Reactions of Benzocyclopropene with Sulfonyl Isocyanates and Nitrones:[1] Cycloadditions through C-C σ-Bond Rupture of Three-Membered Ring

Shinzo KAGABU,* Katsuhiro SAITO,† Hiroyuki WATANABE,†
Kensuke TAKAHASHI,† and Katsuaki WADA††
Department of Chemistry, Faculty of Education, Gifu University,
Yanagido, Gifu 501-11
† Department of Applied Chemistry, Nagoya Institute of Technology,
Gokiso-cho, Showa-ku, Nagoya 466
†† Yuki Research Center, Nihon Tokushu Noyaku Seizo and Co.,
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Alkane- and arenesulfonyl isocyanates were added to benzocyclopropene across the C–C σ-bond of the three-membered ring, giving 2-sulfonyl-1-isoindolinones. The reaction with *C,N*-diphenylnitrone afforded a similar cyclization product, 3,4-dihydro-3,4-diphenyl-1*H*-2,3-benzoxazine. These reactions are considered to proceed through zwitterionic intermediates formed by the fission of the C–C σ-bond of the three-membered ring by the electrophiles.

Highly strained benzocyclopropene (**1**) has recently attracted much interest of chemists.[2] A fusion of the two rings results in a considerable deformation of the benzene ring and, consequently in a reduction of the aromatic stabilization. Of particular note concerning to the unusual molecular geometry has been a solution to the question of bond fixation[3] and the cleavage mechanism of the three-membered ring in the reaction with electrophiles. Recently, Apeloig and Arad[4] depicted a suggestive FMO picture using a 3-21G method, showing that the HOMO has a higher energy than does the benzene, and is localized at both the fused bond C_1–C_6 and the C_3–C_4 bond.

According to FMO theory, an electrophilic attack should, therefore, occur preferably at the fused bond and more readily than on benzene. Some cycloaddition experiments agree with this argument: **1** reacts smoothly with electron-defficient (hetero)dienes in a concerted [2σs+4πs] fashion to give 1,6-methano[10]-annulenes and the hetero analogues.[5,6] Bond localization was also advocated by its almost quantitative reaction with dihalocarbenes.[7] On the other hand, halogenes, acids, and alcohols with metal ion catalysts provoke the reaction in another way: dissociating the σ-bond of the cyclopropene moiety exclusively to form the benzyl cation intermediates.[8]

The dependence of the different cleavage course on the types of electrophiles prompted us to examine the reactions with electrophilic polar double bonds or charge-separated organic species. To date, there have been only a couple of examples reported in this context; thus with arenecarbonitrile oxides[9] and mesoions,[10] and in both cases, the reaction apparently proceeded in a concerted manner to give the cycloaddition products across the fused bond.[11]

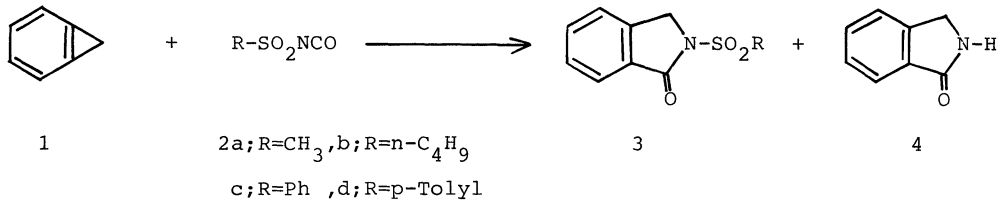
We have examined the reaction with other polar electrophiles to find a contrasting result regarding the yield of [2σ+4π]-type products with some isocyanates and nitrones. These cycloadditions are considered to proceed through an internal coupling of the intermediary zwitterions.

Results

The reaction of benzocyclopropene (**1**) with an equimolar amount of the sulfonyl isocyanate (**2**) was monitored by thin-layer chromatography and NMR spectroscopy. The reactions with methyl and phenyl isocyanates were quite sluggish. The mixture showed practically no change at room temperature over a period of one week.[12] In contrast, the reaction of **1** with *p*-toluenesulfonyl isocyanate (**2d**) proceeded smoothly at 60 °C; the peak at 3.17 ppm of the methylene protons disappeared completely within 40 h. The reaction mixture was subjected to thin-layer chromatography on silica gel to give colorless crystalline 2-*p*-tolylsulfonyl-1-isoindolinone (**3d**) and 1-isoindolinone (**4**) in 39 and 4% yields, respectively. 1-Isoindolinone (**4**) is obviously a secondary product from **3d**, since the isolated **3d** slowly decomposed to **4** in chloroform, and rapidly upon adding a few drops of ammonia water to it.

