ORGANIC LETTERS

2005
Vol. 7, No. 15
3167−3170

Regioselective Single and Double Conjugate Additions to Substituted Cyclohexa-2,5-dienone Monoacetals

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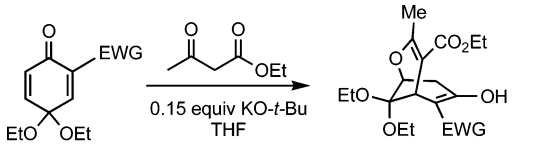
Received April 4, 2005

ABSTRACT



EWG = CO_2Me, C(O)NHPh

A series of quinone monoacetals bearing electron-withdrawing groups was treated with diethyl malonate and other bifunctional nucleophiles in the presence of KO-*t*-Bu in THF. Reactions of ethyl 3-nitropropionate or diethyl malonate resulted in single conjugate addition adducts. When ethyl acetoacetate was used as a nucleophile, bridged bicyclic products were obtained in good yields. The regiochemistry of conjugate addition was dependent on the quinone monoacetal substitution.

Cyclohexa-2,5-dienone monoacetals or masked *para*-benzoquinone acetals have often been used as precursors to structurally complex target molecules.[1] Among the various reaction types demonstrated with these systems, conjugate additions are common and have been performed with a variety of nucleophiles. The placement of alkyl- or heteroatom-containing substituents about the quinone monacetals allows regioselective conjugate additions through adjustment of the steric or electronic characteristics of these systems.[2] On the other hand, we have been unable to find examples of conjugate additions to quinone monoacetals bearing electron-withdrawing substituents.[3] The use of a quinone monoacetal instead of its parent quinone is very useful in complex synthesis because it permits an additional level of regiochemical control and allows differentiation of the two carbonyl groups in subsequent steps. In this letter, we report a series of conjugate additions with a variety of bifunctional nucleophiles that allow the rapid development of polyfunctionalized mono- and bicyclic ring systems.

We were interested in both determining the regiochemistry of conjugate addition within a series of substituted quinone monoacetals as well as exploring the possibility of directed tandem conjugate additions. Previously, it had been demonstrated that nucleophiles add preferentially to the more electrophilic double bond of 1,4-benzoquinones.[4] In addition, double conjugate additions to simple quinone monoacetals have been reported.[5] We hypothesized that the first-formed (i.e., most stable) anion of a bifunctional nucleophile would add to the more electrophilic double bond first. Upon proton

(1) The terms "quinone monoacetal" and "quinone monoketal" may be used interchangeably. For a review of quinone monoacetal chemistry, see: Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004,** *104*, 1383−1430.

(2) For examples of conjugate additions to quinone monoacetals, see ref 1 and the following specific examples. (a) Chenard, B. L.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1980**, *19*, 932−933. (b) Stern, A. J.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1988**, *18*, 1255−1256. (c) Parker, K. A.; Casteel, D. A. *J. Org. Chem.* **1988,** *53*, 2847−2850. (d) Stern, A. J.; Rohde, J. J.; Swenton, J. S. *J. Org. Chem.* **1989,** *54*, 4413−4419. (e) Ciufolini, M. A.; Dong, Q.; Yates, M. H.; Schunk, S. *Tetrahedron Lett.* **1996,** *37*, 2881−2884. (f) Högenauer, K.; Baumann, K.; Mulzer, J. *Tetrahedron Lett.* **2000**, *41*, 9229−9232.

(3) For examples of conjugate additions to quinones containing electron-withdrawing groups, see: (a) Valderrama, J. A.; Cortes, M.; Pessoa-Mahana, D.; Preite, M.; Benites, J. *Tetrahedron Lett.* **2000**, *41*, 3563−3566. (b) Valderrama, J. A.; Pessoa-Mahana, D.; Tapia, R. A.; Rojas de Arias, A.; Nakayama, H.; Torres, S.; Miret, J.; Ferreira, M. E. *Tetrahedron* **2001**, *57*, 8653−8658. (c) Brimble, M. A.; Halim, R.; Petersson, M. *Tetrahedron Lett.* **2002**, *43*, 4777−5758. (d) Brimble, M. A.; Burgess, C.; Halim, R.; Petersson, M.; Ray, J. *Tetrahedron* **2004**, *60*, 5751−5758.

10.1021/ol050715c CCC: $30.25
Published on Web 06/24/2005

transfer to the resulting enolate, intramolecular conjugate addition of the other nucleophilic site to the remaining double bond seemed possible. Such a reaction sequence would allow the direct regioselective formation of functionalized bridged ring systems from simply substituted quinone monoacetals and common nucleophiles.

