ORGANIC LETTERS

2002
Vol. 4, No. 4
493−496

Reactive Dienes: Intramolecular Aromatic Oxidation of 3-(2-Hydroxyphenyl)-propionic Acids

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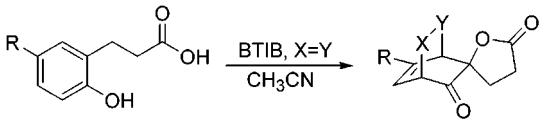
Received October 30, 2001

ABSTRACT

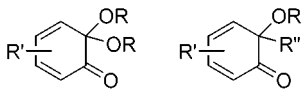


Treatment of 3-(2-hydroxyphenyl)-propionic acids with a hypervalent iodine reagent in the presence of a dienophile initiates a tandem intramolecular aromatic oxidation/Diels–Alder reaction. Herein we report (1) investigations on the scope and limitations of this novel reaction combination and (2) preliminary diastereoselectivity studies using α- and *β*-substituted acids.

Masked *o*-benzoquinones (**1**) or *o*-benzoquinoid structures (**2**) and their Diels−Alder adducts have provided elegant approaches to a variety of structurally diverse organic compounds.[1,2] However, their high propensity toward dimerization via cycloaddition reactions makes them more difficult to handle than the corresponding *p*-benzoquinones, limiting their general applicability as synthetic building blocks.

Since Wessely's first reports in the 1950s,[3] aromatic oxidation reactions of phenols have become one of the preferred methods for generating *o*-benzoquinones, and considerable effort has been directed toward improving and expanding the original procedure.[2] However, to our knowledge, the only example of intramolecular acid trapping of the oxidation intermediate is the one reported by Danishefsky in the synthesis of the tricyclic core of lactonamycin.[4] In the aforementioned example the authors used $Pb(OAc)_4$ to generate a naphthoquinone that was relatively stable against Diels−Alder dimerization, as a result of extended conjugation between the diene and the adjacent aromatic ring.

Scheme 1



1 **2**

We describe herein the development of a tandem Wessely-type oxidation/Diels−Alder reaction of unfused phenols bearing a carboxylic acid moiety suitably tethered for intramolecular trapping.

In the course of our efforts toward the synthesis of CP-263,114[5] we discovered that 3-(2-hydroxyphenyl)-propionic acid (**3**) undergoes a very facile aromatic oxidation in the presence of bis(trifluoroacetoxy)-iodobenzene (BTIB) to furnish spirolactonedienone **4** (observed by NMR), which dimerizes at room temperature to produce **5**.[6] Performing the reaction in the presence of excess methylvinyl ketone

(1) (a) Yates, P.; Bhamare, N. K.; Granger, T.; Macas, T. S. *Can. J. Chem.* **1993**, *71*, 995. (b) Hwang, J. T.; Liao, C. C. *Tetrahedron Lett.* **1991**, *32*, 6583. (c) Singh, V.; Thomas, B. *J. Org. Chem.* **1997**, *62*, 5310. (d) Hsu, P. Y.; Lee, Y. C.; Liao, C. C. *Tetrahedron Lett.* **1998** *39*, 659. (e) Liu, W. C.; Liao, C. C. *J. Chem. Soc., Chem. Commun.* **1999**, 117.

(2) For a review on the chemistry of orthoquinone monoketals and their orthoquinol analogues, see: Quideau, S.; Pouysegu, L. *Org. Prep. Proced. Int.* **1999**, *31*, 617.

(3) (a) Wessely, F.; Lauterbach-Keil, G.; Sinwel, F. *Monatsh. Chem.* **1950**, *81*, 811. (b) Metlesics, M.; Schinzel, E.; Vilsek, H.; Weselly, F. *Monatsh. Chem.* **1957**, *88*, 1069.

