43 (s, 3H, OCH_3), 4.26–4.14 (m, 2H, CH_2), 4.84 (s, 1H, CH), 6.69 (s, 2H, ArH), 6.12 (br s, 1H, OH), 7.00 (s, 1H, ArH). ^{13}C NMR (CDCl$_3$, 50.3 MHz) δ 13.9 (CH_3), 57.5 (OCH_3), 62.0 (OCH_2), 81.2 (CH), 115.4 (=CH), 117.3 (=CH), 118.1 (=CH), 121.0 (*quat-C*), 148.6 (*quat-C*), 149.3 (*quat-C*), 170.8 (C=O). HRMS (ESI, LCMS) for C$_{11}$H$_{14}$O$_5$ [(M+Na)$^+$] calcd 249.0741. Found: 249.0756. Compound **9a**, 72% yield. Colorless solid; mp 89–91 °C. v_{max}(KBr)/cm^{-1} 3443, 2972, 1776, 1736, 1508, 1448, 1370, 1280, 1207, 1092, 1051, 833, 733. ^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.06 (d, 3H, $J = 6.2$ Hz, CH_3), 1.14 (d, 3H, $J = 6.2$ Hz, CH_3), 3.54 (s, 3H, OCH_3), 4.02–3.96 (m, 1H), 6.39 (br s, 1H, OH), 6.68 (d, 2H, $J = 9.0$ Hz), 6.99 (d, 2H, $J = 9.0$ Hz), 7.39–7.31 (m, 3H), 7.71–7.66 (m, 2H). ^{13}C NMR (CDCl$_3$, 50.3 MHz) δ 23.2 (CH_3), 23.5 (CH_3), 52.8 (OCH_3), 68.4 (CH), 101.8 (*quat-C*), 115.6 (=CH), 118.8 (=CH), 126.7 (=CH), 128.1 (=CH), 128.8 (=CH), 137.6 (*quat-C*), 148.5 (*quat-C*), 150.7 (C=O), 170.0 (C=O). HRMS (ESI, LCMS): [(M+Na)$^+$] calcd for C$_{18}$H$_{20}$O$_5$, 339.1209. Found: 339.1228.