To examine this, we synthesized quinone monoacetals **1**−**4** bearing electron-withdrawing groups from simple phenols (Figure 1).[6] Initially, we treated quinone monoacetal ester **1**

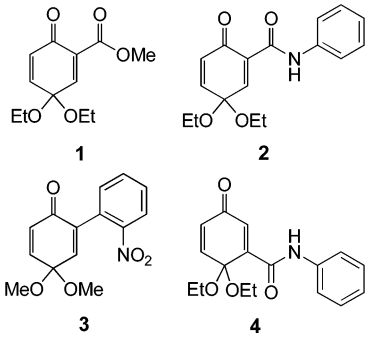


Figure 1. Substituted quinone monacetals used in this study.

with 1.0 equiv of diethyl malonate in the presence of 0.15 equiv of KO-*t*-Bu in THF at room temperature for 10 h. Upon workup and chromatography, phenol **5** was obtained as the result of conjugate addition to C-3 followed by elimination of ethanol. This step was accelerated by treatment of the unstable addition adduct with a catalytic amount of *p*-TsOH in refluxing benzene.[2c]

Three bisnucleophiles were investigated for their propensity to undergo directed tandem conjugate additions (Table 1). Treatment of **3** with ethyl 3-nitropropionate[7] in the presence of KO-*t*-Bu provided the adduct **6** quantitatively as a ca. 10:1 mixture of diastereomers (major diastereomer shown). This adduct underwent extensive aromatization during chromatography on silica gel. When ethyl acetoacetate was used, the double conjugate addition adduct was obtained with the anticipated regiochemistry in good yield. Compound **7** was the result of C-alkylation of the stabilized enolate, followed by O-alkylation at the remaining double bond. Likewise, treatment of quinone monoacetal ester **1** with 2-nitroacetone[8] in the presence of base provided the double conjugate addition adduct **8** in modest yield.

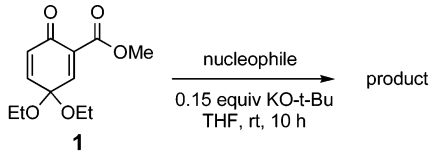
(4) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992; Vol. 9, pp 1−8. (b) Aponick, A.; Buzdygon, R. S.; Tomko, R. J., Jr.; Fazal, A. N.; Shughart, E. L.; McMaster, D. M.; Myers, M. C.; Pitcock, W. H., Jr.; Wigal, C. T. *J. Org. Chem.* **2002**, *67*, 242−244. (c) Towers, M. D. K. N.; Woodgate, P. D.; Woodgate, P. D.; Brimble, M. A. *ARKIVOC* **2003**, *1*, 43−55.

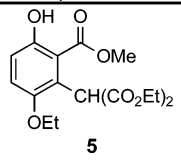
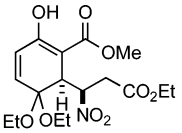
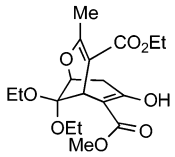
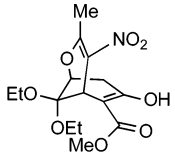
(5) (a) Parker, K. A.; Kang, S.-K. *J. Org. Chem.* **1980**, *45*, 1218−1224. (b) Camps, P.; Gonzalez, A.; Munoz-Torrero, D.; Simon, M.; Zuniga, A.; Martins, M. A.; Font-Bardia, M.; Solans, X. *Tetrahedron* **2000**, *56*, 8141−8151. (c) Carreno, M. C.; Luzon, C. G.; Ribagorda, M. *Chem. Eur. J.* **2002**, *8*, 208−216.

(6) Quinone monoacetals **1**−**4** were generally made by oxidation of the corresponding 4-alkoxy phenol. See Supporting Information for details.

(7) Silva, P. C.; Costa, J. S.; Pereira, V. L. P. *Synth. Commun.* **2001,** *31*, 595−600.

Table 1. KO-*t*-Bu-Catalyzed Reactions of Quinone Monoacetal **1** with Nucleophiles



entry	nucleophile	product	yield (%)
1[a]	diethyl malonate	 **5**	74
2[b]	ethyl 3-nitro-propionate	 *ca. 10:1* **6**	ca. 100[c]
3	ethyl acetoacetate	 **7**	84
4	2-nitroacetone	 **8**	52

[a] Treatment with *p*-TsOH in refluxing benzene converted the unstable adduct to the aromatized product. [b] Diastereomeric ratio determined by crude NMR analysis. [c] Unstable adduct was converted to the corresponding phenol for characterization. See Supporting Information for details.

