[2+3]-Type Addition Reactions of Benzocyclobutadiene with Nitrone Derivatives. Formation of Oxazolidine Derivatives

Katsuhiro SAITO,* Hiroyuki WATANABE, Michihito SAKURA, and Kensuke TAKAHASHI
Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466
(Received August 11, 1992)

Synopsis. The reactions of benzocyclobutadiene with nitrone derivatives afforded oxazolidine derivatives through *endo*- and *exo*-[2+3]-type cycloadditions. The main formations of the *endo*-type adducts were explained by secondary orbital interactions in the transition states.

Nitrone derivatives (**3**) are known to be active 1, 3- dipolar reagents, and have attracted the attention of chemists not only regarding their utility to synthesize heterocyclic compounds, but also due to their own chemical and physical natures.[1] Cyclobutadienes, 4π electron antiaromatic compounds, are very unstable, with exceptional cases of metal complexes or dibenzo derivatives, and their reactions have not been investigated in detail.[2] Benzocyclobutadiene (**2**), which can be generated in situ from *trans*-1,2-dibromo-1,2-dihydrobenzocyclobutene (**1**) by debromination with zink dust, is one of the attracting derivatives of cyclobutadiene. Though **2** is still too unstable to be isolated, its reactivities were studied compared to the other derivatives. However, except for the dimerization or cycloaddition reactions to some kinds of unsaturated hydrocarbons, documents concerning the chemistry of **2** are few.[3]

As a series of studies regarding strained cyclic unsaturated compounds,[4] we investigated the reactions of **2** with nitrone derivatives (**3**) to give oxazolidine derivatives. Here the results are reported here (Fig. 1).

N, α-Diphenylnitrone (**3a**) and three molar equivalents of *trans*-1,2-dibromo-1,2-dihydrobenzocyclobutene (**1**) in THF were reacted in the presence of an excess amount of zink dust[5] to give *endo*-(**4a**) and *exo*-type cycloadducts (**5a**) in 40 and 8% yields, respectively. Analogous reactions using nitrones (**3b**—**3i**) afforded the corresponding *endo*-(**4b**—**4i**) and *exo*-type cycloadducts (**5b**—**5i**) in the yields summarized in Table 1.

The structures of **4** and **5** were deduced on the basis of their spectral, especially NMR, properties. ^{13}C NMR spectra showed that both **4** and **5** had three saturated carbons, except for those of the substituents. The *endo*-structures of **4** and the *exo*-structures of **5** were determined based on the coupling constant values between the methine protons, H_b and H_c, in their ^{1}H NMR spectra. The values (J_{bc}=ca. 0 Hz) in **4** are reasonable for the coupling constants between the vicinal protons with a dihedral angle of 90°.[6] Dreiding models demonstrated that the dihedral angles between protons H_b and H_c were ca. 90° for the *endo*-type adducts, thus showing **4** to be the *endo*-type adducts. Also, the values in **5** (J_{bc}=ca. 7 Hz) are reasonable for the *exo*-type adducts. A good resemblance of these values to the analogous compounds further supported the structures.[7]

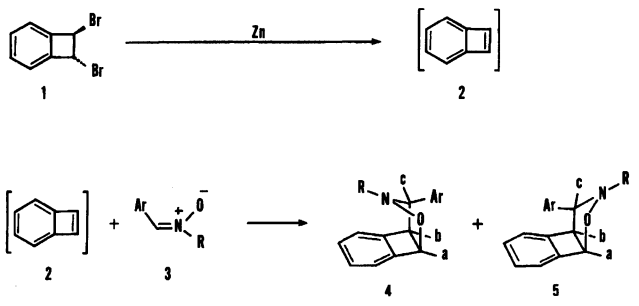

Fig. 1.

