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Unusual cycloadditions of *o*-quinone methides with oxazoles

Christopher C. Lindsey and Thomas R. R. Pettus*

Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, CA 93106, USA

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Abstract—Unusual reactions between various electron-rich oxazoles and *ortho*-quinone methides is described. This combination leads to some interesting adducts.

Until recently, controlled low temperature access to significant quantities of *o*-quinone methide intermediates was almost impossible,[1] a problem which severely limited their use in synthesis. With the development of an anionic generation mechanism triggered at low temperatures,[2] these venerable intermediates have found many additional synthetic uses.[3] These included the first examples of stereoselective inverse demand cycloadditions,[4] which evolved into diastereoselective reactions and enabled the asymmetric synthesis of chiral benzopyrans.[5] In this letter, we demonstrate that the reactivity of *o*-quinone methides proves sufficient to dearomatize and cause a reaction with various 2-amino-4-alkyl oxazoles. However, the reaction manifold (cycloaddition vs 1,4-conjugate addition) depends upon the electronic nature of the 4-alkyl substituent.

Sometime ago, we became interested in constructing elaborate 2*H*-1-benzopyrans such as **A**, bearing alkoxy and alkyl substituents at the 2-position, along with an alkoxy substituent at the 3-position (Fig. 1). This arrangement of atoms can be found in 5,6-aryloxy-spiroketal of heliquinomycin. We envisioned that benzopyran **A** could arise from a regioselective cycloaddition between *o*-quinone methide **B** and the 4-substituted dioxene **C**. However, there are very few methods for the preparation of these fragile dioxenes.[6] The robust oxazole **D** appeared to offer synthetic equivalence for our strategy.

A thorough literature search revealed a single report by Dondoni employing electron-rich 2-amino-oxazoles

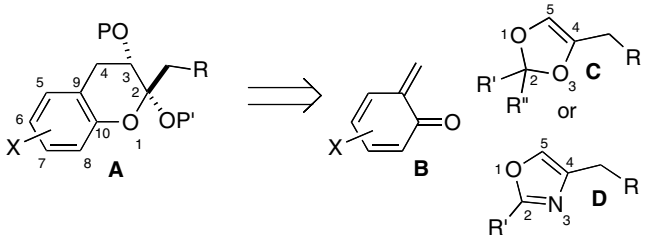

Figure 1. Proposed construction of the elaborate benzopyran **A** by cycloaddition of *o*-quinone methide **B** with heterocycle **C** or **D**.

with several exceedingly electron deficient symmetric 4π dienes (Fig. 2).[7] The yields reported for oxazoles with 4-alkyl substituents were significantly lower than their hydrido counterparts.

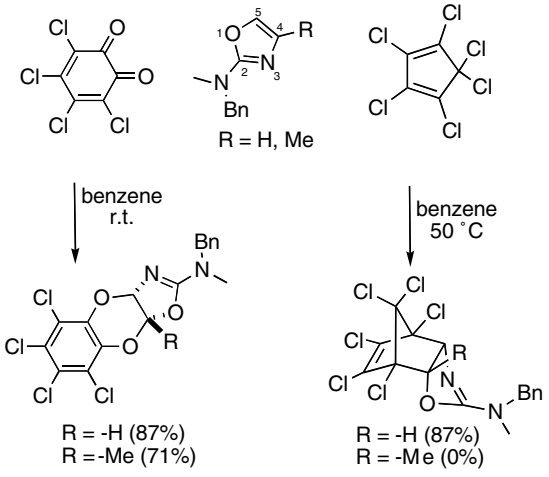

Figure 2. Some of Dondoni's 1986 cycloaddition examples.

* Corresponding author. Tel.: +1 (805) 637 5651; fax: +1 (805) 893 5690; e-mail: pettus@chem.ucsb.edu