Similarly, warming a mixture of 1 and benzenesulfonyl isocyanate (**2c**) at 60 °C for 30 h afforded *N*-benzenesulfonyl derivative (**3c**) in 36% yield along with a small quantity of **4**. The cycloadditions with methanesulfonyl isocyanate (**2a**) and 1-butanesulfonyl isocyanate (**2b**) proceeded rather readily even at room temperature, to afford the corresponding 2-alkylsulfonyl-1-isoindolinones (**3a** and **3b**) in more than 20% yields after 3 days.

On the other hand, in reactions with 1,3-dipoles, such as methyl azidoformate and ethyl diazoacetate, we could not detect the corresponding adducts in any case at 60 °C after 4—6 days. In contrast, electrophilic *C,N*-diphenylnitrone (**5**) was sufficiently reactive toward **1** to produce the cycloadduct, 3,4-dihydro-3,4-diphenyl



1 2a;R=CH3,b;R=n-C4H9 3 4
c;R=Ph ,d;R=p-Tolyl

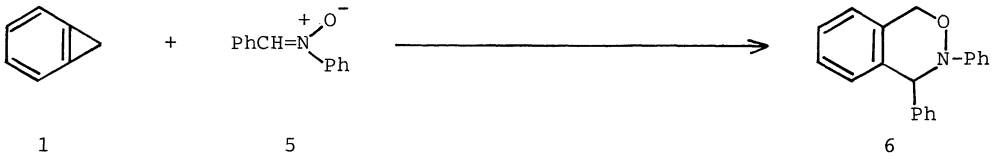


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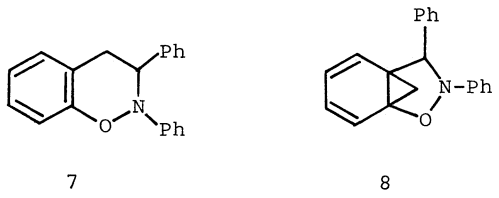
Fig. 1.



7 8

Fig. 2.

9 10

Fig. 3.

1*H*-2,3-benzoxazine (**6**), in 54% yield.

The structures of **3** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopic studies. In ^{1}H NMR spectra the chemical shifts of the methylene protons (around 4.9 ppm) was close to 4.38 ppm of 1-isoindolinone, itself, rather than to 3.50 ppm of the methylene peak of the possible regional isomer, 2-indolinone (**9**). Their ^{13}C NMR spectra indicated carbonyl carbons at between 166 and 167 ppm near to the corresponding value of 158.2 ppm of *N*-methylsaccharin (**10**), composing of the partial structure of $-SO_2NRCO-$.[13] In IR spectra the higher shift of carbonyl absorptions of **3** (around 1720 cm^{-1}) from that of 1-isoindolinone (1680 cm^{-1}) indicated the presence of an electronegative substituent at the nitrogen atom.

In EI mass spectroscopy, the 2-arylsulfonyl-1-isoindolinones (**3c, d**) showed no molecular ion peaks; instead, SO_2-eliminated ions appeared as their parent peaks, which is in contrast with the *N*-alkylsulfonyl derivatives whose parent peaks are 1-oxoisoindolin-2-ylium ion arising from a fragmentation of the alkylsulfonyl radicals. A similar SO_2 extrusion has been observed in *N*-arylsulfonylcarbamates, and the mechanism (not simple cheletropic) has been variously discussed.[14] On the other hand, a milder ionization method (CIMS) using isobutane displayed M$^+$+1 peaks with a distinctively strong intensity.

The structure of the oxazine (**6**) is determined spectroscopically, especially by NMR study. A singlet peak at 5.63 ppm and two doublet peaks at 5.19 and 5.29 ppm with a large geminal coupling constant (J=14 Hz) in ^{1}H NMR as well as the existence of only two aliphatic signals at 67.9 and 70.3 ppm in ^{13}C NMR support the structure (**6**). The formation of a possible regional isomer (**7**) and a norcaradiene derivative (**8**) are excluded.

