Direct Synthesis of the Phenanthroviridone Skeleton Using a Highly Regioselective Nitroquinone Diels–Alder Reaction

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Abstract
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Keywords
Quinones, Electrical properties, Chemical structure, Oxygen, Mathematical methods

Disciplines
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Comments
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Direct Synthesis of the Phenanthroviridone Skeleton Using a Highly Regioselective Nitroquinone Diels–Alder Reaction

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ABSTRACT: A variety of nucleophiles react efficiently with in situ generated nitroquinones. The reaction with substituted resorcinols led to the direct synthesis of the phenanthroviridinone and lagumycin skeleton via a highly regioselective Diels–Alder reaction.

INTRODUCTION

Nitrogen-substituted quinones, both natural and synthetic, have shown useful biological activities. Among these compounds are the jadomycins 1 which exhibit activity against cancer cell lines and against bacteria and yeast. 1 Phomazarin 2 was isolated from Phoma terrestris Hansen (Pyrenochaeta terrestris Hansen). Its structure was determined by Boger through total synthesis.2 Catalin 3, also known as pirenoxine, is an anticytecting agent.3 These quinones are most commonly synthesized via halo- and aminoquinones. 4 An alternative would be to utilize nitrobenzoquinone, shown in Scheme 1. A literature search showed that nitroquinones have been infrequently used in organic synthesis. Nitrobenzoquinone and its analogues have been employed in innovative syntheses by Parker,7 Valderrama,8 and Tapia.9 We report herein that nitrobenzoquinone reacts readily with a wide variety of heterocycles and electron-rich aromatics.8

RESULTS AND DISCUSSION

The optimal conditions for the addition of aromatics to nitrobenzoquinone were determined using 1,3-dimethoxybenzene and 2-methylfuran. Among the oxidants evaluated for the in situ generation of nitrobenzoquinone, two equivalents of silver (I) oxide proved to be the most effective (Table 1). Other oxidants such as iron(III) chloride and manganese(IV) oxide did not provide promising yields. Dichloroethane emerged as the solvent of choice. The reaction was performed at ambient temperature overnight in the absence of light, and the product was isolated simply by loading the crude mixture onto a silica column and eluting with an organic solvent.

Nitrohydroquinone 4, readily prepared from commercially available 1,4-dimethoxybenzene,10 was oxidized in situ to nitrobenzoquinone which reacted successfully with a range of electron-rich heterocycles such as furans, thiophenes, and anilines. The results are shown in Scheme 2. All of the compounds shown in Scheme 2 are new compounds. The ready formation of the 2,4,6-trisubstituted aryl quinone 5b is notable and likely a consequence of the high reactivity of...
nitrobenzoquinone. Other heteroaromatics such as pyrroles afforded the corresponding adducts in moderate yields. It is worth mentioning that aniline derivatives (5j and 5l) and tetrahydroquinolines (5k) reacted readily, presumably due to the electron donating effect of the nitrogen atom.

Surprisingly, the reaction between nitrobenzoquinone with phosphorus ylides afforded benzofurans 5m, 5n, and 5o. The mechanism likely involves a conjugate addition followed by intramolecular cyclization and the expulsion of triphenylphosphine oxide. This chemistry provides an alternative route to nitro-substituted benzofuran structures (Scheme 3).

**Synthetic Applications.** With a good understanding of the reaction patterns of nitrobenzoquinone, a direct synthesis of the phenanthroviridone skeleton was attempted. The reaction of in situ generated nitrobenzoquinone with the tert-butyldimethylsilyl ether of 3,5-dimethoxybenzyl alcohol 6 afforded two products 7a and 7b in a 4:1 ratio which could not be separated (Scheme 4). A Diels–Alder reaction with the inseparable mixture of 7a and 7b favored the reaction at the double bond not bearing the nitro group, presumably because the bulky out-of-plane aryl group blocked the alternative site (Figures 1 and 2). Moreover, the Diels–Alder reaction was highly regioselective, generating structures 8a and 8b as the only isomers, as proved by the oxidative conversion of 8a to 11.

Mild acid-mediated deprotection of the TMS group and oxidative aromatization by PCC produced a separable mixture of naphthoquinones 9a and 9b (Scheme 5). The nitro group in 9a was readily reduced, and the resulting product was oxidized with MnO2 to form aminoquinone 10. Deprotection of the silyl ether using TBAF followed by intramolecular imine

| entry | product | oxidant (200%) | solvent | yield* |
|-------|---------|---------------|---------|--------|
| 1     | 5a      | FeCl₃         | CHCl₃   | N.P.   |
| 2     | 5a      | FeCl₃         | DMF     | <5%    |
| 3     | 5a      | MnO₂         | CHCl₃   | N.P.   |
| 4     | 5a      | MnO₂         | DMF     | <5%    |
| 5     | 5a      | Ag₂O        | CHCl₃   | 51%    |
| 6     | 5a      | Ag₂O        | DCE     | 70%    |
| 7     | 5f      | MnO₂         | CHCl₃   | N.P.   |
| 8     | 5f      | MnO₂         | Acetone | N.P.   |
| 9     | 5f      | MnO₂         | Et₂O    | N.P.   |
| 10    | 5f      | MnO₂         | EtOAc   | N.P.   |
| 11    | 5f      | MnO₂         | DMF     | N.P.   |
| 12    | 5f      | Ag₂O        | CHCl₃   | 95%    |
| 13    | 5f      | Ag₂O        | DCE     | 97%    |

*Isolated yield. *No product detected.