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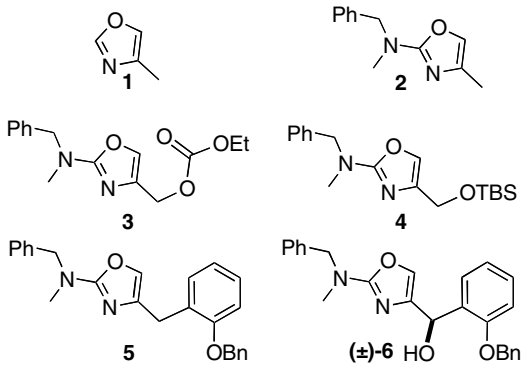
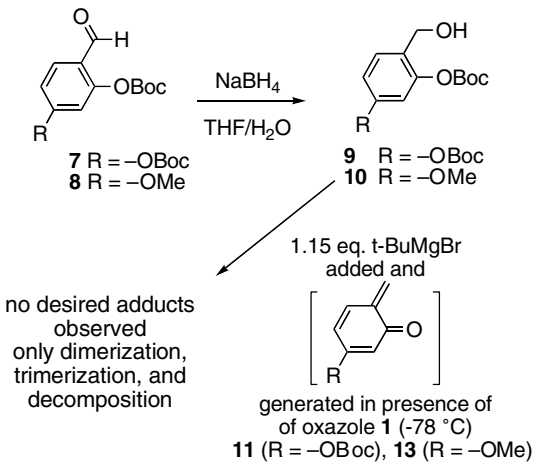


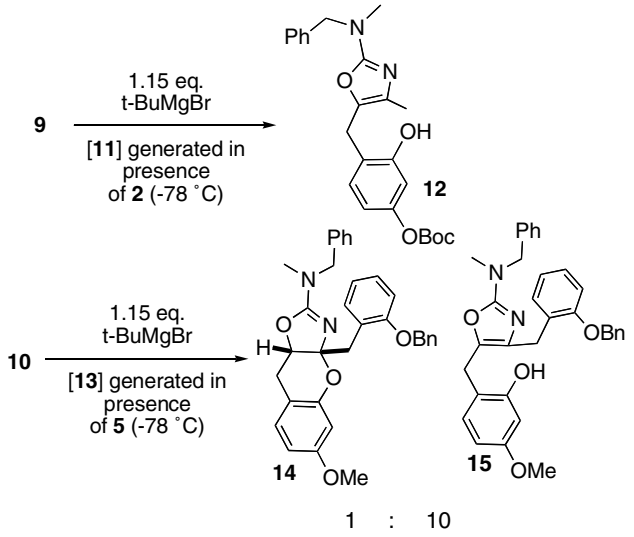
Figure 3. Oxazoles **1**–**6** examined in combination with *o*-quinone methides **11** and **13**.

Because of our experience with *o*-quinone methide reactivity, we first examined their capacity for reaction with commercially available 4-alkyl oxazole **1** (Fig. 3). Deprotonation of either of the *ortho*-OBoc hydroxymethyl aromatic compounds (**9** or **10**,[8] 0.1 M in Et_2O or THF) with *tert*-butyl magnesium bromide leads to –OBoc migration and subsequent β-elimination furnishing the corresponding *o*-quinone methide intermediate (cf. **11** and **13**, Scheme 1). Although these *o*-quinone methide species are exceedingly reactive, 4-methyl-oxazole (**1**) proved ineffective as a nucleophile. Instead, *o*-quinone methide intermediate undergoes self-destruction through known manifolds, such as Diels–Alder dimerization and trimerization.

Next, we examined 2-amino-4-methyl-oxazole (**2**) for which Dondoni has developed an efficient synthesis.[9] The initial findings, though unexpected, were encouraging—the 1,4-conjugate addition adduct **12**[10] forms as the sole product in a respectable 60% yield (Scheme 2). In our past experiences with these *o*-quinone methides, the conjugate addition adduct only arises with highly polarized 2π dienophiles such as enamines. We designed and synthesized several more elaborate oxazoles, such as **3**–**6**.[11] Generation of *o*-quinone methide **13** from **10** in the presence of oxazole **5** leads to two adducts in a



Scheme 1. Dissatisfactory outcome between *o*-quinone methides **11** and **13** with oxazole **1**.

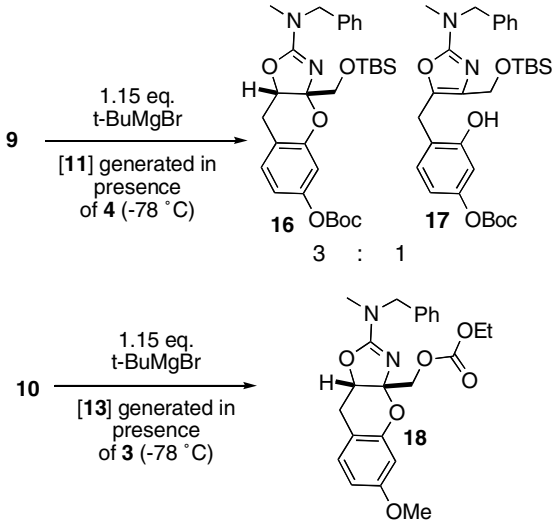


Scheme 2. Cycloadditions of oxazoles **2** and **5** with *o*-quinone methides **11** and **13**.

