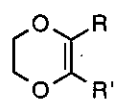
PREPARATION OF 1,4-DIOXENES FROM α-DIAZO-β-KETOESTERS

Ramona Hilgenkamp, John B. Brogan, and Charles K. Zercher*

Department of Chemistry, University of New Hampshire,
Durham, NH 03824, USA

Abstract - A novel preparation of 1,4-dioxenes is reported in which a rhodium carbenoid generated from an α-diazo-β-ketoester reacts with a 1,2-diol. Insertion of the carbenoid into the O-H bond followed by hemiacetal formation and acid-catalyzed dehydration generates the targeted 1,4-dioxene.

Substituted 1,4-dioxenes (**1**) are useful substrates for a wide variety of organic transformations and have been utilized for the preparation of diverse functionality.[1] The traditional starting material for the preparation of these electron-rich olefins has been the unfunctionalized 1,4-dioxene (**2a**) which is easily prepared by



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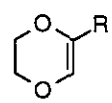
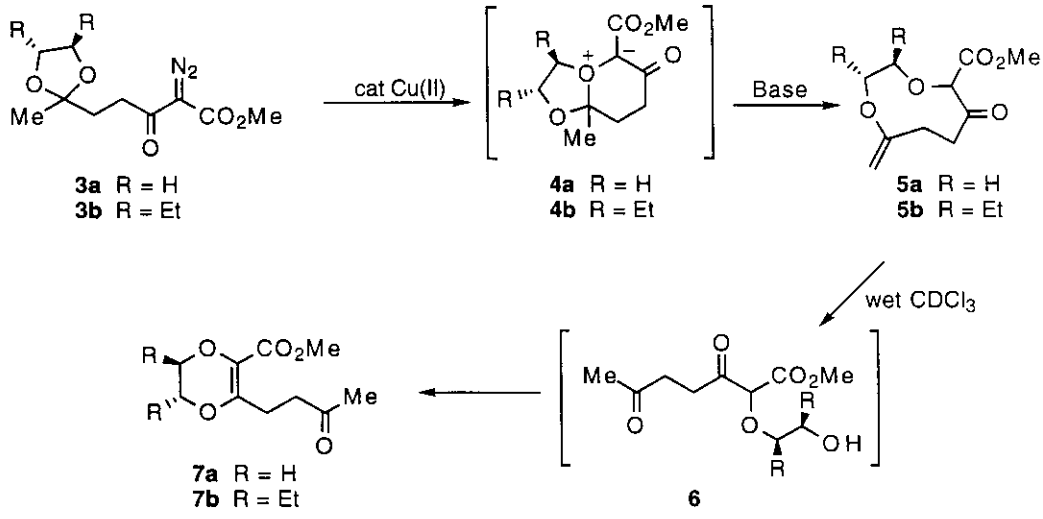


2 a R = H
b R = Li

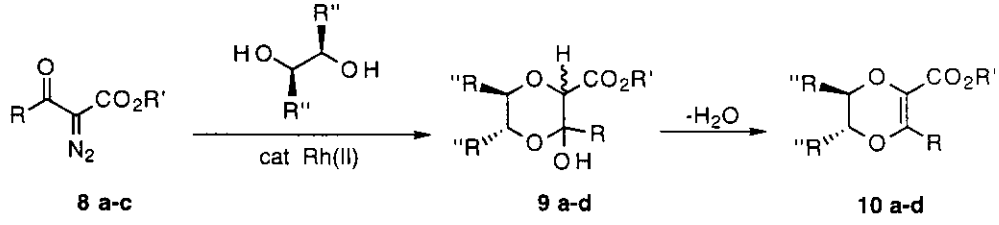
refluxing ethylene glycol in the presence of copper chromite and potassium bisulfate.[2] Although **2a** can be converted to a variety of 2-substituted dioxenes by the alkylation of 2-lithio-1,4-dioxene (**2b**),[1b] no systematic method has been reported for the preparation of differentially-substituted 2,3-disubstituted 1,4-dioxenes. Alternative synthetic approaches would dramatically increase the utility of the dioxenes.
We reported previously that the generation of an ylide (**4**) in the presence of trace amounts of water can result in the formation of the β-elimnation product (**5**) which cleanly rearranges in chloroform to provide the dioxenes (**7**).[3] A proposed mechanism for this rearrangement (Scheme 1) involves hydration and dehydration with the production of the acyclic intermediate (**6**) and its isomeric hemiacetals.
Although no evidence of the acyclic keto alcohol (**6**) or the related hemiacetals was observed in the $CDCl_3$ solution, it was envisioned that similar intermediates could be approached by the direct carbenoid-mediated OH-insertion of a diol into an analogous diazo carbon.[4,5] Reaction between a 1,2-diol and an α-diazo-β-keto ester (**8**) would result in the formation of an acyclic compound in equilibrium with a hemiacetal (**9**).



