The Cycloaddition of *N*,α-Diarylnitrones and Substituted *p*-Benzoquinones

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N,α-Diarylnitrones reacted with 2,5- or 2,6-dialkyl-*p*-benzoquinones at their C=C bond regioselectively to give fused isoxazolidine cycloadducts. These cycloadducts were proved to undergo retrocycloaddition. *p*-Benzoquinones having electron-withdrawing substituents did not give any cycloadduct.

p-Benzoquinone derivatives play an important role in bioorganic redox reactions and the modification reactions of *p*-benzoquinones were paid much attention in the synthetic chemistry. 1,3-Dipolar cycloaddition reaction is known as a versatile synthetic reaction because of its regioselectivity and mild reaction conditions. 1,3-Dipolar cycloaddition reaction of *p*-benzoquinones was reported with many 1,3-dipoles; nitrile ylide,[1] phenyl azide,[2] diazoalkane[3] etc., but site selectivity or regioselectivity of the reactions is still uncertain. As dipolarophile, *p*-Benzoquinones have two kinds of potential reactive sites, i.e. C=C and C=O bonds, and were considered to be good probe compounds for such investigation. In the previous papers,[4] cycloaddition reactions of substituted *p*-benzoquinones with aromatic nitrile *N*-oxides were reported and discussed.

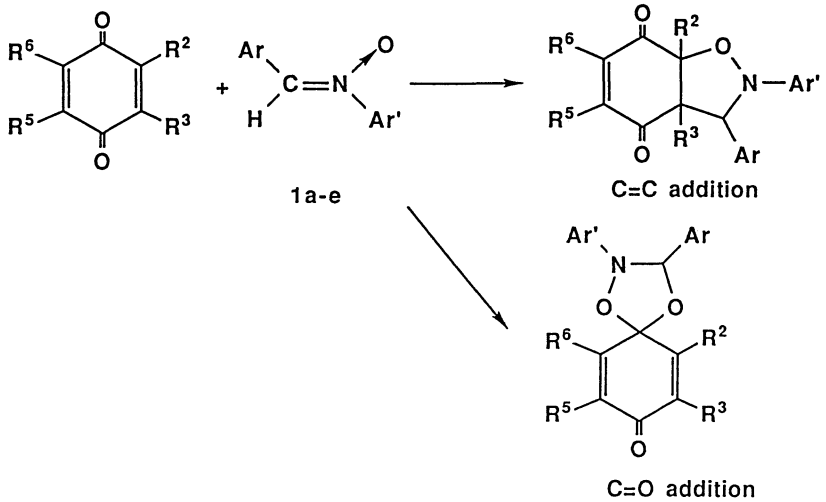
Nitrones compose a class of typical 1,3-dipoles and their cycloaddition reactions have been widely investigated. However, very few reports on the reactions with *p*-benzoquinones have been reported. Mourad and Nour-el-Din[5] described the formation of charge transfer complex between substituted *N*,α-diarylnitrones and *p*-benzoquinones having electron-withdrawing substituents. Schultz et al. reported successful intramolecular nitrone–quinone cycloaddition, attempted intermolecular cycloaddition being unsuccessful.[6]

In this paper, we report the reactions of substituted *p*-benzoquinones with *N*,α-diarylnitrones, some of which gave cycloaddition products. This is the first example of the successful intermolecular nitrone–quinone cycloaddition.

Results and Discussion

As nitrones, *N*,α-diphenylnitrone (**1a**) and *N*,α-bis(substituted phenyl)nitrones (**1b**—**e**) were employed. The nitrones were prepared from the corresponding arenecarbaldehydes and *N*-arylhydroxylamines by a known method.

Nitrones were allowed to react with quinones in refluxing benzene, unless otherwise noted. In the reaction of **1a** with 2,5-dimethyl-*p*-benzoquinone (25DMQ), practically no color change was observed at the initial stage of the reaction, but with the progress of the reaction the color changed gradually from yellow to light orange. The progress of the reaction was followed by TLC or HPLC analyses during the reaction period and it was confirmed that the reaction gave one product, except for the decomposition of **1a** (less than 5%), along with the decrease of **1a** and 25DMQ. After two days, the product was isolated from the reaction mixture by chromatographic technique followed by recrystallization from hexane, and the product was



Scheme 1. Possible reaction course of the nitrone–quinone cycloaddition.

