Nitrone Cycloaddition to Quinones: A Novel Strategy for the Synthesis of Benzisoxazolidenes

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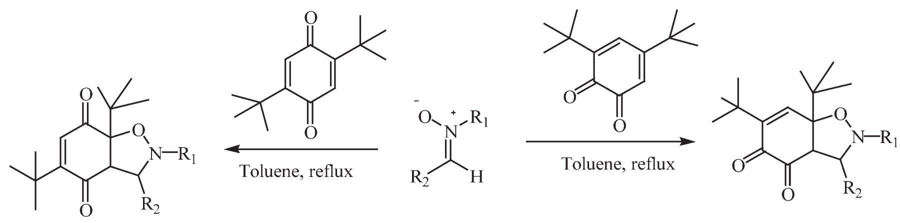

1,3-Dipolar cycloaddition reaction involving nitrones and benzoquinones resulting in the formation of benzisoxazolidene is described. As the nitrone is selectively added to carbon–carbon double bond of the benzoquinone, the quinone-nitrone reaction is considered as a special case among quinone-1,3-dipole cycloaddition reactions. Molecular orbital calculation was performed to examine the electronic effects involved in the regioselectivity of the reaction.

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INTRODUCTION

The 1,3-dipolar cycloaddition reactions of nitrones with alkenes leading to the formation of isoxazolidenes is a fundamental reaction in organic chemistry [1]. In 1982 Deshong *et al.* reported the first 1,3-dipolar cycloaddition reaction of electron rich alkenes, such as vinyl acetate and vinyl ethers, with nitrones [2]. This work was extended to other functionalized alkenes synthesizing a variety of isoxazolidenes that served as key synthetic intermediates in the synthesis of γ-amino acids, β-lactams, amino sugars, and alkaloids [3]. A variety of isoxazolidines have been prepared using 1,3-dipolar nitrone cycloaddition to functionalized alkenes. In most cases, the nitrone cycloadditions to alkenes proceeded with high regioselectivity to yield isoxazolidenes with three new contiguous stereogenic centers. The stereoselectivity seems to be influenced by both electronic and steric factors. Recently, several asymmetric syntheses of isoxazolidines giving special emphasis on their effective use as chiral auxilaries in the synthesis of biologically active molecules have been reported [3e,4]. Shortly, decades ago itself nitrone cycloaddition chemistry was enriched with versatility of substrates, catalysts, and solvents used in the reaction. Still, organic chemistry demands for new reactions for the synthesis of appropriately substituted isoxazolidenes.

The quinones and their derivatives have attracted the continuous attention in view of their antitumor activities [5]. The biological processes involved with the antitumor activities of quinones are DNA intercalation, bioreductive alkylation of biomolecules, and generation of oxyradicals through redox cycling. The chemistry of *o*-quinones has invoked considerable interest, and the cycloaddition reactions of these versatile compounds have been the subject of a number of investigations [1,6]. A wide variety of dipolar species, including diazomethane [3], nitrile oxides [7–10], and mesoionic compounds [11–15], have been used in these reactions. Most of the dipolar cycloadditions to quinones, however, involved addition across carbon–oxygen double bonds. In contrast, nitrone cycloaddition occur across carbon–carbon double bond of the *o*-quinones to afford substituted benzisoxazolidenes, and it is the subject matter of present investigations.

RESULTS AND DISCUSSION

Present studies were initiated by the reaction of 3,5-di-*tert*-butyl-1,2-benzoquinone with 1,2-diphenylnitrone. Preliminary investigations showed that the nitrone cycloaddition to 1,2-benzoquinone occured at carbon–carbon

Scheme 1

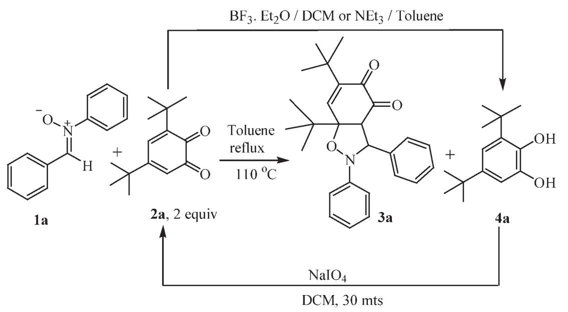

Table 1

The reaction of 3,5-di-*tert*-butyl-1,2-benzoquinone **2** with 1,2-diphenylnitrone **1**.

