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Photochemistry of 5-nitro-1,2-benzisothiazole derivatives: effects of substituents, solvents and excitation wavelength

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Abstract

3-R-5-Nitro-1,2-benzisothiazole derivatives (**1**, R = substituents) in solution, undergo photochemical isomerization to produce 2-R-5-nitro-1,2-benzothiazole derivatives. Here, generalizations and limitations by the substituent, solvent, and excitation wavelength for the photoisomerization reaction of 5-nitro-1,2-benzisothiazoles are reported.

Keywords: Photoisomerization; Benzisothiazole; Benzothiazole; Substituent effect; Photochemistry

Benzisothiazoles (BIT) and benzothiazoles (BT) are often found in pharmaceutical and agricultural chemicals, and possess key functions. For example, ziprasidone which has a BIT skeleton, is approved by US-FDA[1] and is now being used as an antipsychotic drug, while the BT riluzole is an authorized medicine for ALS.[2] The BT IKF-230 is also used as an antifungal agricultural chemical.[3] If BIT-BT photoisomerization occurs, the reaction could become a valuable tool in the synthesis of BIT and BT derivatives having similar skeletons, as these are currently synthesized by completely separate routes.

Five-membered aromatic compounds consisting of two heteroatoms, such as isothiazoles–thiazoles[4–7] or isooxazoles-oxazoles[4–7] have been studied in depth and are known to undergo the reversible photoisomerization. However, the photochemical behavior of their condensed ring analogues has not been widely studied. The present work will focus on the BIT-BT isomerization reaction, which is becoming increasingly important. For example, partial photoisomerization was observed during photostability testing of ziprasidone,[8] therefore a better understanding of this reaction may be important in the design of new drugs. This Letter deals with nitrobenzo-isothiazoles, as reactions involving the nitro group are easy to detect, and allow conversion to various functional groups, such as amines, imines, and amides and halides.

When a solution of 5-nitro-1,2-benzisothiazole (**1a**,[9] R = H) in acetonitrile (10 mL, 1.5×10^{-2} M) was exposed to a 400 W Xe-arc lamp through a quartz tube using UV30 glass filter (>300 nm), no photochemical reactions were observed; however, using no filter (>200 nm) for 8 h, UV–vis absorption analyses showed clear isosbestic points at 228, 268, and 286 nm, and almost all of the reactants were consumed, giving a product showing IR absorption assigned to CN triple bond at 2240 cm^{-1}.[10] Previously, Ohashi et al.[11] showed that 1,2-benzoisothiazole under the same conditions yields bis(2-cyanophenyl)disulfide generated by the dimerization reaction of sulfinil radicals, which are generated by homolytic cleavage of the S–N bond in the isothiazole ring. Similar phenomena occurred with **1a** to give bis(2-cyano-4-nitrophenyl)disulfide (**3a**).[12]

Substituents effects at the 3-position of **1a** were then investigated (Fig. 1). First, we examined typical

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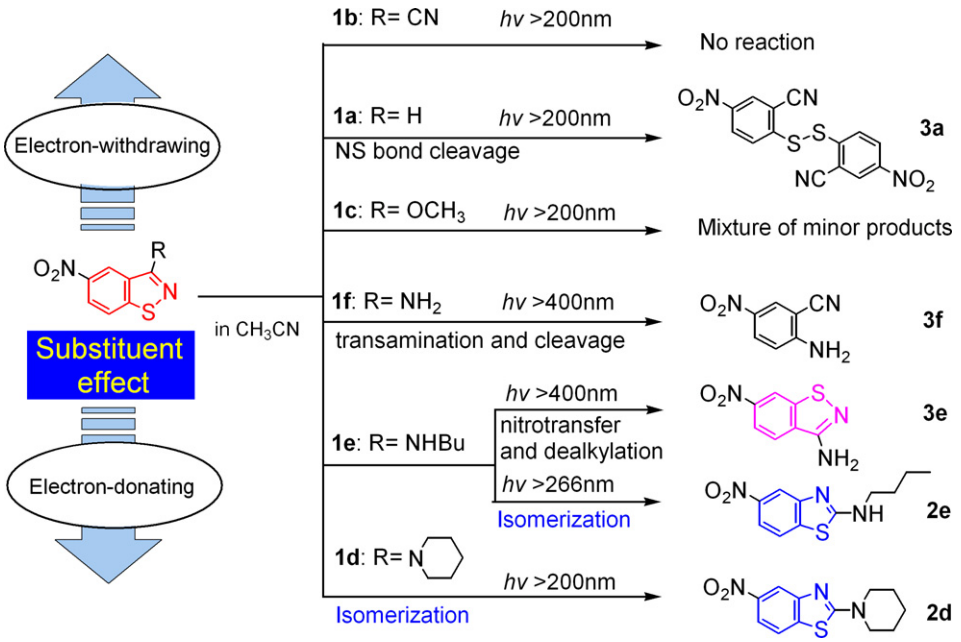