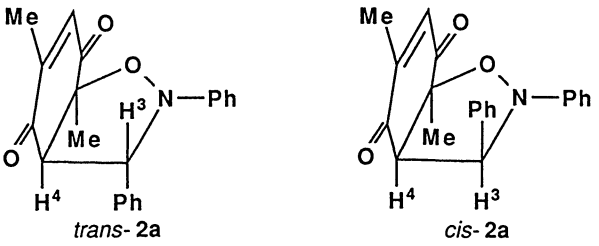
obtained as light orange powder.

The structure of the product was determined by IR, ^{1}H and ^{13}C NMR, mass spectra and elemental analyses. Elemental analyses and mass spectra showed that the product was 1 : 1 adduct of the nitrone and the quinone.

To determine the structure of this adduct, the first problem is the site selectivity of this addition; the addition to the C=C double bond to give a fused isoxazolidine derivative, or to C=O double bond to give spirodioxazolidine derivative (Scheme 1). ^{13}C NMR spectrum has two signals around 195 ppm which are assignable to carbonyl carbons. The IR spectrum showed a strong absorption at 1680 cm^{-1}. These facts suggest that two carbonyls arising from 25DMQ remain in the product, suggesting that the addition reaction proceeded at the C=C double bond.

^{1}H NMR spectrum showed two doublets at δ=3.68 and 5.00 having coupling constants J=7 Hz and integrating each one proton. This is well-consistent with the structure **2a**, 3,6-dimethyl-8,9-diphenyl-7-oxa-8-azabicyclo[4.3.0]-3-nonen-2,5-dione, and not with the regio-isomer **2a'** (Scheme 2).

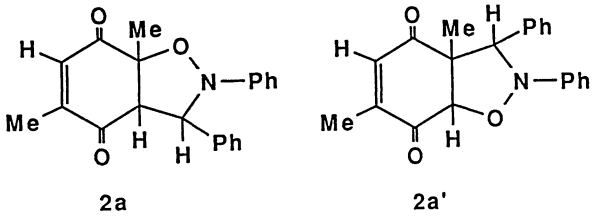
Two stereoisomers are possible for the structure **2a** (Scheme 3). The coupling constant of two protons at 3- and 4-position in isoxazolidine ring was 7 Hz, suggesting the protons being in *cis*-position. The coupling constants reported for *N,α*-diarylnitrones–*N*-phenylmaleimide cycloadducts[7] were 8 Hz when the two protons were in *cis*-position and 1 Hz in *trans*. However,



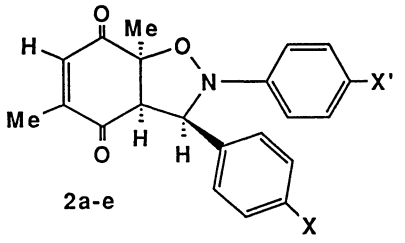
Scheme 3. Possible stereoisomer of the cycloadduct **2a**.

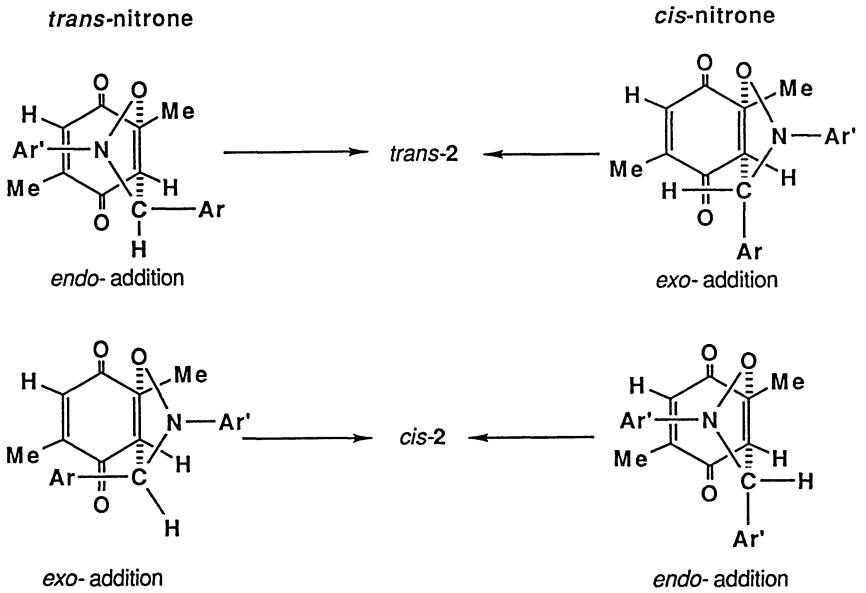
Table 1. The Reactions of 25DMQ with Various Nitrones (**1a**—**e**)

Nitrones	X	X'	Products	Yields/%
1a	H	H	**2a**	20
1b	Cl	H	**2b**	11
1c	NO_2	H	**2c**	19
1d	Me	H	**2d**	4
1e	H	Cl	**2e**	9



Scheme 2. Regioselectivity of the cycloaddition reaction of **1a** with 25DMQ.