Scheme 1

Exposure of the hemiacetal to dehydrating conditions would result in the formation of the substituted 1,4-dioxene (**10**) (Scheme 2).

A three-step method for the preparation of a series of dioxenes from readily available β-keto esters has been developed (Table 1). The reaction between ethylene glycol and the rhodium-carbenoid of various α-diazo-β-keto esters[6] (entries a-c) was complicated by the poor solubility of ethylene glycol in benzene and methylene chloride which are the common solvents used for rhodium carbenoid chemistry. The O-H



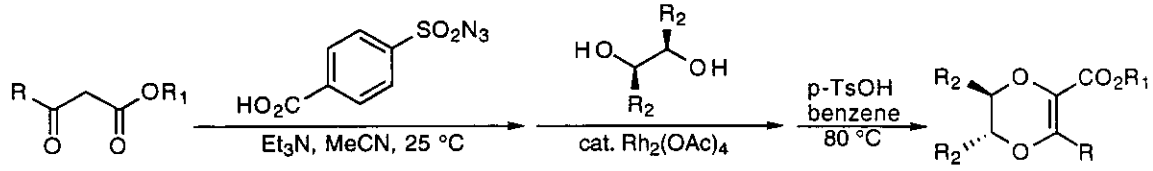
Scheme 2

insertion reaction was successfully performed by utilizing ethylene glycol as the solvent at 80 °C, although the yields were compromised by retro-Claisen reactions induced by nucleophilic attack of the alcohol. The solid diol, *trans*-1,2-cyclohexanediol (Table 1, entry d) has limited solubility in methylene chloride, yet the O-H insertion reaction proceeded with modest efficiency.

Although many reaction conditions were screened, the most effective dehydration conditions consisted of azeotropic removal of water in the presence of *p*-TsOH. The OH-insertion and the dehydration reactions can be performed without purification of the intermediate hemiacetal and, in general, the overall yield of the dioxene benefited by the avoidance of chromatographic purification of the hemiacetal.

One solid diol which did not present solubility problems was catechol (**12**). Exposure of catechol to α-diazo-β-keto ester (**11**) resulted in the production of the β-keto ester (**14**) and the generation of a deep

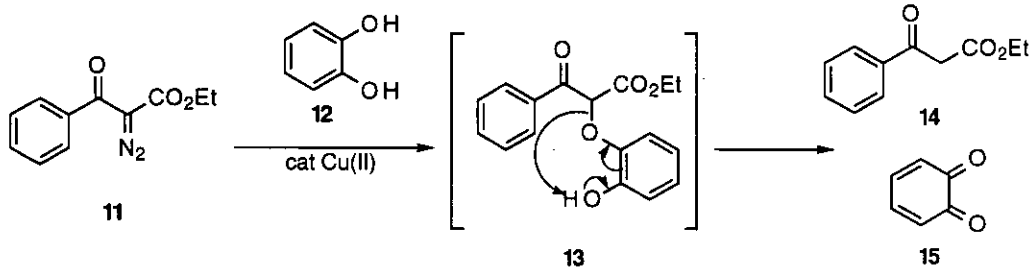
Table 1: Dioxene Formation via Diazo Generation, O-H Insertion, and Dehydration



entry	R	R_1	R_2	solvent[a]	temp[b]	yield(%)[c]
a	Ph	Et	H	none[d]	80 °C	22
b	PhCH=CH	Me	H	none[d]	80 °C	42
c	n-C_4H_9	Et	H	none[d]	80 °C	33
d	Ph	Et	-$(CH_2)_4$-[e]	CH_2Cl_2	35 °C	42