Discussion

The smooth reaction of **1** with strongly electrophilic sulfonyl isocyanates reflects well the electron-donating nature of **1**. One explanation for the product is that the reaction proceeds in the fashion of an electrophilic aromatic substitution in which an electrophile attacks the HOMO-π-system located at C_1 to form the annelated cyclopropylium ion (**11**). A subsequent ring opening with a relief of strain energy forms a zwitterionic intermediate (**13**), which then recloses to give **3**. However, considering the enormously high strain energy (290 kJ mol^{-1}) of **1**, owing to the fused cyclopropene construction, it is not deniable that at first a σ-bond rupture on the three-membered ring occurs through an intermediate **12**, leading to the zwitterion (**13**). The preferable path between the π-

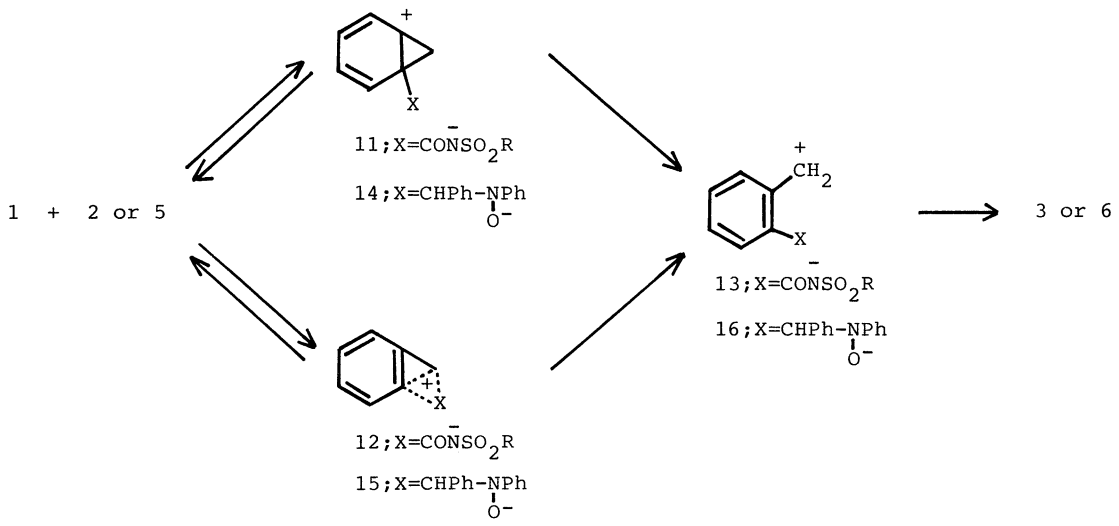


Fig. 4.

and σ-route has not yet been decided at the present stage, due to a lack of information regarding the stability of the intermediates.

Cycloaddition reactions of 1,3-dipoles have been highly studied over the past 20 years by Huisgen and others.[15] Houk et al. have discussed the reactivity and regioselectivity in synchronous dipolar additions in terms of FMO theory.[16] Among various types of 1,3-dipoles, nitrones and nitrile oxides having lower LUMO energies are expected to exert a considerable orbital interaction with the HOMO of **1**, especially when they are perturbated by the phenyl substituent.

The finding by Nitta and his co-workers is in accord with the theoretical prediction; they isolated a bridged norcaradiene, stable up to 120 °C, by a reaction with aromatic nitrile oxides.[9] In our study with diphenyl nitrone (**5**), however, we could not detect the formation of the tricyclic system (**8**); also, the possibility of a [1,3] sigmatropic shift of **8** to **6** is unrealistic under the reaction conditions.

It is most likely that the formation of **6** involved a stepwise process through a zwitterionic intermediate (**16**), which was derived via **14** or **15**. The regioselectivity of the addition is rationally accounted for by a CNDO/2 calculation on **5**, estimating that the LUMO coefficient on the carbon atom is greater than that on the oxygen atoms.[16] Thus, the orbital overlapping between the carbon atom of the nitrone and the π- or σ-bond of the three-membered ring develops as they approach to form the zwitterion (**16**), which leads to the product (**6**) by the resulting internal coupling. However, despite having a close LUMO energy level to that of nitrle oxide, why the nitrone does not add across the fused bond of **1** is still unclear.