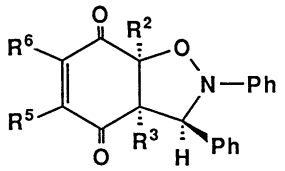


Scheme 4. Relationship of transition states of cycloaddition and the product configurations.

Table 2. Reactions of *N*,α-Diphenylnitrone (**1a**) and Substituted *p*-Benzoquinones

Nitrones	Quinones				Method[a]	Products	Yields/%
	R^1	R^2	R^3	R^4			
1a	Me	H	Me	H	A	**2a**	20
1a	Me	Me	H	H	A	**2f**	16
1a	*t*-Bu	H	*t*-Bu	H	A	**2g**	10
1a	*t*-Bu	*t*-Bu	H	H	A,B	—	Trace
1a	H	H	H	H	A	—	0
1a	Cl	Cl	Cl	Cl	B	—	0
1a	Cl	Cl	CN	CN	B	—	0

a) Method A; in refluxing benzene. B; in refluxing 1,2-dichroloethane. Yield shows quinone conversion by HPLC analysis. (For details, see experimental section.)



2a,f,g

various values were reported to the coupling constants of isoxazolidine ring protons,[8] and these values are not always the same due to the changes in the conformation of isoxazolidine ring. Therefore, the structure determination by X-ray diffraction analysis was desirable, but attempts to obtain well-crystallized sample of **2a** were unsuccessful.

The reactions of 25DMQ with substituted *N*,α-diarylnitrones (**1b**—**e**) were summarized in Table 1. All of these reactions gave 1 : 1-C=C adducts (**2b**—**e**) as the sole product. The spectral pattern of the products was very similar to those of **2a**. There was no marked difference in the yield with the substitution on either benzene rings.

There are two possible reaction patterns for the formation of *cis*-adduct, *exo*-addition of the *trans*-nitrone and *endo*-addition of the *cis*-nitrone (Scheme 4). In all of these reactions, *cis*-adduct was the sole product. It is known that **1d** exists exclusively as a *trans*-form under the temperature conditions where the reactions are carried out.[9] Therefore, the *endo*-addition of the *cis*-nitrone could be ruled out. Thus, diarylnitrones are proved to react with 2,5-dimethyl-*p*-benzoquinone at C=C site, in such an orientation as forming *cis*-adducts via *exo*-cycloaddition.

The reactions of **1a** with other *p*-benzoquinones were also examined (Table 2). The reactions of **1a** with 2,6-dimethyl-*p*-benzoquinone and with 2,5-di-*t*-butyl-*p*-benzoquinone gave corresponding adducts **2f** and **2g**, respectively. In each of these reactions, **2f** or **2g** was the only product which was recognized by chromatographic analyses. The reaction of **1a** with 2,6-di-*t*-butyl-*p*-benzoquinone gave an indication of the formation of a trace amount of an product from **1a** and quinone in HPLC analysis, but the isolation of the product was not successful.

The reaction of **1a** with unsubstituted *p*-benzoquinone gave a tarry material and attempts to isolate a definite product were unsuccessful. In the reaction of *p*-benzoquinone and benzonitrile *N*-oxide, it is known that the reaction gave isoxazoline cycloadduct and the adduct and starting materials undergo complex redox reactions.[10] In this reaction, similar complex reactions were thought to be involved but nothing was clarified.

In the reactions of **1a** with *p*-benzoquinones having electron-withdrawing substituents, e.g. chloranil and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), instantaneous color changes were observed when the solution of the nitrone and the quinone was mixed (yellow to red in the reaction with chloranil, and yellow to blue with DDQ) presumably due to the formations of charge-transfer complexes.[5] HPLC analyses of the reaction mixtures showed gradual degradation of **1a** and no adduct formation.