Entry	Reaction conditions	Yield (%) 3a	4a
1	DCM, rt, 48 h	0	0
2	DCM, $BF_3.Et_2O$, rt, 1 h	0	12
3	DCM, Net3, rt, 1 h	0	48
4	Acetonitrile, 70 °C, 18 h	0	7
5	Benzene, 70 °C, 18 h	0	0
6	Toluene, 110 °C, 18 h, Ar	15	61
7	Toluene (excess), 110 °C, 18 h	32	19
[a]8	Toluene (excess), 110 °C, 18 h	57	23
9	Toluene, 110 °C, 48 h	Complex reaction mixture	
10	Xylene, 140 °C, 2 h	Complex reaction mixture	

[a] Quinone nitrone = 2:1.

double bond to afford benisoxazolidene **3a**, which is a rare case among the 1,3-dipole-quinone cycloaddition reactions. Then, suitable reaction condition for the proposed cycloaddition was identified by treating 3,5-di-*tert*-butyl-1,2-benzoquinone with 1,2-diphenylnitrone under different conditions (Scheme 1, Table 1). Under most of the reaction conditions, the quinone was easily reduced to corresponding catechol. To our surprise, even under perfectly dry conditions using aprotic solvents like benzene and toluene, the catechol formation dominated over the product formation. Close investigations on the reaction made us to conclude that any proton source including the cycloaddition product facilitate the catechol formation, and so, the yield of the reaction is decreased. At higher temperature, quinone underwent cycloaddition with another molecule of quinone, and the nitrones were fragmented to corresponding amines and aldehydes. However, the expected cycloaddition product was obtained in moderate yield, when a dilute solution of 3,5-di-*tert*-butyl-1,2-benzoquinone and 1,2-diphenyl nitrone in toluene was refluxed at 110°C for 18 h. The yield was further optimized by screening the number of equivalents of the substrates. Thus, when 3,5-di-*tert*-butyl-1,2-benzoquinone (2 mmol) was treated with 1,2-diphenyl nitrone (1 mmol) in toluene (20 mL) for 18 h at 110°C, bezisoxazolidene **3a** was obtained in 57% yield. The product **3a** was characterized on the basis of common spectroscopic analysis and ultimately by single crystal X-ray analysis (Fig. 1).

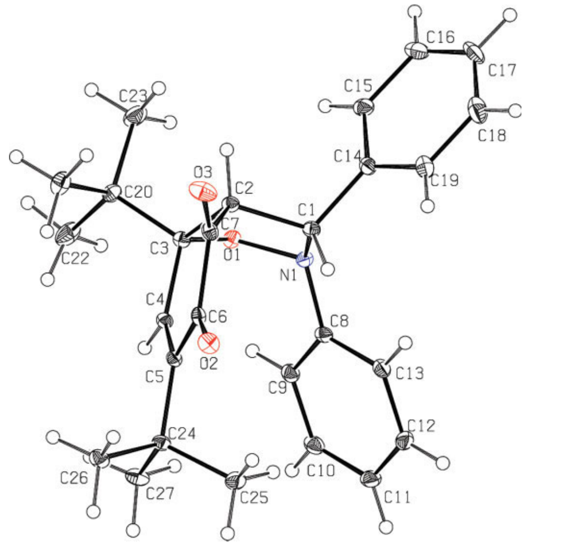

Figure 1. Energy level diagram for HOMOnitrone-LUMOquinone interaction. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

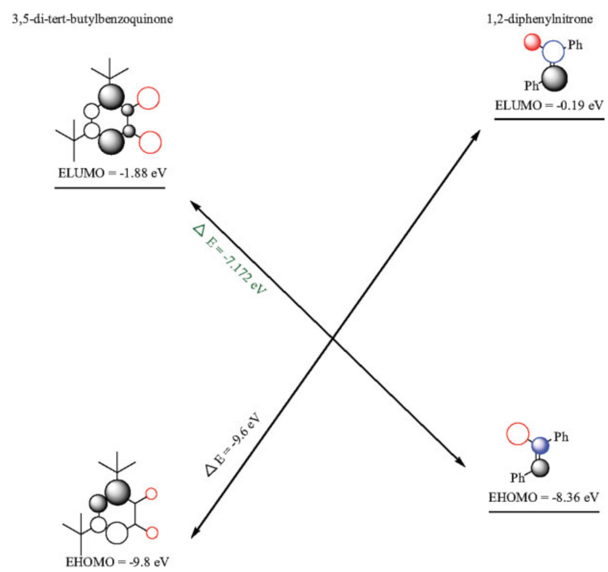

Figure 2. ORTEP diagram (40% probability factor for the thermal ellipsoids) of compound 6,7a-di(*tert*-butyl)-2,3-diphenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione **3a.** [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Scheme 2

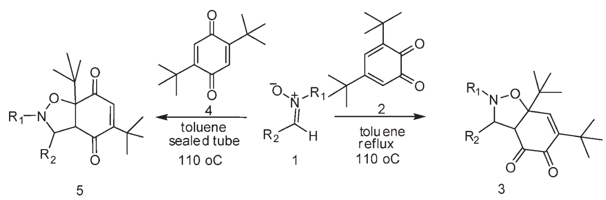

Table 2

Synthesis of tetrahydrobenzisoxazolediones **3** and **5**.