Obviously, the reactions of **2** and **3** proceeded with stereoselectivity to form *endo*-type adducts as the main products. The steric repulsions caused by the substituents at the carbon atom (Ar) or the nitrogen atom (R) of nitrones may be responsible for this selectivity. In order to ascertain the existence of these steric effects, the reactions of nitrones possessing a naphthyl group at the carbon atom (**3g** and **3h**) or a nitrone with a methyl group at the nitrogen atom (**3i**) were investigated. No remarkable change was detected in the stereoselectivity of these reactions, compared to the reactions of the other nitrones. This result is considered to show that the stereoselectivity in these reactions is not the result of steric effects (Fig. 2).

Molecular orbital calculations by the MNDO method showed that the orbital energies of the HOMO and LUMO of **2** were −8.361 and −0.295 eV, respectively, and those of **3a** were −8.738 eV (HOMO) and −0.423 eV (LUMO).[8] Thus, the energy difference between the HOMO of **2** and the LUMO of **3** is smaller than that

Table 1.

Nitrones	Substituents		Yields/%		Ratio
	Ar	R	**4**	**5**	**4/5**
3a	C_6H_5	C_6H_5	40[a)]	8[a)]	5.0
3b	*p*-ClC_6H_4	C_6H_5	51[a)]	12[a)]	4.3
3c	*p*-BrC_6H_4	C_6H_5	61[a)]	10[a)]	6.1
3d	*p*-CNC_6H_4	C_6H_5	40[a)]	5[a)]	8.0
3e	*p*-MeC_6H_4	C_6H_5	40[a)]	8[a)]	5.0
3f	*p*-$MeOC_6H_4$	C_6H_5	24	5	4.8
3g	1-Naphthyl	C_6H_5	38[a)]	9[a)]	4.2
3h	2-Naphthyl	C_6H_5	38[a)]	8[a)]	4.8
3i	C_6H_5	Me	11	3	3.7

a) The yields were determined using NMR spectra.

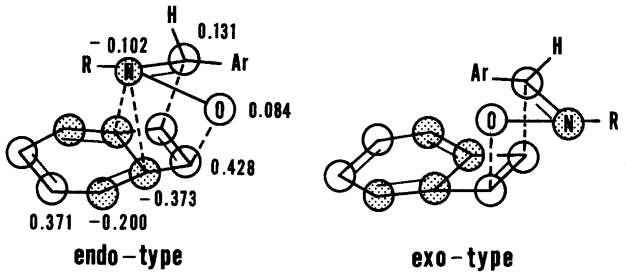

Fig. 2. The numerals in the figure are the coefficients of the HOMO of **2** and the LUMO of **3a**.

of the opposite combination (LUMO of **2** and HOMO of **3**), suggesting that the reactions were influenced by interactions between the HOMO of **2** and the LUMO of **3**.

Figure 2 shows that the interactions between the HOMO of **2** and the LUMO of **3** form bonding-type secondary orbital interactions in the *endo*-type transition states.[9] Contrary to this, no such stabilizations by secondary orbital interactions could be found in the *exo*-type transition states. As a result, mainly the *endo*-type additions proceeded.[1b,10]

Experimental

The melting points were uncorrected. NMR spectra were measured using a Varian XL-200 spectrometer with tetramethylsilane as the internal standard. Only the chemical shifts of the saturated carbons were listed in the data of the ^{13}C NMR spectra. IR, UV, and MS spectra were measured using JASCO FT/IR 3100, Hitachi 220A, and Hitachi M-2000S spectrometer, respectively. Only a typical reaction is described below.

Reaction of 2 with 3a. To a solution of **1** (790 mg, 3.0 mmol) and **3a** (200 mg, 1.0 mmol) in THF (7 ml) was added activated zinc dust (1.5 g). The reaction proceeded exothermically. After stirring at room temperature for 2 h the zinc dust was separated by filtration. After solvent evaporation the residue was chromatographed on alumina to give an oil (290 mg). ^{1}H NMR spectra showed that this oil contained **4a** (240 mg, 40%) and **5a** (50 mg, 8%). Repeated separation with thin-layer chromatography on silica gel using hexane–ethyl acetate (4 : 1) as a developing solvent gave colorless crystals **4a** and a colorless oil **5a**.