As described above regarding the reaction with sulfonyl isocyanates and nitrones, the adjoining σ-bond to the benzene ring of **1** is formally replaced by a new σ-bond supplied from the entering electrophiles. Such an exceptional facile leaving of C–C bond from the aromatic ring is obviously ascribed to a highly strained cyclic system.

Experimental

The melting points were recorded on a Yanagimoto micro melting point apparatus and were uncorreced. The IR spectra were determined on a JASCO A-100 or a JASCO A-102 spectrometers. The NMR spectra were recorded by using a JNM GX-270 or a Varian XL-200 spectrometers in $CDCl_3$ solution with tetramethylsilane as an internal standard. Low- and high-resolution mass spectra were measured using a Shimadzu 9020-DF or a JMX DX-300 spectrometers. The UV spectra were recorded on a Hitachi 210 spectrometer. The solvents used were purified according to the standard procedures.[17] Methyl and phenyl isocyanates and benzene- and *p*-toluenesulfonyl isocyanates were commercially available. Methane- and 1-butanesulfonyl isocyanates were prepared by a method described in the literature.[18] Plates for preparative thin-layer chromatography were prepared with Merck Silica gel PF-254 or Wako gel B5-F.

General Procedure for the Reaction of Sulfonyl Isocyanates with 1. A solution of **1** (1.0 mmol) in chloroform (2.0 ml) was added to an ice-cold solution of sulfonyl isocyanate (**2**) (1.0 mmol) in the same solvent (3.0 ml). The combined solution was gently bubbled with dry nitrogen gas for ten min and allowed to stand at room temperature, or warmed. After the solvent was evaporated, the residual crude reaction mixture was chromatographed on TLC plates using chloroform–ethyl acetate–hexane (2:1:3) as a developing solvent to give crystalline products, which were further purified by recrystallization from 2-propanol. The yields were determined when the sample showed a single spot on TLC and contained practically no contaminates on the NMR spectra. 1-Isoindolinone (**4**) was identified by a comparison of TLC (R_f=0.1) and the melting point of 151—153 °C (Lit,[19] 155—156 °C) with an authentic sample.[19]

2-Methylsulfonyl-1-isoindolinone (3a): Yield: 21%. Colorless needles, mp 162 °C, R_f=0.3. Found: C, 51.17; H, 4.33; N, 6.67; S, 15.32%. Calcd for $C_9H_9NO_3S$: C, 51.17; H, 4.30; N, 6.63; S, 15.18%. EIMS *m/z* (rel intensity) 211 (M^+, 24), 133 (30), 132 (100), 105 (23), 104 (38), 77 (39). CIMS (isobutane) *m/z* (rel intensity) 212 (M^++1, 78), 134 (79), 57 (C_4H_9+1, 100). IR (KBr) 1720, 1340, 1142, 1130, 1092 cm^{-1}. ^1H NMR ($CDCl_3$) δ=3.42 (s, 3H), 4.89 (s, 2H), 7.2—7.6 (m, 2H), 7.71 (dd, 1H, *J*=7.3 and 7.3 Hz), 7.92 (d, 1H, *J*=7.7 Hz). ^{13}C NMR ($CDCl_3$) δ=41.1 (q), 49.2 (t), 123.5 (d), 125.2 (d), 129.0 (d), 130.0 (s), 134.2 (d), 141.2 (s), 167.2 (s).

2-Butylsulfonyl-1-isoindolinone (3b): Yield 26%. Calorless needles, mp 102.5 °C, R_f=0.7. Found: C, 56.70; H, 5.93; N, 5.60; S, 12.71%. Calcd for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.97; N, 5.53; S, 12.66%. EIMS *m/z* (rel intensity) 253 (M^+, 21), 134 (51), 133 (100), 132 (70), 105 (24), 104 (23), 77 (46). CIMS (isobutane) *m/z* (rel intensity) 254 (M^++1, 49), 134 (79), 57 ($C_4H_9^+$, 100). IR (KBr) 1720, 1340, 1320, 1155, 1105 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.94 (t, 3H, *J*=7.3 Hz), 1.48 (m, 2H), 1.83 (m, 2H), 3.61 (t, 2H, *J*=8.1 Hz), 4.88 (s, 2H), 7.5—7.6 (m, 2H), 7.70 (dd, 1H, *J*=6.6 and 6.6 Hz), 7.92 (d, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ=13.5 (q), 21.4 (t), 24.9 (t), 49.7 (t), 53.2 (t), 123.5 (d), 125.2 (d), 129.0 (d), 130.1 (s), 134.1 (d), 141.3 (s), 167.1 (s).