Fig. 1. Scheme of the substitution effect on photochemistry of 5-nitro-1,2-benzisothiazole derivatives.

electron-withdrawing and -donating substituents (cyano and methoxy groups, respectively). Under similar reaction conditions as used for compound **1a**, 3-cyano-5-nitro-1,2-benzisothiazole (**1b**,[9] R = CN) was photolyzed (either at >200 nm or >300 nm) for 8 h, the compound was very stable and did not yield any photochemical products. On the other hand, although the irradiation of 3-methoxy- 5-nitro-1,2-benzisothiazole (**1c**,[9] R = MeO) with >300 nm light gave no reaction products, irradiation with >200 nm light induced gradual degradation of the reactant, and after 14 h, a complex mixture of the products was obtained. The complexity of this mixture inhibited isolation and complete identification of the products.

The effect of electron-donating amino groups at the 3-position of 5-nitro-1,2-benzisothiazole was then examined, and marked variations in the photochemistry of 5-nitro-1,2-benzisothiazole derivatives were observed. Under similar reaction conditions as used for compound **1a**, 5-nitro-3-piperidino-1,2-benzisothiazole (**1d**, R = piperidino)[13] was photolyzed for 160 min. The UV–vis spectral change during the irradiation is shown in Figure 2. This spectral change showed clear isosbestic points at 248 and 322 nm, thus indicating this reaction is very clean. The final spectrum measured at 160 min almost completely matched the absorption spectrum of separately synthesized 5-nitro-2-piperidinobenzothiazole (**2d**).[14] The ^{1}H NMR and GC–MS spectra also support this identification. The aromatic proton signals shift to a higher magnetic field indicating lower electron density in the benzene ring of BT when compared to that of BIT. The isolated yield was 88%. Irradiation of **2d** did not produce **1d**; therefore, this isomerization is not reversible.

This reaction was also examined under oxygen saturated acetonitrile, however, the spectral change was identical

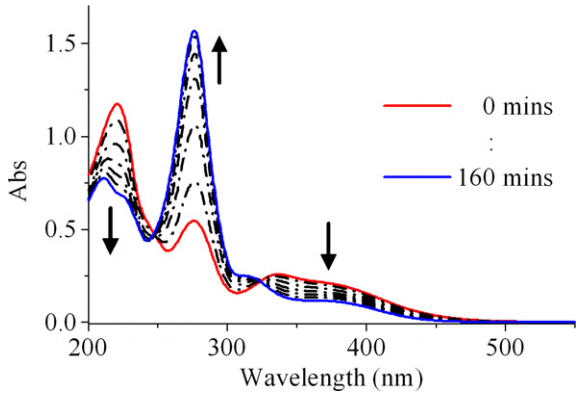

Fig. 2. Spectral change by photoirradiation of **1d** at >200 nm in acetonitrile.

with those under argon. Therefore, this reaction was not quenched by oxygen and may occur via a singlet excited state having short lifetime. In addition, the isomerization reaction did not proceed in non-polar solvents such as *n*-hexane, but was accelerated by twofold in methanol.

The effects of amino groups were then examined. Benzisothiazole derivatives with tertiary amino groups, such as piperidino and piperazino groups, have been isomerized to give benzothiazoles. Therefore, the effect of amino groups was investigated, using 3-*n*-butylamino- (secondary, **1e**) and amino (primary, **1f**) groups as substituents.

The reaction of 3-*n*-butylamino-5-nitro-1,2-benzisothiazole (**1e**)[13] showed remarkable dependence on excitation wavelength. Excitation at >400 nm using L-40 glass filter resulted in the dealkylation of the amino group with quantitative yield (91%). However, this dealkylation was not simple, as the product was not 3-amino-5-nitro-1,2-benzisothiazole (**1f**), but rather was 3-amino-6-nitro-1,2-

benzisothiazole (**3e**). This positional isomerization of nitro group may be induced by the isomerization of isothiazole ring; however, the detailed mechanism is unclear at present. In addition, the formation of **3e** did not occur by a stepwise reaction, as the intermediate dealkylation product **1f** did not give **3e** during photolysis. We have no experimental data at this moment to indicate the intermediacy of a sulfur atom migrated intermediates for **3e**, however, DFT calculation result for **2d** showed an energetic possibility via a sulfur atom migration from **1e** to **3e**, as similar route as shown dashed arrows for the mechanism of **2d** in Figure 5. More calculation for intermediates of **3e** is underway.