4a: Mp 160—161°C. Found: C, 83.71; H, 5.77; N, 4.67%. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68%. HRMS, Found: *m/z* 299.1337. Calcd for $C_{21}H_{17}NO$: M, 299.1331. MS *m/z* (rel intensity) 299 (M^+, 100), 268 (66). IR (KBr) 3023, 1595 cm^{-1}. UV (EtOH) 249 nm (log ε, 3.97), 264 (sh. 3.74). ^{1}H NMR ($CDCl_3$) δ=4.60 (d, H_b, J= 4.5 Hz), 5.10 (s, H_c), 5.90 (d, H_a, J=4.5 Hz), 6.60—7.50 (14H, m, Ph). ^{13}C NMR ($CDCl_3$) δ=62.4, 68.9, 80.8.

5a: HRMS, Found: *m/z* 299.1333. Calcd for $C_{21}H_{17}NO$: M, 299.1309. MS *m/z* (rel intensity) 299 (M^+, 91), 208 (100). IR (oil) 3026, 1599 cm^{-1}. UV (EtOH) 251 nm (log ε, 4.03), 272 (3.84). ^{1}H NMR ($CDCl_3$) δ=4.30 (d, H_c), 4.70 (dd, H_b), 5.70 (d, H_a), 6.40—7.60 (14H, m, Ph). Coupling constants in Hz: J_{ab}=4.0, J_{bc}=7.0. ^{13}C NMR ($CDCl_3$) δ= 61.7, 70.2, 78.8.

4b: Mp 146—147°C. Found: C, 75.45; H, 4.93; N, 4.18%. Calcd for $C_{21}H_{16}NOCl$: C, 75.56; H, 4.83; N, 4.20%. HRMS, Found: *m/z* 333.0926. Calcd for $C_{21}H_{16}NOCl$: M, 333.0919. MS *m/z* (rel intensity) 333 (M^+, 51), 118 (100). IR (KBr) 3067, 1597 cm^{-1}. UV (EtOH) 245 nm (log ε, 3.98), 272 (sh. 3.62). ^{1}H NMR ($CDCl_3$) δ=4.52 (d, H_b, J= 3.9 Hz), 5.09 (s, H_c), 5.86 (d, H_a, J=3.9 Hz), 6.60—7.40 (13H, m, Ph). ^{13}C NMR ($CDCl_3$) δ=62.2, 68.0, 80.5.

5b: HRMS, Found: *m/z* 333.0941. Calcd for $C_{21}H_{16}NOCl$: M, 333.0920. MS *m/z* (rel intensity) 333 (M^+, 19), 77 (100). IR (KBr) 3067, 1491 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=4.27 (d, H_c), 4.62 (dd, H_b), 5.70 (d, H_a), 6.40—7.40 (13H, m, Ph). Coupling constants in Hz: J_{ab}=4.0, J_{bc}=6.8. ^{13}C NMR ($CDCl_3$) δ=61.4, 69.4, 78.8.

4c: Mp 143—145°C. HRMS, Found: *m/z* 377.0410. Calcd for $C_{21}H_{16}NOBr$: M, 377.0414. MS *m/z* (rel intensity) 377 (M^+, 32), 149 (100). IR (KBr) 3065, 1595 cm^{-1}. UV (EtOH) 243 nm (sh, log ε, 4.18), 272 (sh, 3.87). ^{1}H NMR ($CDCl_3$) δ=4.55 (d, H_b, J=3.8 Hz), 5.10 (s, H_c), 5.89 (d, H_a, J=3.8 Hz), 6.64—7.48 (13H, m, Ph). ^{13}C NMR ($CDCl_3$) δ=62.1, 68.0, 80.5.