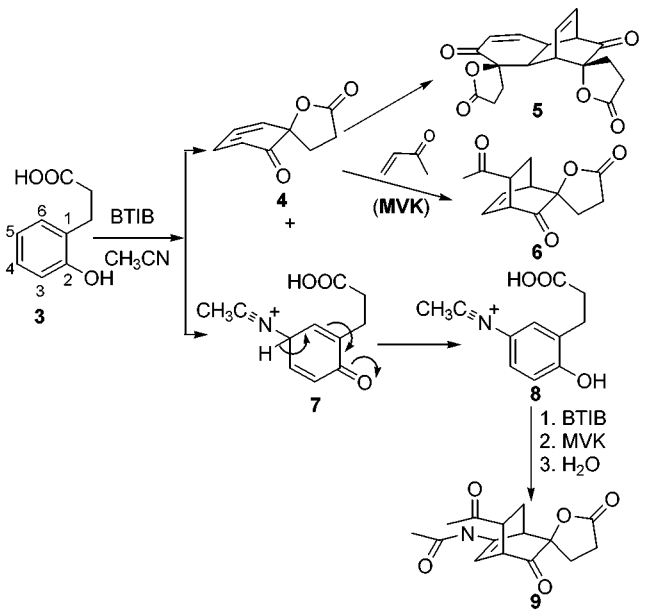
(4) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3493.

(5) Njardarson, J. T.; McDonald, I. M.; Spiegel, D. A.; Inoue, M.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2435.

10.1021/ol0169776 CCC: $22.00
Published on Web 01/31/2002

(MVK) afforded the corresponding adduct **6**,[6] albeit in low yield (<40%), accompanied by dimer **5** and adduct **9**. We believe **9** arises from an initial Ritter-type attack of the solvent at the activated 5-position of the aromatic ring, followed by rearomatization and subsequent oxidation of the substituted acid **8** (Scheme 2). The diastereoselectivity in

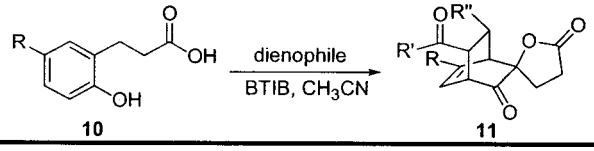
Scheme 2



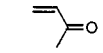
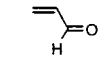
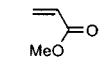
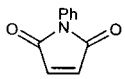
the cycloaddition step is consistent with previous reports for similar compounds,[7] the attack occurring from the oxygen-bearing face of the diene. The same facial selectivity applies to the dienophile in the formation of dimer **5**, whereas adduct **6** arises from the expected *endo* orientation of MVK. The regioselectivity of the cycloaddition is consistent with predictions based on frontier molecular orbital theory.[8]

To suppress the formation of undesired side products, we sought to prepare and analyze a series of 3-(2-hydroxyphenyl)-propionic acids bearing substituents with a range of electronic properties. It is known that *o*-benzoquinoid structures such as **2** are less prone to dimerization than the corresponding *o*-benzoquinone monoacetals (**1**),[9] and therefore we believed that minimal substitution of the aromatic ring would prove sufficient for eliminating dimerization. Substitution *para* to the phenolic oxygen seemed most desirable for the purpose of avoiding unwanted *para* trapping in the oxidation step (vide supra). Thus we initiated our studies with a series of *p*-substituted substrates. We were pleased to observe that when treated with BTIB in the presence of various dienophiles all substituted acids **10**[10] produced the desired Diels−Alder adducts **11** in good yields as single isomers (Table 1).[11,12]

Table 1. Oxidation of 5-Substituted 3-(2-Hydroxyphenyl)-propionic Acids in the Presence of Electron-Deficient Dienes



10 11

Dienophile	Yield[a]		
	R =I[b]	R =Ac[c]	R =CH_3[c]
	89%	65%	84%
	70%	56%	51%
	71%	75%	62%
	79%	73%	59%

[a] Isolated yields after flash chromatography. [b] By performing the oxidation in the absence of dienophile we were able to isolate the intermediate spirolactonedienone in 98% yield. [c] Oxidation in the absence of dienophile afforded upon concentration a mixture of spirolactonedieneone and dimerization product.

The yield and selectivity of the Diels−Alder step are minimally influenced by the electronic profile of the diene, making it a versatile diversity-building tool, especially considering the capacity of vinyl iodides to act as valuable handles for the introduction of a variety of functional groups.

The next step in testing the scope of the oxidation/Diels−Alder reaction was the use of electron-deficient acetylenic dienophiles to build systems such as **12**, which possess a variety of reactive sites that could be further manipulated for synthetic purposes. In our hands these dienophiles proved to be less reactive than their olefinic counterparts toward the investigated dienones (elevated temperatures were required to promote the cycloaddition and the yields were typically lower).[13] We observed a correlation between the electronic properties of the substrate and the yield of the reaction, suggesting a direct electronic demand interaction with electron-rich substrates giving better results than electron-poor ones.