X-ray crystallographic analysis of the major isomer of **6** showed that the nitro ester side chain was oriented pseudo-axially (Figure 2). Thus, we wondered if the stabilized enolate **9**, the immediate result of conjugate addition with ethyl 3-nitropropionate, was preventing a subsequent in-

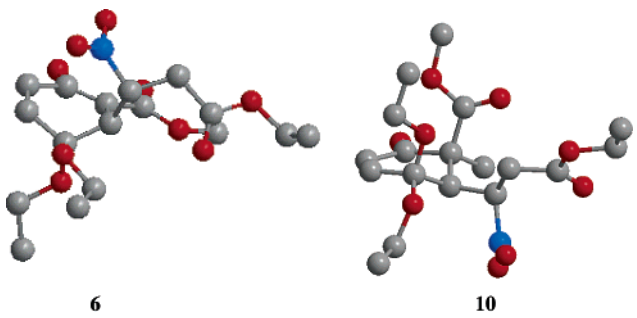
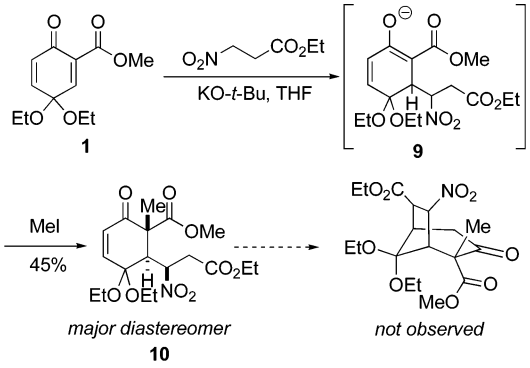


Figure 2. Ball-and-stick depiction of the X-ray crystallographic analyses of **6** and **10**.

tramolecular conjugate addition with the carbon α to the ethyl ester and the remaining double bond (Scheme 1). When

Scheme 1. Conjugate Addition and Methylation of **9** and Attempted Intramolecular Conjugate Addition of **10**

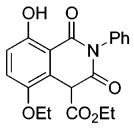
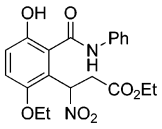
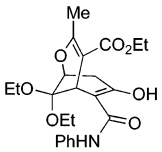
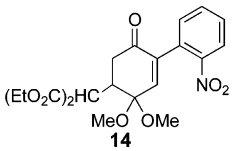
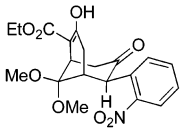


quinone monoacetal **1** was treated with ethyl 3-nitropropionate and MeI in the presence of 1.0 equiv of KO-*t*-Bu, enone **10** was isolated in 45% yield as a diastereomeric mixture. In this case, ca. 10:1 selectivity for the nitro center relative to the adjacent methine was observed, while the methyl group and hydrogen at the ring junctions were exclusively trans. Resubmission of **10** to KO-*t*-Bu in THF failed to provide the intramolecular conjugate addition adduct. A brief survey of other base/solvent systems did not afford bridged products, and in several cases starting quinone monoacetal was isolated. So far, the formation of 6,6-bridged ring systems from these double conjugate additions has been facile, but we have not yet succeeded in accomplishing the formation of 6,5-bridged ring systems using this strategy. We suspect that the position α to the ethyl ester in **10** may not be sufficiently acidic to permit double cylization to occur in this and related examples.

To extend our study to a variety of substituted quinone monoacetals, we treated quinone monoacetal **2** with diethyl malonate in the presence of KO-*t*-Bu in THF. Acidic treatment of the unstable addition adduct provided the aromatized condensation product, imide **11**, in 77% yield (Table 2). Similar treatment with ethyl 3-nitropropionate and quinone monoacetal **2** gave phenol **12** in 57% yield following acidic treatment. We isolated adduct **13**, resulting from double conjugate addition, when ethyl acetoacetate and quinone monoacetal **2** were reacted. The regiochemistry and mode of alkylation were in line with our results from the reactions of 1,3-bisnucleophiles with the quinone monoacetal ester **1**.