Temperature effect on the reaction of **1a** with 25DMQ was also examined (Table 3). No significant difference was observed in the reactions at room temperature, in refluxing benzene (80 °C), and in refluxing toluene (110 °C). However, in refluxing xylene (140 °C), the reaction mixture after the removal of the solvent left black tarry material, and no cycloadduct nor any definite product could be isolated. Thermal analyses of **2a** (TG and DTA) showed thermal degradation of the compound just above the melting point (>92 °C).

The retrocycloaddition reaction was observed when

Table 3. The Reaction of 2,5-Dimethyl-*p*-benzoquinone with **1a** at Various Temperature

Solvent	Temperature/°C	Reaction time/d	Yields/%
Benzene	Room temp.	7	18
Benzene	80(reflux)	2	20
Toluene	110(reflux)	2	18
Xylene	140(reflux)	2	0

2a was placed in the cycloaddition reaction conditions. The reaction was confirmed with NMR and HPLC analyses. (see experimental section). This retroaddition was thought to be responsible to the low yields of the cycloaddition reactions. The reason of the result of Schultz et al. that *C*-phenyl-*N*-methylnitrone and 2,6-dimethyl-*p*-benzoquinone did not give any adduct[6] may be ascribed to that the nitrone is less reactive than *N*,α-diarylnitrones[9] as well as that the lack of *N*-aryl group destabilize the isoxazolidine to be labile to undergo the retroaddition reaction.

In conclusion, *N*,α-diarylnitrones cycloadded to alkyl-substituted *p*-benzoquinones at quinone C=C double bond to give fused isoxazolidine derivatives but electron-deficient quinones did not give any adduct. The isoxazolidines were found to undergo retrocycloadditions.

Experimental

Melting points were measured with a micro melting point measuring apparatus (Yazawa BY-1) and are uncorrected. The IR spectra were recorded with a JASCO IRA-1 spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$, unless otherwise indicated, with JEOL JMN-MH100 and GX-270 spectrometers respectively, and chemical shifts were reported in ppm from internal tetramethylsilane. Mass spectra were recorded with a Hitachi RMU-7M spectrometer. Thermal analysis (DTA and TGA) was measured with Shimadzu DT-30 apparatus.

Materials. *p*-Benzoquinone, 2,5-di-*t*-butyl-*p*-benzoquinone, 2,6-di-*t*-butyl-*p*-benzoquinone, chloranil and 2,3-dicyano-5,6-dichloro-*p*-benzoquinone(DDQ) were commercially obtained. 2,5-dimethyl-*p*-benzoquinone and 2,6-dimethyl-*p*-benzoquinone were synthesized with Jones oxidation of 2,5-xylenol and 2,6-xylenol, respectively[11] and purified by column chromatography. All of the quinones except for DDQ were recrystallized from hexane. *N*,α-Diarylnitrones (**1a—e**) were prepared in dry ethanol from corresponding arenecarbaldehydes and *N*-arylhydroxylamines[12] which were synthesized by the zinc mediated reduction of the corresponding nitroaryl compounds.

Reactions of *N*,α-Diphenylnitrones(1a) with 2,5-Dimethyl-*p*-benzoquinone. Method A: To 50 ml of benzene, 592 mg of **1a** (3.00 mmol) and 408 mg of 2,5-dimethyl-*p*-benzoquinone (3.00 mmol) were dissolved. The mixture was heated to reflux for 2 d. The reaction was followed by TLC analysis (Merck, Kieselgel 60 F-254, benzene as an eluent). After the reaction, solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel (Wakogel C-200, Wako Chemicals Co., Ltd.) using benzene as an eluent. 2,5-Dimethyl-*p*-benzoquinone and the product were eluted in this order. After the evaporation of the solvent, 207 mg (51%) of 2,5-dimethyl-*p*-benzoquinone was recovered. The fraction of the product was concentrated under reduced pressure, triturated with hexane and recrystallized from hexane and 198 mg (20%) of 1 : 1 cycloadduct (**2a**) was obtained. The reactions with other nitrones (**1b—e**) or with other benzoquinones were performed with the same procedures. In all of these reaction, the 1 : 1-C=C cycloadduct was a sole product (**3b—g**) and no other product formation was observed in TLC analyses in each of these reactions.