(6) The structure was confirmed by preliminary single-crystal X-ray analysis.

(7) Auksi, H.; Yates, P. *Can. J. Chem.* **1981**, *59*, 2510.

(8) For a detailed discussion concerning the behavior of masked *o*-benzoquinones in normal and inverse electronic demand Diels−Alder reaction and possible FMO explanations, see: Liao, C. C.; Chu, C. S.; Lee, T. H.; Rao, P. D.; Ko, S.; Song, L. D.; Shiao, H. C. *J. Org. Chem.* **1999**, *64*, 4102.

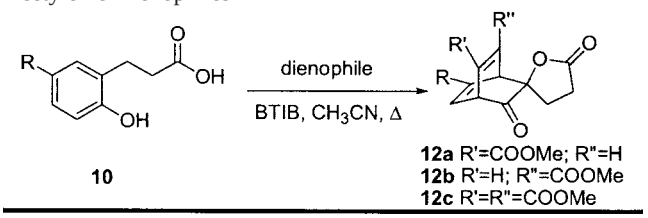
(9) (a) Holmberg, K. *Acta Chem. Scand.* **1974**, *B28*, 857. (b) Metlesics, W.; Wessely, F. *Monatsh. Chem.* **1957**, *88*, 108.

(10) Readily available from commercial starting materials. For experimental details see Supporting Information.

(11) **General Procedure for Experiments in Table 1.** The acid (0.25 mmol) and the dienophile (2.5 mmol, 10 equiv) were dissolved in 5 mL of dry CH_3CN. A solution of BTIB (0.3 mmol, 1.2 equiv) was added, and the reaction mixture was allowed to stir overnight. The solvent was evaporated, and the residue was purified by flash chromatography on silicagel. For details, see Supporting Information.

(12) In a chemical correlation experiment, the Diels−Alder adduct **11** (R = I, dienophile = MVK) was reduced to the known structure **6**, using Bu_3SnH, confirming that the regio- and stereochemistry of addition are not affected by substitution.

Table 2. Substituent Effects in Diels−Alder Reactions with Acetylenic Dienophiles



10

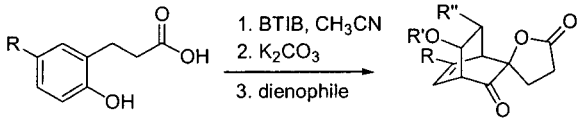
12a R'=COOMe; R"=H
12b R'=H; R"=COOMe
12c R'=R"=COOMe

Dienophile	Yield		
	R =I	R =Ac	R =CH_3
CO_2Me	41% **12a**:**12b**[a] 6:1	28% **12a**[a] exclusively	53% **12a**:**12b**[a] 6:1
MeO_2C—≡—CO_2Me	51%	40%	56%

[a] Ratio determined by NMR. Structural assignment is based on 2D ^{1}H NMR experiments.

Taking into consideration the preference for the less electron-deficient olefin in the dimerization reaction (a well precedented behavior of quinoid dienes),[8,14] we anticipated that our spirodienones would be excellent substrates for inverse electronic demand Diels−Alder reactions. We again observed a marked substituent effect on the rate of the reaction, with electron-deficient dienes giving excellent yields and the 5-Me substrate reacting with great difficulty, as expected.[15] In all cases, however, single isomers of the products were obtained.[16]