(a) Solvent used for the OH insertion reaction. (b) The temperature of the OH insertion reaction. (c) Isolated yield for the three-step preparation of purified dioxene. (d) 100 equiv of ethylene glycol used. (e) 5 equiv of *trans*-1,2-dihydroxycyclohexane was used.

reddish color in the benzene solvent (Scheme 3). Although rhodium(II) has been implicated in the reduction of α-diazo-β-keto esters,[4a] we believe that reduction of this diazo functionality was coupled to the oxidation of catechol to the *ortho*-quinone (**15**). Presumably, OH-insertion is followed by elimination to provide the corresponding *ortho*-quinone. Although the *ortho*-quinone has not been successfully trapped, the nearly quantitative preparation of the β-keto ester (**14**) and the immediate generation of the deep red color attests to



Scheme 3

the efficiency of this transformation. It is interesting to contrast this result with the report in which treatment of catechol with the rhodium carbenoid of a trialkyl diazophosphonoacetate provided the simple OH insertion product with no oxidation to the *ortho*-quinone.[5b]

In conclusion, the generation of functionalized dioxenes from β-keto esters has been accomplished in an operationally simple three-step sequence. This method nicely complements the intramolecular reactions reported earlier. Further efforts to extend this method for the production of additional dioxenes and related heterocycles are underway.

EXPERIMENTAL

General Methods

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. The *p*-carboxybenzenesulfonazide was prepared through the method of Hendrickson.[7] All other reagents were commercially available and distilled prior to use. Methylene chloride was distilled from phosphorous pentoxide. All reactions were performed under a nitrogen atmosphere using magnetic stirrers unless indicated otherwise. Proton NMR spectra were obtained at 360 MHz (referenced to TMS at 0 ppm) and carbon spectra at 90 MHz (referenced to TMS at 0 ppm). TLC plates supplied by EM (Merck) of silica gel 60 F_{254} at 250 mm thickness were used and were visualized with short wave UV and anisaldehyde stain. Flash chromatography was conducted according to the procedure of Still and coworkers[8] using Baker 40 mm flash chromatography silica gel. Low Resolution Mass Spectrometry and High Resolution MS was performed by the University of California at Riverside Mass Spectrometry Facility. Elemental microanalysis was performed in the University of New Hampshire Instrumentation Center.

General Experimental Methods

General procedure for the formation of the diazo compounds: A solution of the β-keto ester (1 equiv) and triethylamine (2.2 equiv) in CH_3CN (0.4 M) was charged with 4-carboxybenzenesulfonazide (1.2 equiv) at rt and stirred for 2.5 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether. The combined ether washes were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica to yield the α-diazo-β-keto ester.

Ethyl 2-diazo-3-oxo-3-phenylpropanoate (8a):[9] oil; 95%; ^{1}H NMR ($CDCl_3$) δ 7.56 (m, 2H), 7.42 (m, 1H), 7.30 (m, 2H), 4.15 (q, 2H, J = 5.0 Hz), 1.15 (t, 3H, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$) δ 186.9, 161.0, 137.1, 132.2, 128.3, 127.9, 76.0, 61.6, 14.2.

Methyl 2-diazo-3-oxo-5-phenyl-*E*-4-pentenoate (8b):[10] oil; 95%; ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 1H, J = 15.6 Hz), 7.67 (d, 1H, J = 15.6 Hz), 7.51 (m, 2H), 7.28 (m, 3H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 181.1, 161.6, 142.7, 134.6, 130.5, 128.8, 128.6, 121.6, 76.6, 52.1.

Ethyl 2-diazo-3-oxoheptanoate (8c): oil; 95%; ^{1}H NMR ($CDCl_3$) δ 4.27 (q, 2H, J = 7.3 Hz), 2.82 (t, 2H, J = 4.3 Hz), 1.59 (m, 2H), 1.29 (m, 2H), 1.25 (t, 3H, J = 7.3 Hz), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 192.8, 161.4, 75.7, 61.4, 40.0, 26.6, 22.5, 14.4, 13.9. Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12. Found: C, 54.91; H, 7.19.