5c: HRMS, Found: *m/z* 377.0435. Calcd for $C_{21}H_{16}NOBr$: M, 377.0415. MS *m/z* (rel intensity) 377 (M^+, 13), 77(100). IR (KBr) 3065, 1489 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=4.28 (d, H_c), 4.66 (dd, H_b), 5.74 (d, H_a),6.42—7.50 (13H, m, Ph). Coupling constants in Hz:J_{ab}=4.1, J_{bc}=6.6. ^{13}C NMR ($CDCl_3$) δ=61.4, 69.4, 78.8.

4d: Mp 97—99°C. Found: C, 80.94; H, 5.28%. Calcd for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97%. HRMS, Found: *m/z* 324.1259. Calcd for $C_{22}H_{16}N_2O$: M, 324.1561. MS *m/z* (rel intensity) 324 (M^+, 38), 118 (100). IR (KBr) 3065, 2228, 1597 cm^{-1}. UV (EtOH) 234 nm (sh, log ε, 4.32), 273 (3.61). ^{1}H NMR ($CDCl_3$) δ=4.57 (d, H_b, J=3.8 Hz), 5.10 (s, H_c), 5.90 (d, H_a, J=3.8 Hz), 6.66—7.65 (13H, m, Ph). ^{13}C NMR ($CDCl_3$) δ=61.9, 68.1, 80.5.

5d: HRMS, Found: *m/z* 324.1238. Calcd for $C_{22}H_{16}N_2O$: M, 324.1263. MS *m/z* (rel intensity) 324 (M^+, 19), 91 (100). IR (KBr) 3069, 2227, 1597 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=4.36 (d, H_c), 4.68 (dd, H_b), 5.74 (d, H_a), 6.30—8.00 (13H, m, Ph). Coupling constants in Hz: J_{ab}=4.1, J_{bc}=6.9. ^{13}C NMR ($CDCl_3$) δ=61.4, 69.4, 79.0.

4e: HRMS, Found: *m/z* 313.1464. Calcd for $C_{22}H_{19}NO$: M, 313.1465. MS *m/z* (rel intensity) 313 (M^+, 47), 205 (100). IR (oil) 3025, 1597 cm^{-1}. UV (EtOH) 249 nm (log ε, 3.94), 272 (sh, 3.66). ^{1}H NMR ($CDCl_3$) δ=2.31 (3H, s, Me), 4.59 (d, H_b, J=3.9 Hz), 5.12 (s, H_c), 5.88 (d, H_a, J=3.9 Hz), 6.45—7.40 (13H, m, Ph). ^{13}C NMR ($CDCl_3$) δ=20.9, 62.3, 68.3, 80.5.

5e: HRMS, Found: *m/z* 313.1489. Calcd for $C_{22}H_{19}NO$: M, 313.1467. MS *m/z* (rel intensity) 313 (M^+, 29), 77 (100). IR (KBr) 3024, 1597 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=2.36 (3H, s, Me), 4.29 (d, H_c), 4.65 (dd, H_b), 5.72 (d, H_a), 6.45—7.40 (13H, m, Ph). Coupling constants in Hz: J_{ab}=4.2, J_{bc}=6.8. ^{13}C NMR ($CDCl_3$) δ=21.0, 61.6, 70.0, 78.7.

4f: Mp 78—80°C. Found: C, 80.55; H, 5.81; N, 3.94%. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25%. HRMS, Found: *m/z* 329.1410. Calcd for $C_{22}H_{19}NO_2$: M, 329.1414. MS *m/z* (rel intensity) 329 (M^+, 29), 221 (100). IR (KBr) 3061, 1597 cm^{-1}. UV (EtOH) 246 nm (sh, log ε, 3.77), 273 (3.68). ^{1}H NMR ($CDCl_3$) δ=3.72 (3H, s, OMe), 4.55 (d, H_b, J=3.9 Hz), 5.07 (s, H_c), 5.87 (d, H_a, J=3.9 Hz), 6.60—7.35 (13H, m, Ph). ^{13}C NMR ($CDCl_3$) δ=55.0, 62.2, 68.1, 80.5.