62% combined yield. In this instance, the 1,4-addition product **15**[12] predominates in the mixture, and the [4+2] cycloadduct **14** arises in small amounts (10:1).

Given the preceding result, we were surprised to find that the silylated 4-hydroxymethyl oxazole **4** undergoes reaction with *o*-quinone methide **11** generated under similar conditions to afford in 66% combined yield a 3:1 mixture favoring the [4+2] adduct **16**[13] over the 1,4-conjugate addition product **17**[14] (Scheme 3). In addition, the carbonate protected 4-hydroxymethyl oxazole **3**, undergoes cycloaddition with quinone methide **13** and affords benzopyran **18**[15] in 46% yield as the only identifiable product.

It seemed that a subtle allylic stereoelectronic inductive effect governed the outcome of the reaction (Fig. 4).



Scheme 3. Cycloadditions of oxazoles **3** and **4** with *o*-quinone methides **11** and **13**.

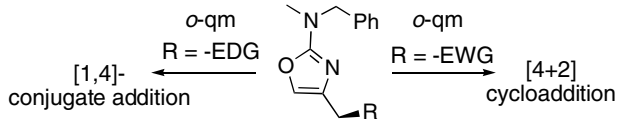
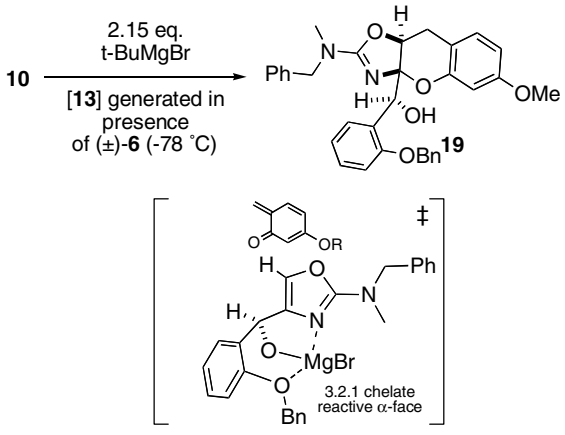


Figure 4. Kinetic reaction manifold (cycloaddition vs 1,4-addition) appears R-substituent dependant.

The 2-amino oxazoles displaying an electron rich substituent at the 4-position (R = H, Bn) underwent highly asynchronous reactions leading to 1,4-conjugate addition adducts, while the oxazoles displaying an electron-withdrawing substituent at the 4-position (R = –OTBS, $-OCO_2Et$) underwent a synchronous reaction affording the [4+2]-cycloadduct.

To test this supposition, we generated *o*-quinone methide **13** in the presence of the deprotonated oxazole (±)-**6**—an analog of 4-benzylated oxazole **5** that had led almost exclusively to 1,4-conjugate addition adduct **15** (Scheme 2). In the case of the deprotonated oxazole (±)-**6**, however, the reaction proceeds to the cycloadduct **19** (Scheme 4).[16] The fact that none of the corresponding 1,4-addition adduct is observed further substantiates our claim—less polarized 2-amino-oxazoles proceed through synchronous cycloadditions, while the more polar systems resemble enamines in their asynchronous reactivity. The stereointegrity of the reaction attests to the kinetic preference for a single *endo* transition state. Therefore, if a method was available for procuring the hydroxyl stereocenter in oxazole **6**, then the stereochemistry of the benzopyran would be accessible in an absolute sense.

Chromatography illuminates a thermodynamic equilibrium between the conjugate addition and cycloaddition adducts of the preceding schemes with mild acid (Fig. 5). For example, if the purified oxazole **15** is subjected to trace acid, a 3:1 mixture of the cycloadduct **14** and oxazole **15** forms. The purified oxazoles **12** and **18** also proceed to a mixture of [4+2] and 1,4-addition adducts; (approximately 1:1 in both of these cases) upon



Scheme 4. Diastereoselective cycloaddition.