Entry	3, 5	R[1]	R[2]	Yield (%)
1	**3a**	C_6H_5	C_6H_5	57
2	**3b**	4-$CH_3C_6H_5$	C_6H_5	72
3	**3c**	4-ClC_6H_5	C_6H_5	98
4	**3d**	4-$CH_3C_6H_5$	4-$CH_3C_6H_5$	33
5	**3e**	2-Naphthyl	C_6H_5	45
6	**3f**	9-Anthracenyl	C_6H_5	0
7	**5a**	C_6H_5	C_6H_5	22
8	**5b**	4-$CH_3OC_6H_5$	C_6H_5	9

To explain the mechanism of cycloaddition of nitrone to quinone, we have carried out some MNDO and AM1 calculations on 3,5-di-*tert*-butyl-1,2-benzoquinone and 1,2-diphenyl nitrone using MOPAC (version 5.01) program. The HOMO and LUMO energies were derived from this program. Most of the 1,3-dipolar cycloaddition reactions of *o*-quinones undergo inverse electron demand Diels-Alder reaction (Type II mechanism) [4–13] at carbon–oxygen double bond. The molecular orbital coefficients calculated from the eigen vectors for the orbital interactions of 3,5-di-tert-butyl-1,2-benzoquinone and 1,2-diphenyl nitrone (Fig. 2) favoured the addition of nitrone oxygen to a highly substituted carbon atom to form 6,7a-di(*tert*-butyl)-2,3-diphenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione **3a**, which follows a normal diels-Alder mode of cyclization involving $HOMO_{nitrone}$-$LUMO_{quinone}$ interaction (Type I mechanism).

On extending the strategy to other benzoquinones and diaryl nitrones, tetrahydrobenzisoxazolediones **3a-f** and **5a-b** were synthesized (Scheme 2, Table 2). However, the presence of bulky substituents like anthraceneyl groups on nitrone and diphenylmethane group on quinone adversely affected the product formation.

CONCLUSION

The reaction of nitrones with benzoquinones resulted in the formation of benzisoxazolidenes. As the nitrone is selectively added to carbon–carbon double bond of the benzoquinone, the quinone–nitrone reaction is considered as a special case among quinone-1,3-dipole cycloaddition reactions.

EXPERIMENTAL

General remarks. Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C), respectively on a Brüker Avance DPX-300 MHz NMR spectrometer. Chemical shifts are reported (δ) relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer. IR spectra were recorded on Nicolet Impact 400D FTIR spectrophotometer. Commercial grade solvents were distilled before use.

General procedure for the synthesis of 6,7a-di(*tert*-butyl)-2,3-diaryl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-diones (3a-e) and 5,7a-Di(*tert*-butyl)-2,3-diphenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,7-dione (5a-b). A solution of 3,5-di-*tert*-butyl-1,2-benzoquinone (220 mg, 1 mmol) and 1,2-diaryl nitrone (0.5 mmol) in toluene (10 mL) was refluxed at 110°C for 18 h. The solvent was removed under vacuum, and the crude reaction mixture was purified by silica gel (100-200 mesh) column chromatography using hexane-ethyl acetate (98:2) as the eluent to get the title compounds in good to moderate yields.

6,7a-Di(*tert*-butyl)-2,3-diphenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione (3a). This compound was obtained as yellow crystalline solid; mp: 144–146°C; yield: 119 mg (57%); ^{1}H NMR: δ = 0.82 (s, 9H, CH_3), 1.05 (s, 9H, CH_3), 3.88 (d, 1H, *J* = 9 Hz, CH), 4.77 (d, 1H, *J* = 9 Hz, CH), 6.78–6.85 (m, 4H, ArH), 7.12–7.19 (m, 3H, ArH), 7.23–7.31 (m, 4H, ArH) ppm; ^{13}C NMR: δ = 25.9, 28.1, 35.0, 37.3, 66.5, 71.6, 93.7, 112.6, 121.2, 126.1, 128.3, 128.9, 129.2, 140.0, 147.5, 150.2, 152.3, 181.5, 191.0 ppm; hrms (EI): m/z calcd for $C_{27}H_{31}NO_3$: 417.2304; found: 417.1793; ir (KBr): 3030, 2914, 1663, 1643, 1566 cm^{-1}.