5f: HRMS, Found: *m/z* 329.1431. Calcd for

$C_{22}H_{19}NO_2$: M, 329.1415. MS m/z (rel intensity) 329 (M^+, 7), 211 (100). IR (oil) 3063, 1599 cm^{-1}. UV (EtOH) 252 nm (log ε, 3.74), 273 (3.70). ^1H NMR ($CDCl_3$) δ=3.80 (3H, s, OMe), 4.27 (d, H_c), 4.64 (dd, H_b), 5.74 (d, H_a), 6.52—7.40 (13H, m, Ph). Coupling constants in Hz: J_{ab}=3.9, J_{bc}=6.9. ^{13}C NMR ($CDCl_3$) δ=55.1, 61.6, 69.9, 78.7.

4g: HRMS, Found: m/z 349.1460. Calcd for $C_{25}H_{19}NO$: M, 349.1464. MS m/z (rel intensity) 349 (M^+, 26), 156 (100). IR (oil) 3025, 1597 cm^{-1}. UV (EtOH) 251 nm (log ε, 3.99), 273 (4.00), 283 (3.96). ^1H NMR ($CDCl_3$) δ=4.62 (d, H_b, J=4.0 Hz), 5.85 (d, H_a, J=4.0 Hz), 5.92 (s, H_c), 6.60—8.35 (16H, m, Ph). ^{13}C NMR ($CDCl_3$) δ=62.5, 66.1, 81.4.

5g: HRMS, Found: m/z 349.1454. Calcd for $C_{25}H_{19}NO$: M, 349.1467. MS m/z (rel intensity) 349 (M^+, 36), 77 (100). IR (KBr) 3063, 1597 cm^{-1}. ^1H NMR ($CDCl_3$) δ=4.97 (dd, H_b), 5.16 (d, H_c), 5.85 (d, H_a), 6.00—7.40 (16H, m, Ph). Coupling constants in Hz: J_{ab}=4.2, J_{bc}=7.0. ^{13}C NMR ($CDCl_3$) δ=60.0, 65.1, 79.1.

4h: HRMS, Found: m/z 349.1466. Calcd for $C_{25}H_{19}NO$: M, 349.1466. MS m/z (rel intensity) 349 (M^+, 26), 155 (100). IR (oil) 3065, 1597 cm^{-1}. UV (EtOH) 248 nm (log ε, 4.37), 273 (3.98). ^1H NMR ($CDCl_3$) δ=4.65 (d, H_b, J=3.9 Hz), 5.32 (s, H_c), 5.93 (d, H_a, J=3.9 Hz) 6.58—8.00 (16H, m, Ph). ^{13}C NMR ($CDCl_3$) δ=62.4, 68.9, 80.8.

5h: HRMS, Found: m/z 349.1466. Calcd for $C_{25}H_{19}NO$: M, 349.1467. MS m/z (rel intensity) 349 (M^+, 26), 77 (100). IR (KBr) 3057, 1595 cm^{-1}. ^1H NMR ($CDCl_3$) δ=4.46 (d, H_c), 4.71 (dd, H_b), 5.75 (d, H_a), 6.29—8.00 (16H, m, Ph). Coupling constants in Hz: J_{ab}=4.2, J_{bc}=6.7. ^{13}C NMR ($CDCl_3$) δ=61.7, 70.3, 78.8.

4i: Mp 106—108°C. HRMS, Found: m/z 237.1154. Calcd for $C_{16}H_{15}NO$: M, 237.1153. MS m/z (rel intensity) 237 (M^+, 50), 118 (100). IR (KBr) 3071, 1599 cm^{-1}. UV (EtOH) 266 nm (log ε, 3.18), 273 (3.10). ^1H NMR ($CDCl_3$) δ=2.41 (3H, s, Me), 4.17 (bs, H_c), 4.53 (dd, H_b), 5.73 (d, H_a), 7.20—7.45 (9H, m, Ph). Coupling constants in Hz: J_{ab}=3.9, J_{bc}=1.1. ^{13}C NMR ($CDCl_3$) δ=38.9, 62.1, 74.6, 79.9.