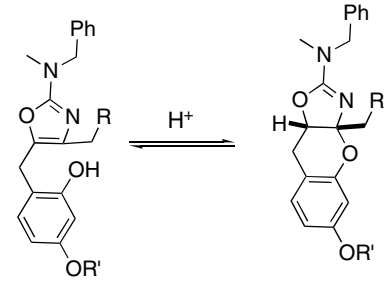
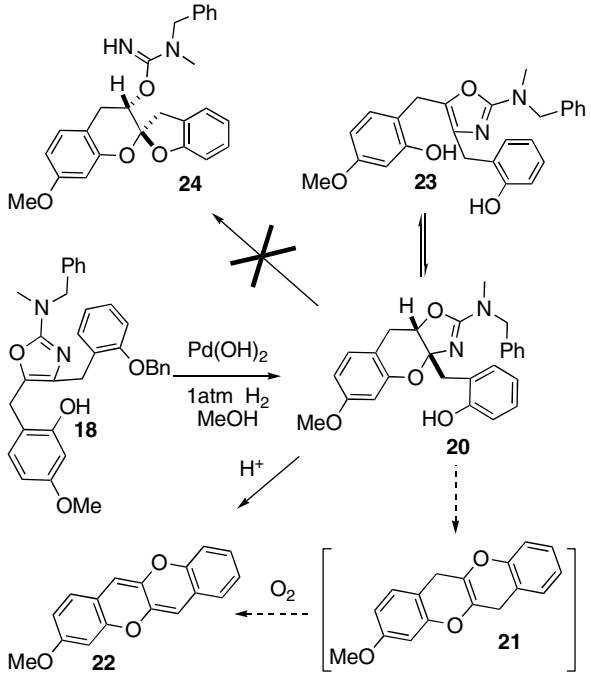


Figure 5. Thermodynamic equilibrium discovered.

addition of trace acid or by standing in $CDCl_3$ for prolonged periods.

With oxazole **18** in hand, and knowledge of the acid-mediated equilibrium, we were curious to see the outcome upon hydrogenolysis to phenol **20**.[17] In principle, the resulting phenolic benzopyran **20** might undergo spiroketalization to 5,6-aryloxyspiroketal **24**, a structural ensemble similar to that found in rubromycin and heliquinomycin. Our initial experiments proved disappointing. In all our attempts to induce spiroketalization, the undesired tetracyclic compound **22**[18] forms. We speculate that chromene **21** may precede compound **22**, and that it succumbs to rapid air oxidation. However, further experiments are required to substantiate this hypothesis (Scheme 5).

In conclusion, the unknown reactivity of some *o*-quinone methides and 2-amino-oxazoles has been revealed. Their combination leads to an interesting assortment of benzopyrans and oxazoles. Access to these heterocyclic compounds may prove to be of some therapeutic interest in the future.



Scheme 5. New chromene formed.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.168.