When aryl quinone monoacetal **3** was treated with nucleophiles, we observed a change in regiochemistry. When diethyl malonate and this quinone monoacetal were reacted under the usual reaction conditions (catalytic KO-*t*-Bu in THF), adduct **14** was isolated, the result of addition to C-5, para to the nitroaryl group. This adduct did not aromatize

Table 2. KO-*t*-Bu-Catalyzed Reactions of Quinone Monoacetals **2** and **3** with Nucleophiles[a]

entry	quinone	nucleophile	product	yield %
1[b]	**2**	diethyl malonate	 **11**	77
2[b,c]	**2**	ethyl 3-nitropropionate	 **12**	57
3	**2**	ethyl acetoacetate	 **13**	42
4	**3**	diethyl malonate	 **14**	ca. 100
5	**3**	ethyl 3-nitropropionate	*No reaction*	
6	**3**	ethyl acetoacetate	 **15**	76

[a] Reactions were performed with 1.0 equiv of quinone monoacetal, 1.0 equiv of nucleophile, and 0.15 equiv of KO-*t*-Bu in dry THF. [b] Treatment with *p*-TsOH in refluxing benzene converted the unstable adduct to the aromatized product. [c] *tert*-Butyl alcohol was used in the conjugate addition step.

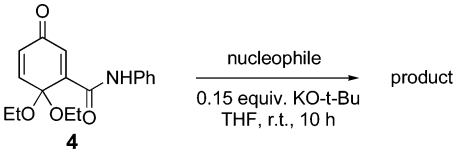
upon treatment with *p*-TsOH but rather proved to be stable. Similar treatment with ethyl 3-nitropropionate did not afford conjugate addition adduct. Interestingly, treatment of the starting aryl quinone monoacetal with ethyl acetoacetate gave adduct **15** in 76% yield. In this case, the regiochemistry of addition mirrors that for diethyl malonate with this aryl quinone monoacetal. Moreover, this adduct was the result of C-alkylation in both addition events, in contrast to our previous findings. It is unclear at present which factors favor C- or O-alkylation in this system, as the mode of addition was unaffected by using additives such as hexamethyl phosphoramide or 18-crown-6. Other solvents (*t*-BuOH and ethanol) and bases (LiO-*t*-Bu, K_2CO_3, Cs_2CO_3) led to the same products but often in lower yields.

To complete our survey of conjugate additions to substituted quinone monoacetals, we subjected **4**, which has opposing dipoles, to reactions with nucleophiles (Table 3).[9] When treated with diethyl malonate in the presence of

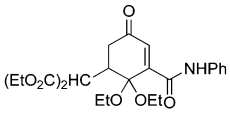
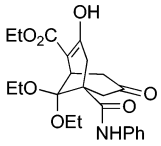
(8) Jung, M. E.; Grove, D. D.; Khan, S. I. *J. Org. Chem.* **1987,** *52,* 4570−4573.

(9) Danishefsky, S.; Schuda, P.; Kato, K. *J. Org. Chem.* **1976**, *41*, 1081−1088.

Table 3. KO-*t*-Bu-Catalyzed Reactions of Quinone Monoacetal **4** with Nucleophiles



4

entry	nucleophile	product	yield (%)
1	diethyl malonate	 **16**	58
2	ethyl 3-nitro-propionate	*No reaction*	
3	ethyl acetoacetate	 **17**	69

KO-*t*-Bu in THF, adduct **16** was isolated in 58% yield, which resulted from exclusive addition to the enone rather than the enamide. Although this reaction failed with ethyl 3-nitropropionate, ethyl acetoacetate again gave double conjugate addition adduct **17** in 69% yield. In this case, the C-alkylated bridged system was obtained to the exclusion of the O-alkylated product that was seen in most of the previous examples. At this time, we do not have an explanation for this phenomenon.

We have demonstrated that the regiochemistry of conjugate addition reactions to quinone monoacetals depends on both the placement and the nature of the substituent. Furthermore, double conjugate additions to quinone monoacetals with 1,3-bisnucleophiles, in particular ethyl acetoacetate, are generally useful. Further work will focus on the use of the highly functionalized bridged products of these tandem conjugate additions in total synthesis.

Acknowledgment. We thank the National Institutes of Health (GM-49093) for funding this work. S.G. acknowledges a Madison and Lila Self Graduate Fellowship, and A.D.W. thanks the American Chemical Society and Abbott Laboratories for an Organic Chemistry Division Fellowship. We are also grateful to Doug Powell for X-ray crystallographic data.

Supporting Information Available: Experimental procedures, characterization data for new compounds, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL050715C