6,7a-Di(*tert*-butyl)-3-(4-methylphenyl)-2-phenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione (3b). This compound was obtained as yellow crystalline solid, mp: 132–134°C; yield: 155 mg (72%); ^{1}H NMR: δ = 0.89 (s, 9H, CH_3), 1.11 (s, 9H, CH_3), 2.34 (s, 3H, CH_3), 3.93 (d, 1H, *J* = 7.8 Hz, CH), 4.80 (d, 1H, *J* = 7.8 Hz, CH), 6.85 (d, 2H, *J* = 8 Hz, ArH), 6.89 (s, 1H, vinylic), 7.15-7.33 (m, 7H, ArH) ppm; ^{13}C NMR: δ = 21.2, 25.8, 28.2, 35.0, 37.3, 67.1, 93.7, 112.8, 125.8, 126.1, 128.1, 129.6, 129.8, 130.8, 136.9, 138.0, 150.1, 152.4, 181.5, 190.9 ppm; hrms (EI): m/z calcd for $C_{28}H_{33}NO_3$: 431.2460; found: 431.2700; ir (KBr): 3029, 2916, 1659, 1645, 1563 cm^{-1}.

3-(4-Chlorophenyl)-6,7a-di(*tert*-butyl)-2-phenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione (3c). This compound was obtained as yellow crystalline solid, mp: 126–128°C; yield: 221 mg (98%); ^{1}H NMR: δ = 0.88 (s, 9H, CH_3), 1.11 (s, 9H, CH_3), 3.90 (d, 1H, *J* = 9 Hz, CH), 4.82 (d, 1H, *J* = 9 Hz, CH), 6.81-6.93 (m, 4H, ArH), 7.19–7.26 (m, 2H, ArH), 7.30–7.36 (m, 4H, ArH) ppm; ^{13}C NMR: δ = 25.9, 28.2, 35.1, 37.3, 66.2, 93.7, 112.6, 121.4, 127.4, 128.3, 129.0, 129.4, 129.8, 134.3, 138.5, 147.3, 150.3, 152.0, 181.2, 190.7 ppm;

hrms (EI): m/z calcd for $C_{27}H_{30}ClNO_3$: 451.1914; found: 451.0599; ir (KBr): 3026, 2915, 1659, 1643, 1560 cm^{-1}.

6,7a-Di(*tert*-butyl)-2,3-di(4-methylphenyl)-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione (3d). This compound was obtained as yellow crystalline solid, mp: 102–104°C; yield: 73 mg (33%); ^{1}H NMR: δ = 0.91 (s, 9H, CH_3), 0.96 (s, 9H, CH_3), 2.26 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.92 (d, 1H, J = 9 Hz, CH), 4.77 (d, 1H, J = 9 Hz, CH), 6.75 (d, 2H, J = 9Hz, ArH), 6.86 (s, 1H, vinylic), 7.00 (d, 2H, J = 9Hz, ArH), 7.15 (d, 2H, J = 9Hz, ArH), 7.24 (d, 2H, J = 9Hz, ArH) ppm; ^{13}C NMR: δ = 21.2, 25.9, 28.2, 30.1, 35.0, 37.4, 71.6, 93.3, 113.0, 119.1, 122.3, 126.1, 126.6, 129.3, 129.9, 130.6, 137.0, 137.9, 147.8, 149.8, 181.5, 191.0 ppm; hrms (EI): m/z calcd for $C_{29}H_{35}NO_3$: 445.5931; found: 445.5021; IR (KBr): 3029, 2914, 1659, 1642, 1561 cm^{-1}.

6,7a-Di(*tert*-butyl)-3-(2-naphthyl)-2-phenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,5-dione (3e). This compound was obtained as yellow crystalline solid, mp: 114–116°C; yield: 105 mg (45%); ^{1}H NMR: δ = 0.91 (s, 9H, CH_3), 1.14 (s, 9H, CH_3), 4.03 (d, 1H, J = 9 Hz, CH), 5.01 (d, 1H, J = 9 Hz, CH), 6.87 (s, 1H, vinylic), 6.90 (d, 2H, J = 9Hz, ArH), 7.21 (t, 3H, J = 9Hz, ArH), 7.46–7.52 (m, 3H, ArH), 7.79–7.90 (m, 4H, ArH) ppm; ^{13}C NMR: δ = 25.4, 28.3, 35.1, 37.4, 67.0, 93.8, 112.4, 123.1, 124.3, 125.1, 125.9, 127.0, 127.2, 127.8, 128.1, 129.2, 133.4, 137.2, 150.3, 152.3, 181.5, 190.9 ppm; hrms (EI): m/z calcd for $C_{31}H_{33}NO_3$: 467.5987; found: 467.6065; IR (KBr): 3030, 2914, 1660, 1643, 1562 cm^{-1}.