5i: HRMS, Found: m/z 237.1154. Calcd for $C_{16}H_{15}NO$: M, 237.1153. MS m/z (rel intensity) 237 (M^+, 66), 118 (100). IR (oil) 3065, 1599 cm^{-1}. UV (EtOH) 262 nm (log ε, 3.35), 272 (3.43). ^1H NMR ($CDCl_3$) δ=2.62 (3H, s, Me), 3.51 (d, H_c), 4.51 (dd, H_b), 5.60 (d, H_a), 7.10—7.40 (9H, m, Ph). Coupling constants in Hz: J_{ab}=4.0, J_{bc}=6.6. ^{13}C NMR ($CDCl_3$) δ=43.1, 61.2, 74.3, 79.2.

References

1) a) S. P. Ashburn and R. M. Coates, *J. Org. Chem.*, **50**, 3076 (1985); T. Hisano, K. Harano, T. Matsuoka, H. Yamada, and M Kurihara, *Chem. Pharm. Bull.*, **35**, 1049 (1987); S. Kagabu, K. Saito, H. Watanabe, K. Takahashi, and K. Wada, *Bull. Chem. Soc. Jpn.*, **64**, 106 (1991); K. Saito, A. Yoshino, H. Watanabe, and K. Takahashi, *Heterocycles*, **34**, 497 (1992); b) M. Burdisso, A. Gamba, R. Gandolfi, and L. Toma, *J. Org. Chem.*, **55**, 3311 (1990); M. Burdisso, R. Gandolfi, and P. Grunanger, *J. Org. Chem.*, **55**, 3428 (1990).

2) G. F. Emerson, L. Watts, and R. Pettit, *J. Am. Chem. Soc.*, **87**, 131 (1965); T. Bally and S. Masamune, *Tetrahedron*, **36**, 343 (1980).

3) M. Nitta, S. Sogo, and T. Nakayama, *Chem. Lett.*, **1979**, 1431; H. Kato and S. Toda, *J. Chem. Soc., Chem. Commun.*, **1982**, 1510; J. W. Barton, D. V. Lee, and M. K. Shepherd, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1407.

4) K. Saito, H. Ishihara, and S. Kagabu, *Bull. Chem. Soc. Jpn.*, **60**, 4141 (1987); S. Kagabu and K. Saito, *Tetrahedron Lett.*, **29**, 675 (1988); S. Kagabu, K. Saito, H. Watanabe, K. Takahashi, and K. Wada, *Bull. Chem. Soc. Jpn.*, **64**, 106 (1991); K. Saito, K. Ito, K.Takahashi, and S. Kagabu, *Org. Prep. Proced. Int.*, **23**, 196 (1991); K. Saito, H. Watanabe, and K. Takahashi, to be published in *Chem. Pharm. Bull.*.

5) O. L. Chapman, C. C. Chang, and N. R. Rosenquist, *J. Am. Chem. Soc.*, **98**, 261 (1976); O. A. Teim, M. C. Goodlan, and J. F. W. McOmie, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 2659.

6) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).

7) A. M. Nourel-Din, A. E. Mourad, and H. Abdel-Nabi, *J. Chem. Eng. Data*, **31**, 259 (1986).

8) The authors are indebted to the Computer Center of the Institute for Molecular Science for molecular orbital caluclations using MOPAC program: J. J. P. Stewart, *Q. C. P. E. Bull.*, **3**, 43 (1983).

9) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **11**, 781 (1969); H. Takeshita, T. Hatsui, I. Shimooda, and H. Mametsuka, *Bull. Chem. Soc. Jpn.*, **55**, 2291 (1982).

10) Gandolfi et al.[1b] suggested that the secondary orbital interactions have limited effects on the stereochemistries of the cycloaddition reactions of nitrones with several kinds of olefins.