Table 4. Characterization Data of Cycloadducts (**3a—g**)

Adducts	θ/°C		Anal./% Found	Anal./% Calcd	$\nu_{C=O}$
2a	90.5—92	C	75.63	75.66	1680
		H	5.63	5.74	
		N	4.33	4.20	
2b	110.5—111.5	C	68.80	68.57	1670
		H	5.03	4.93	
		N	3.84	3.81	
2c	140—141	C	66.77	66.66	1680
		H	4.53	4.79	
		N	7.71	7.40	
2d	91—94	C	75.92	76.06	1680
		H	5.80	6.09	
		N	4.06	4.03	
2e	164—165.5	C	68.78	68.76	1680
		H	4.88	4.67	
		N	3.79	3.81	
2f	112.5—114	C	75.71	75.66	1670,1685
		H	5.81	5.74	
		N	4.19	4.20	
2g	137.5—139.5	C	77.93	77.67	1680
		H	7.41	7.48	
		N	3.33	3.35	

Table 5. ^{1}H NMR Spectra of the Adducts (**2a—g**)[a]

Adducts	Chemical shifts (δ)
2a	1.59 (s, 3H), 2.00 (s, 3H), 3.68 (d, 1H, *J*=7 Hz), 5.00 (d, 1H, *J*=7 Hz), 6.62 (s, 1H,), 7.0—7.9 (m, 10H)
2b	1.56 (s, 3H), 1.98 (s, 3H), 3.62 (d. 1H, *J*=7 Hz), 4.98 (d, 1H, *J*=7 Hz), 6.62 (s, 1H,), 6.9—7.7 (m, 9H)
2c	1.73 (s, 3H), 2.06 (s, 3H), 3.78 (d, 1H, *J*=7 Hz), 5.40 (d, 1H, *J*=7 Hz) 6.88 (s,1H,), 7.0—8.7 (m, 9H)
2d	1.58 (s, 3H), 1.98 (s, 3H), 2.36 (s, 3H),[b] 3.68 (d, 1H, *J*=7 Hz), 4.98 (d, 1H, *J*=7 Hz), 6.67 (s, 1H,), 7.0—7.7 (m, 9H)
2e	1.52 (s, 3H), 1.64 (s, 3H), 4.00 (d, 1H, *J*=7 Hz), 5.00 (d, 1H, *J*=7 Hz), 6.56 (s, 1H), 6.9—7.7 (m, 9H)
2f	1.66 (s, 3H), 2.10 (s, 3H), 3.81 (d, 1H, *J*=7 Hz), 5.35 (d, 1H, *J*=7 Hz), 6.83 (s, 1H,), 7.0—8.0 (m, 10H)
2g	1.12 (s, 9H), 1.32 (s, 9H), 3.97 (d, 1H, *J*=7 Hz), 4.63 (d, 1H, *J*=7 Hz), 6.69 (s, 1H,), 6.8—7.7 (m, 10H)

a) Assignment Alkyl moieties H^{7a} H^8 Vinyl proton Aromatic moieties

b) Signal of Substituent Methyl Group at 9-*p*-Tolyl Moiety.

The yields and characterization data for these products were summarized in Tables 1 and 2, and in Tables 4 and 5, respectively.

Method B: The reaction was carried out in refluxing 1,2-dichloroethane (80 °C) with the same concentration as Method A. The reaction progress was followed by HPLC analysis (ODS column, 85% acetonitrile as an eluent, detector (UV) wavelength 254 m, 100 mg of biphenyl as an internal stan-

dard). After 2 d, the solution was worked up in the same manner as described in method A.

Temperature Effect on the Reaction of 2a with 25DMQ. The reaction was carried out in benzene (room temperature), refluxing benzene (80 °C), toluene (110 °C), or xylene (140 °C). The other reaction conditions and the treatments after the reaction were the same as method A. The results of the reactions were summarized in Table 3.

Retrocycloaddition Reaction of 2a. Compound **2a** (100 mg) was dissolved in 50 ml of 1,2-dichloroethane, and allowed to reflux overnight. After the reaction, the reaction mixture was subjected to HPLC analysis. The chromatogram indicated that **2a** was decomposed almost completely and **1a** and 25DMQ were produced. It was found that some amount of **1a** (less than 10%) was decomposed. But the identification of the degradation product was unsuccessful. ^{1}H NMR analysis was also performed. Compound **2a** (4 mg) was dissolved in 2 ml of benzene-d_6 and heated to 80 °C for 2 d. The reaction mixture was subjected to ^{1}H NMR analysis. The spectrum showed the overlap of **1a** (confirmed with the multiplet signal at 8.5 ppm), 25DMQ (confirmed with two singlet signals at 6.1 ppm and 2.6 ppm), and **2a**. The other signals were very weak and negligible (less than 5% from the integral intensity). The integral ratio of 25DMQ : **2a** was about 3 : 1.

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