5,7a-Di(*tert*-butyl)-2,3-diphenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,7-dione (5g). This compound was obtained as yellow crystalline solid, mp: 108–110°C; yield: 46 mg (22%); ^{1}H NMR: δ = 1.09 (s, 9H, CH_3), 1.27 (s, 9H, CH_3), 3.89 (d, 1H, J = 9 Hz, CH), 4.52 (d, 1H, J = 9 Hz, CH), 6.60 (s, 1H, vinylic), 6.88 (d, 2H, J = 9Hz, ArH), 7.12 (t, 3H, J = 9Hz, ArH), 7.25–7.38 (m, 5H, ArH) ppm; ^{13}C NMR: δ = 26.0, 30.0, 35.5, 36.5, 68.4, 73.8, 92.5, 115.3, 122.0, 127.0, 128.5, 128.5, 129.1, 136.1, 138.9, 149.9, 158.8, 194.7, 199.0 ppm; hrms (FAB): m/z calcd. for $C_{27}H_{31}NO_3$: 417.2304; found: 417.1175; IR (KBr): 3026, 2966, 1651, 1483, 1474, 1438, 796, 686 cm^{-1}.

5,7a-Di(*tert*-butyl)-3-(4-methoxyphenyl)-2-phenyl-2,3,3a,7a-tetrahydro-1,2-benzisoxazole-4,7-dione (5b). This compound was obtained as yellow crystalline solid, mp: 144–146°C; yield: 20 mg (9%); ^{1}H NMR: δ = 1.09 (s, 9H, CH_3), 1.26 (s, 9H, CH_3), 3.86 (d, 1H, J = 9 Hz, CH), 3.89 (s, 3H, OCH_3), 4.52 (d, 1H, J = 9 Hz, CH), 6.59 (s, 1H, vinylic), 6.85–6.90 (m, 3H, ArH), 6.99 (d, 2H, J = 9Hz, ArH), 7.09–7.20 (m, 5H, ArH) ppm; ^{13}C NMR: δ = 26.3, 33.0, 35.8, 37.5, 55.7, 68.2, 73.6, 92.7, 115.8, 121.0, 127.0, 128.5, 128.5, 129.4, 133.1, 133.9, 149.9, 158.8, 159.3, 194.7, 199.0 ppm; hrms (FAB): m/z calcd for $C_{28}H_{33}NO_4$: 447.2410; found: 447.2292; IR (KBr): 3029, 1844, 1444, 687 cm^{-1}.

3a: X-ray crystallographic data. Single crystals were grown from $CDCl_3$. Crystal system: triclinic; space group: P-1; T = 100 (2) K; a = 9.8727 (8) A°, b = 10.6520 (8) A°, c = 22.0592 (17) A°, α = 94.8130 (10)°, β = 92.3670 (10)°, γ = 90.1150 (10)°, z = 4, D_{calcd} = 1.201 mg/m^3; crystal size 0.66 × 0.45 × 0.12 mm; θ range for data collection 1.85° to 28.27°. Limiting indices −13h12, −14k13, −29l29; reflections collected 20146, independent reflections: 10519. Refinement method: full-matrix least squares on F^2; goodness of fit on F^2: 1.053; final R indices [I > 2σ (I)] R_1 = 0.0623, wR_2 = 0.1329; largest difference peak and hole o.422 and −0.224 eA$^{\circ -3}$. Selected bond lengths (A°) and angles (°): O(1)-C(3): 1.454(2), C(1)-C(2): 1.557(2), O(1)-N(1): 1.4296(18), N(1)-C(1): 1.478(2), C(3)-C(7): 1.506(2), C(3)-C(20): 1.5496(2), C(5)-C(24): 1.532(2), C(1)-C(14): 1.514(2), N(1)-C(8): 1.417(2), O(1)-C(3)-C(4): 106.51(13), O(1)-C(3)-C(2): 102.19(13), C(2)-C(7)-C(6): 116.44(14), C(1)-C(2)-C(7): 111.06(14), N(1)-C(1)-C(2): 104.95(13), O(1)-N(1)-C(1): 107.33(12), C(4)-C(5)-C(24): 123.40(16), C(4)-C(3)-C(20): 113.92(14), O(1)-C(3)-C(20): 106.48(13).

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