2-Phenylsulfonyl-1-isoindolinone (3c): The reaction was carried out in benzene. Yield: 36% (1-isoindolinine (**4**) was by-produced in 4% yield). Colorless needles, mp 193.5 °C, R_f=0.5. Found: C, 61.58; H, 3.97; N, 5.08; S, 11.53%. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.15; S, 11.53%. EIMS *m/z* (rel intensity) 209 (M^+-SO_2, 68), 208 (100), 132 (25), 77 45). CIMS (isobutane) *m/z* (rel intensity) 274 (M^++1, 76), 134 (79), 57 ($C_4H_9^+$, 100). IR (KBr) 1722, 1360, 1182, 1175, 1100 cm^{-1}. ^1H NMR ($CDCl_3$) δ=4.92 (s, 2H), 7.4—7.7 (m, 6H), 7.82 (d, 1H, *J*=8.1 Hz), 8.16 (m, 2H). ^{13}C NMR ($CDCl_3$) δ=49.9 (t), 123.4 (d), 125.1 (d), 128.1 (d), 128.9 (d), 129.1 (d), 130.1 (s), 133.9 (d), 134.1 (d), 138.4 (s), 141.0 (s), 166.1 (s).

2-*p*-Tolylsulfonyl-1-isoindolinone (3d): Yield: 39% (1-isoindolinone (**4**) was by-produced in 4% yield). Colorless needles, mp 218 °C, R_f=0.6. Found: C, 62.63; H, 4.60; N, 4.94; S, 11.15%. Calcd for $C_{15}H_{13}NO_3S$: C, 62.67; H, 4.56; N, 4.88; S, 11.16%. EIMS *m/z* (rel intensity) 223 (M^+-SO_2, 100), 222 (62), 132 (22), 91 (36). CIMS (isobutane) *m/z* (rel intensity) 288 (M^++1, 81), 134 (67), 57 ($C_4H_9^+$, 100). IR (KBr) 1720, 1340, 1142, 1130, 1092 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.41 (s, 3H), 4.91 (s, 2H), 7.33 (d, 2H, *J*=8.4 Hz), 7.4—7.5 (m, 2H), 7.63 (ddd, 1H, *J*=1.1, 7.0, and 9.0 Hz), 7.80 (dd, 1H, *J*=1.1 and 8.1 Hz), 8.03 (d, 2H, *J*=8.4 Hz). ^{13}C NMR ($CDCl_3$) δ=21.7 (q), 49.8 (t), 123.3 (d), 125.0 (d), 128.2 (d), 128.8 (d), 129.8 (d), 130.2 (s), 133.8 (d), 135.5 (s), 141.0 (s), 145.2 (s), 166.1 (s).

Reaction of 1 with 5. A solution of **1** (33 mg, 0.37 mmol) and **5** (145 mg, 0.74 mmol) in deuteriochloroform (0.5 ml) was heated at 60 °C for 70 h. After evaporation of the solvent the resluting mixture was subjected to this-layer chromatography on silica gel using hexane–ethyl acetate (7:3) as a developing solvent to give colorless crystals **6** (57 mg, 54%, R_f=0.74).

6: Mp 104 °C. HRMS *m/z* 287.1309. Calcd for $C_{20}H_{17}NO$ *m/z* 287.1309. EIMS *m/z* (rel intensity) 287 (M^+, 100), 269 (50), 180 (90), 165 (42). IR (KBr) 3050, 3010, 1600, 1500, 760 cm^{-1}. UV (MeOH) 245 nm (log ε, 3.97). ^1H NMR ($CDCl_3$) δ=5.19 (d, 1H, *J*=14.0 Hz), 5.29 (d, 1H, *J*=14.0 Hz), 5.63 (s, 1H), 7.26 (bs, 14H). ^{13}C NMR ($CDCl_3$) δ=67.9, 70.3, 118.3, 122.8, 124.0, 126.6, 127.7, 128.1, 128.4, 129.9, 133.6, 135.9, 139.3, 148.6.

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1a 1b

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ten hours **1** disappeared on TLC and NMR spectra. However, the viscous brown liquid remained proved to be intractable and nospectroscopic data could be obtained after TLC.

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