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8. Compound **10**: A transparent oil. Isolated yield 71%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (d, 8.5 Hz, 1H), 6.81 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.7$ Hz, 1H), 6.70 (d, 2.5 Hz, 1H), 4.55 (d, $J = 4.7$ Hz, 2H), 3.81 (s, 3H), 2.06 (br s, 1OH) 1.57 (s, 9H); HRMS (ESI) calcd for $C_{13}H_{18}O_5$ 254.115424, found 254.115703.
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10. Compound **12**: clear oil. Isolated yield 60%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.22 (m, 5H), 7.06 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.2$ Hz, 1H), 6.69–6.67 (m, 2H), 4.51 (s, 2H), 3.81 (s, 2H), 2.93 (2, 3H), 2.03 (s, 3H), 1.56 (s, 9H).
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12. Compound **15**: yellow solid. Isolated yield 55%. mp = 44–46 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.12 (m, 12H), 6.89–6.81 (m, 2H), 6.43 (br s, OH), 6.33–6.31 (m, 2H) 5.02 (s, 2H), 4.45 (s, 2H), 3.84 (s, 2H), 3.67 (s, 3H), 3.60 (s, 2H), 2.88 (s, 3H); HRMS (ESI) calcd for $C_{33}H_{32}N_2O_4$ 520.236208, found 520.235058.
13. Compound **16**: white solid. Isolated yield 51%. mp = 113–114 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.20 (m, 3H), 7.06 (d, $J = 8.0$ Hz, 1H), 6.87–6.82 (m, 4H), 5.25 (dd, $J_1 = 3.2$ Hz, $J_2 = 2.9$ Hz, 1H), 4.34 (br s, 2H), 4.13 (d, $J = 10.7$ Hz, 1H), 3.87 (d, $J = 10.5$ Hz, 1H), 3.03 (dd, $J_1 = 15.4$ Hz, $J_2 = 2.5$ Hz, 1H), 2.90 (dd, $J_1 = 15.6$ Hz, $J_2 = 3.2$ Hz, 1H), 2.71 (s, 3H), 1.56 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); MS (ESI) *m/z* 555 (100.0), 500 (11.7), 499 (32.5), 413 (9.70) HRMS (ESI) calcd for $C_{30}H_{42}N_2O_6Si$ 555.2890, found 555.2905 (M+H).
14. Compound **17**: yellow oil. Isolated yield 17%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (br s, OH), 7.32–7.20 (m, 3H), 7.19–7.14 (m, 3H), 6.69 (d, $J = 2.3$ Hz, 1H), 6.65 (dd, $J_1 = 8.2$ Hz, $J_2 = 2.5$ Hz, 1H), 4.78 (s, 2H), 4.48 (s, 2H), 3.94 (s, 2H), 2.89 (s, 3H), 1.56 (s, 9H), 0.99 (s, 9H), 0.22 (s, 6H); HRMS (ESI) 555 (100.0), 553 (46.1), 537 (22.6), 499 (19.1), 423 (20.8), calcd for $C_{30}H_{42}N_2O_6Si$ 577.2710, found 577.2698 (M+Na).
15. Compound **18**: isolated yield 46%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20–7.14 (m, 3H), 7.00 (d, 8.2 Hz, 1H), 6.75 (m, 2H), 6.66 (d, $J = 2.3$ Hz, 1H), 6.61 (dd, $J_1 = 8.1$ Hz, $J_2 = 2.2$ Hz, 1H), 5.19 (t, $J = 3.2$ Hz, 1H), 4.7 (d, $J = 11.2$ Hz, 1H), 4.40 (d, $J = 11.1$ Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 3.77 (s, 3H), 3.02 (dd, $J_1 = 15.5$ Hz, $J_2 = 2.5$ Hz, 1H), 2.92 (dd, $J_1 = 15.5$ Hz, $J_2 = 2.7$ Hz, 1H), 2.71 (s, 3H), 1.33 (t, $J = 7.2$ Hz, 3H); ^{13}C (100.6 MHz) δ 158.9, 155.1, 155.0, 136.9, 129.2, 128.7, 127.4, 127.2, 116.1, 109.6, 105.2, 102.6, 82.7, 71.2, 64.5, 55.5, 53.4, 29.5, 27.8, 14.5.
16. Compound **19**: viscous yellow oil. Isolated yield 31%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, 7.5 Hz, 1H), 7.45 (m, 2H), 7.35–7.16 (m, 7H), 7.02 (m, 1H), 6.90 (m, 2H), 6.72 (br s, 2H), 6.64 (d, $J = 2.3$, 1H), 6.56 (dd, $J_1 = 8.3$ Hz, $J_2 = 2.3$ Hz, 1H), 5.72 (s, 1H), 5.23 (s, 1H), 5.10 (s, 2H), 4.36 (d, $J = 15.6$ Hz, 2H), 3.76 (s, 1H), 3.30 (br s, OH), 2.80 (dd, $J_1 = 15.2$ Hz, $J_2 = 2.6$ Hz, 1H), 2.72 (br s, 3H), 2.33 (dd, $J_1 = 15.2$ Hz, $J_2 = 2.6$ Hz, 1H).
17. Compound **20**: yellow solid. Isolated yield 46%. mp = 65–67 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.4 (br s, NH), 7.27–7.11 (m, 7H), 7.02–6.90 (m, 2H), 6.88 (td, $J_1 = 7.2$, $J_2 = 1.2$ Hz, 1H), 6.77–6.61 (m, 2H), 5.10 (dd, $J_1 = 3.0$ Hz, $J_2 = 2.8$ Hz, 1H), 4.4 (br s, 2H), 3.79 (s, 3H), 3.75 (d, $J = 14.0$ Hz, 1H), 3.12 (d, $J = 14.0$ Hz, 1H), 3.04 (dd, $J_1 = 15.5$, $J_2 = 2.7$ Hz, 1H), 2.95 (dd, $J_1 = 15.0$, $J_2 = 2.5$ Hz), 2.77 (br s, 3H); MS (ESI) *m/z* 430 (23.6), 323 (23.2), 136 (43.3), 90 (100.0), 76 (10.6), HRMS (ESI) calcd for $C_{26}H_{26}N_2O_4$ 430.189258, found 430.189231.
18. Compound **22**: yellow oil. Isolated yield 31%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (dd, $J_1 = 4.3$ Hz, $J_2 = 0.7$ Hz, 1H), 7.58 (dd, $J_1 = 8.6$ Hz, $J_2 = 0.7$ Hz, 1H), 7.50 (d, 8.6 Hz, 1H), 7.35–7.35 (m, 3H), 7.09 (m, 3H) 3.90 (s, 3H).