General procedure for the OH insertion reactions: The diol (excess) was dissolved in the appropriate solvent (see Table 1 for details) and the α-diazo-β-keto ester added followed by a catalytic amount of the $Rh_2(OAc)_4$. The solution was heated slowly to 80 °C and maintained at temperature for approximately three h. The organic products were extracted into ether which was repeatedly washed with water and brine to remove excess diol. The solution was dried with Na_2SO_4, filtered, and evaporated. The

crude material was chromatographed (ethyl acetate:hexanes) on silica to yield the purified mixture of hemiacetals.

General procedure for the dehydration reactions: The crude or purified O-H insertion product was dissolved in benzene and *p*-toluenesulfonic acid added. Water was removed through use of a Dean-Stark trap. Ethyl ether was added and the organic solution was washed with $NaHCO_3$ and brine, and dried with Na_2SO_4. Chromatography (ethyl acetate:hexanes) on silica yielded the purified dioxene.

2-Carboxyethyl-3-phenyl-1,4-dioxene (10a): 23%; mp = 51.0 - 52.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 5H), 4.32 (m, 2H), 4.25 (m, 2H), 4.06 (q, 2H, *J* = 7.1 Hz), 1.03 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 163.7, 147.7, 134.6, 129.3, 127.9, 126.7, 65.8, 64.0, 60.8, 13.9; IR (film) 2950, 1716, 1325, 1300, 1130, 1110 cm^{-1}; MS (CI, NH_3) 252 (52), 236 (53), 235 (100), 234 (56), 189 (20), 105 (67); HRMS (CI, NH_3) MH^+ calcd for $C_{13}H_{15}O_4$ 235.0970, found 235.0973.

2-Carboxymethyl-3-(*E*-2-phenylethenyl)-1,4-dioxene (10b): oil; 44%; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1H, *J* = 16.0 Hz), 7.24 -7.49 (m, 5H), 7.07 (d, 1H, *J* = 16.0 Hz), 4.27 (m, 2H), 4.21 (m, 2H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 163.9, 145.3, 137.0, 131.5, 128.8, 128.4, 127.2, 119.7, 64.7, 64.0, 52.2; IR (film) 3150, 1700, 1575, 1300, 1100 cm^{-1}; MS (CI, NH_3) 264 (21), 248 (48), 247 (100), 246 (40), 187 (13), 131 (42); HRMS (CI, NH_3) MH^+ calcd for $C_{14}H_{15}O_4$ 247.0970, found 247.0977.

2-Carboxyethyl-3-butyl-1,4-dioxene (10c): oil; 35%; ^{1}H NMR ($CDCl_3$) δ 4.18 (q, 2H, *J* = 6.0 Hz), 4.06 (m, 2H), 4.00 (m, 2H), 2.55 (t, 2H, *J* = 7.0 Hz), 1.45 (m, 2H), 1.25 (m, 5H), 0.85 (t, 3H, *J* = 3.0 Hz); ^{13}C NMR ($CDCl_3$) δ 163.6, 151.4, 125.0, 65.0, 63.2, 60.4, 30.7, 29.6, 22.3, 14.3, 13.8; IR (film) 2950, 1735, 1475, 1185 cm^{-1}; MS (CI, NH_3) 232 (54), 216 (52), 215 (100), 214 (55), 169 (16); HRMS (CI, NH_3) MH^+ calcd for $C_{11}H_{19}O_4$ 215.1283, found 215.1279.

(±)-5R, 10R-2-Carboxyethyl-3-phenyl-1,4-dioxabicyclo[4.4.0]dec-2-ene (10d): 44%; mp = 95.0 - 96.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.3-7.4 (m, 5H), 3.96 (q, 2H, *J* =7.0 Hz), 3.75 (m, 1H), 3.59 (m, 1H), 2.32 (m, 1H), 2.20 (m, 1H), 1.84 (m, 2H), 1.29-1.51 (m, 4H), 0.96 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 163.9, 147.0, 134.8, 129.1, 128.9, 127.7, 126.4, 77.8, 75.9, 60.5, 29.7, 23.7, 13.7; IR (KBr) 2950, 2850, 1725, 1600, 1465, 1275 cm^{-1}; MS (CI, NH_3) 306 (14), 291 (12), 290 (56), 289 (100), 288 (49), 243 (10), 105 (52); HRMS (DCI, NH_3) MH^+ calcd for $C_{17}H_{21}O_4$ 289.1440, found 289.1440. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.80; H, 6.84.

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