**Scheme 2. Reaction Scope**

**Scheme 3. Synthesis of Benzofuran**

**Scheme 4. Regioselective Diels–Alder Reaction**

**Scheme 5. Synthesis of Naphthoquinone**
formation with MnO₂ afforded the phenathroviridone skeleton 11, as shown in Scheme 5. The structure of 11 was confirmed by single crystal diffraction experiment.

Using the common intermediate 10, the lagumycin B skeleton 12 was synthesized by an acid-catalyzed intramolecular cyclization process. This is shown in Scheme 6.

**Scheme 5. Synthesis of the Phenathroviridone Skeleton**

**Scheme 6. Synthesis of the Lagumycin B Skeleton**

Two separate optimizations were performed on 5b. The first optimization imposed no symmetric or rotational constraints, and its lowest energy geometry can be found in Figure 1. When allowed to freely rotate, the nitro group distorts to 63.7° out of the plane of the quinone, most likely due to the steric interactions between the nitro and carbonyl oxygens. The phenyl group also distorts from the expected 90−58.8° out of the plane of the quinone. Another feature of the low energy geometry is the positioning of the quinone oxygens, each distorted out of the plane of the ring, but in opposite directions. The oxygen at C1 presents a dihedral of 3.8°, while the oxygen at C4 sits 8.4° out of the plane of the ring. A Hessian calculation confirmed that the structure is a minimum on the potential energy surface (PES) with zero imaginary frequencies.

A second optimization was performed on the same substituted quinone, imposing symmetric constraints using the C₅ plane of symmetry, referred to as 5b_sym. Optimizations were performed with both nitro oxygens in the plane of the quinone and the phenyl group perpendicular. The optimized geometry of 5b_sym can be found in the Supporting Information. The symmetry optimized structure was found to be 13.7 kcal/mol higher in energy than the lowest energy (unrestricted) geometry. Torsional analysis shows that the relaxation of the nitro group out of the plane of the quinone accounts for ~6 kcal/mol. A Hessian calculation on 5b_sym found 3 imaginary frequencies, indicating that the conformer is not a stationary point on the PES.

The optimized molecular orbitals for 5b were used to calculate 2D molecular electrostatic potentials (MEPs). The MEP is defined as the potential felt by a positive charge given the molecular charge density at a given point within a grid. These calculations were achieved by first rotating the structure, so the ring containing the C₅−C₆ bond was situated in the xy-plane. A diagram depicting the locations of the MEP planes can be found in Figure 2. Then, 2D MEPs were calculated 2 Å above and 2 Å below the plane of the ring and can be found in Figure 3a,b, respectively. As seen in Figure 3, at 2 Å above the plane, the negative charge density is higher in the region around C₆, whereas at 2 Å below the plane, the charge density is much more evenly distributed.

Population analysis of the dienophile carbons shows negligible differences between the C₅ and C₆ of the quinone, but both Mulliken and Löwdin populations show significant differences between the C1 and C4 of the diene. The populations and partial charges the both that indicate the terminal carbon, C4, is more electronegative than C1. A rudimentary frontier molecular orbital (FMO) analysis finds C4 of the diene aligned with C5 of the quinone ring and C1 of the diene aligned with C6 of the quinone; these data can be found in the Supporting Information. The electronegativity difference within the diene, the skewed MEP 2 Å above the
Figure 3. 2D molecular electrostatic potentials for nitroquinone (5b): (a) MEP calculated 2 Å above the plane of the C5–C6 double bond; (b) MEP calculated 2 Å below the plane of the C5–C6 double bond. The red contours are regions of positive potential (negative charge density), and the blue contours are regions of negative potential (positive charge density). The inset in the upper righthand corner of shows the orientation of the system with the C5 and C6 carbons labeled.

dienophile, and the FMO results are all consistent with the regioselectivity found in experiment.

CONCLUSIONS

To conclude, the use of nitrobenzoquinone enabled a direct synthesis of lagumycin B and phenathroviridone skeletons. The synthetic route is flexible and scalable and will permit the synthesis of other potential analogues.

EXPERIMENTAL SECTION

General Procedure for Electron-Rich Aromatic Addition to Nitroquinone 4. 2′,4′-Dimethoxy-6-nitro-[1,1′-biphenyl]-2,5-dione (5a). To a 5 mL round bottom flask, 2-nitrobenzene-1,4-diol 4 (47 mg, 0.3 mmol, 1.0 equiv.), silver (I) oxide (139 mg, 0.6 mmol, 2.0 equiv.) in dry DCE, and 1,3-dimethoxybenzene (62 mg, 0.45 mmol, 1.5 equiv.) was added. The reaction mixture was allowed to stir at ambient temperature without light (the flask was fully covered with aluminum foil) overnight. After the reaction is completed (tracked by TLC), the crude mixture was loaded directly on a silica column. Using ethyl acetate/hexane (1:3) as the eluent the desired product 5a was isolated as a highly colored solid (61 mg, 70% yield). 1H NMR (400 MHz, chloroform-d): δ 7.06 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 10.2 Hz, 1H), 6.92 (d, J = 10.3 Hz, 1H), 6.54 (d, J = 8.5 Hz, 1H), 6.49 (s, 1H), 3.84 (s, 3H), 3.73 (s, 3H). 13C NMR (101 MHz, chloroform-d): δ 184.64, 177.43, 163.98, 158.84, 137.54, 135.20, 134.82, 131.31, 109.12, 105.53, 99.27, 55.83, 55.76. HRMS (ESI-QTOF): calcd for C16H12NO6 [M + H]+, 290.0660; found, 290.0656.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00201.

General materials, experimental procedures, and 13C NMR and 1H NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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