Table 3. Substituent Effects in Diels−Alder Reactions with Electron-Rich Olefins



10 **13**

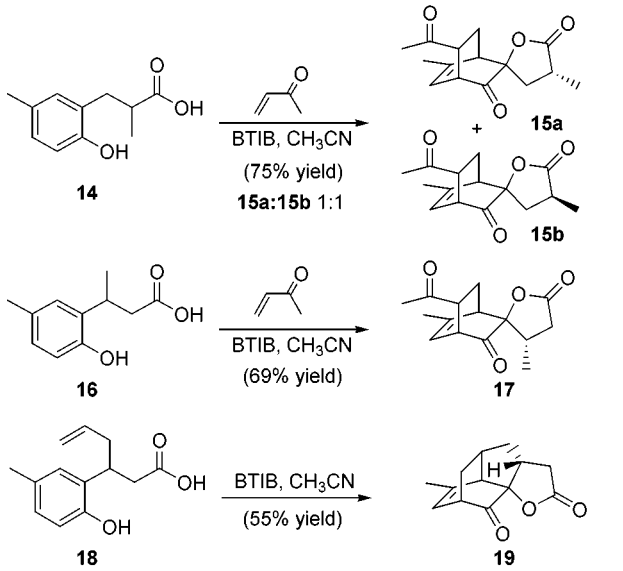
Dienophile	Yield		
	R =I	R =Ac	R =CH_3
OEt	90%	91%	24%
O	74%	85%	0%[a]

[a] If the reaction mixture was maintained at room temperature for several days, significant amounts (~45% yield) of dimer could be isolated.

Having demonstrated a potentially general oxidation/Diels−Alder sequence with respect to both the aromatic substrate and the dienophile, we sought next to exploit the intramolecular character of the oxidation step and investigate the possibility of inducing substrate control over all newly created stereogenic centers by means of appropriate substitution of the propionic acid chain.

In preliminary studies, we prepared the α- and β-methyl derivatives of 3-(2-hydroxy-5-methylphenyl)-propionic acid) and we subjected these substrates to the standard oxidation conditions in the presence of MVK (Scheme 3). Interestingly,

Scheme 3



while the β-methylated derivative provided exclusively one adduct, in the case of the α-methyl acid practically no selectivity could be observed, the reaction yielding a 1:1 mixture of diastereomers (Scheme 3). Although somewhat surprising, the results are in good agreement with the proximity of the resident and newly formed stereogenic centers.

These results led us to explore the construction of an isotwistane skeleton, similar to that utilized in our approach toward the synthesis of the phomoidrides.[5]

To our delight, treatment of the β-allyl substrate **18** with BTIB under standard conditions furnished the desired isotwistane **19** in 55% unoptimized yield, as a single diastereomer.

(13) **General Procedure for Experiments in Table 2.** The acid (0.25 mmol) and the dienophile (2.5 mmol, 10 equiv) were dissolved in 5 mL of dry CH_3CN, and the reaction was heated to 60 °C. A solution of BTIB (0.3 mmol, 1.2 equiv) was added over 4 h (via syringe pump), and the reaction mixture was allowed to stir overnight at 60 °C. The reaction was cooled to room temperature, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silicagel. For details, see Supporting Information.

(14) (a) Gao, S. Y.; Ko, S.; Lin, Y. L.; Peddinti, R. K.; Liao, C. C. *Tetrahedron* **2001**, 57, 297. (b) Arjona, O.; Mendel, R.; Plumet, J. *Tetrahedron Lett.* **1999**, *40*, 8431.

(15) **General Procedure for Experiments in Table 3.** The acid (0.25 mmol) was dissolved in 5 mL of dry CH_3CN. A solution of BTIB (0.3 mmol, 1.2 equiv) was added, and the reaction mixture was allowed to stir for 10 min. Solid K_2CO_3 (200 mg) was added, followed (after 5 min) by the dienophile (2.5−12.5 mmol, 10−50 equiv), and the reaction was allowed to stir overnight. The solvent was evaporated, and the residue was purified by flash chromatography on silicagel. For details, see Supporting Information.

(16) Structural assignments are based on 2D ^{1}H NMR experiments and previous reports on similar systems (see ref 14).

In this case, the reversed facial selectivity is dictated by the one-carbon tether, which prevents trapping from the oxygenated face of the diene.

In summary, we have begun to establish the broad scope of a tandem intramolecular oxidation/Diels−Alder reaction that is applicable to the construction of complex polycyclic systems and proceeds with good substrate control. Investigations are currently being conducted for obtaining improved diastereoselectivity for the α-substituted series, as well as for the development of an enantioselective version of this reaction.

Acknowledgment. We acknowledge the support of this work by Bristol-Myers Squibb, Eli Lilly, Glaxo-Wellcome, Merck, Pfizer, Yamanouchi, and Zeneca through their Faculty Awards Programs and the Camille and Henry Dreyfus Foundation for a Teacher-Scholar Award.

Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0169776