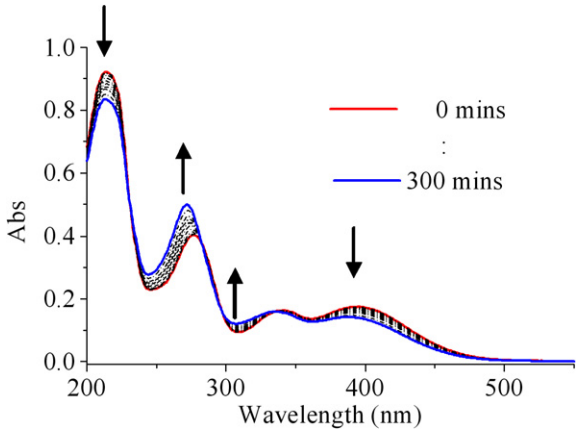

Fig. 3. Spectral change by photoirradiation of **1e** at >200 nm.

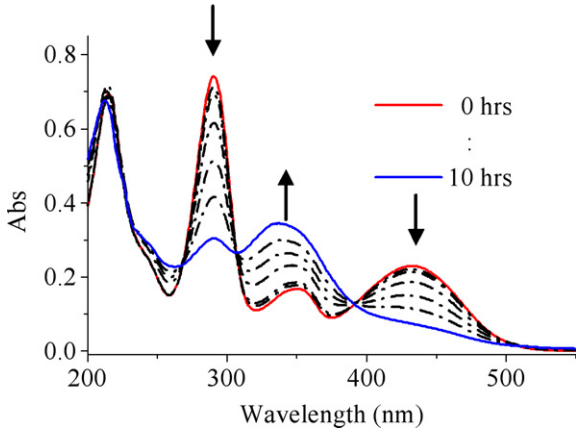

Fig. 4. Spectral change by photoirradiation of **1f** at >400 nm in acetonitrile.

Irradiation of **1e** at >200 nm in acetonitrile gave 2-*n*-butylamino-5-nitrobenzothiazole (**2e**)[14] as an isomerization product. Figure 3 shows the UV–vis spectral changes of **1e** by irradiation in acetonitrile.

Irradiation (>400 nm) of a primary amine, 3-amino-5-nitro-1,2-benzisothiazole (**1f**) did not lead to an isomerization reaction. Figure 4 shows the spectral changes of **1f** using >400 nm light. The spectral change showed clear isosbestic points at 270, 308, and 392 nm. This change was very clean, and thought to be due to isomerization, but ^{1}H NMR and IR (2260 cm^{-1}) measurements revealed thiazole ring opening and the formation of a cyano group. Similarities between this product and a standard sample separately prepared indicate that the product was 2-amino-5-nitrobenzonitrile (**3f**).[15] The mechanism for this reaction was proposed by Ohashi et al., however, additional experiments are underway.[11]

The reactions of **1d** and **1f** were examined in the presence of trifluoroacetic acid (TFA) as a protonation reagent for amino group. For **1d**, TFA had no effect on the photochemical isomerization reaction; however, the formation of **3f** was completely quenched by the presence of TFA. Quaternarization of the amino group acts as an important step in the mechanism to inhibit transamination. Further detailed investigations are underway.

Figure 5 indicates a plausible reaction mechanism of **1d**–**2d**, and this scheme is based on the experimental results and the relative energies of intermediates, as shown in Figure 6. In this case, the reaction starts from singlet excited state (energy was estimated from UV absorption) generated by excitation, followed by the formation of a Dewar-type isomer or spiroazacyclopropene (azirine). Other isomeric benzothiazole intermediates may not be formed, as these have higher energies than those of the

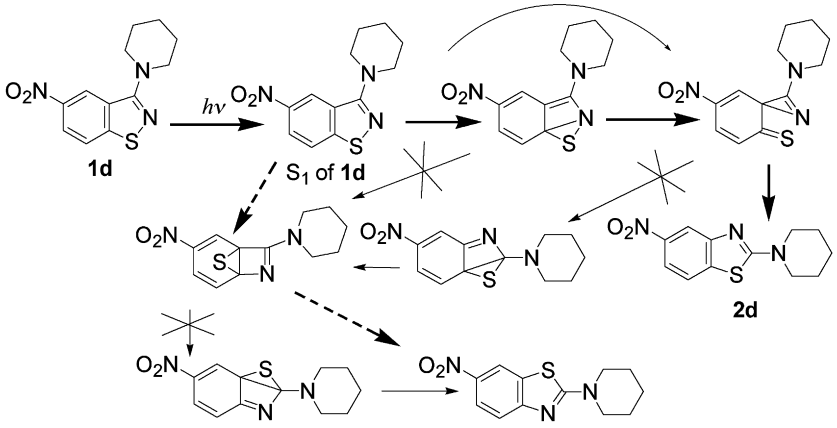

Fig. 5. Plausible mechanism of the isomerization of **1d**.

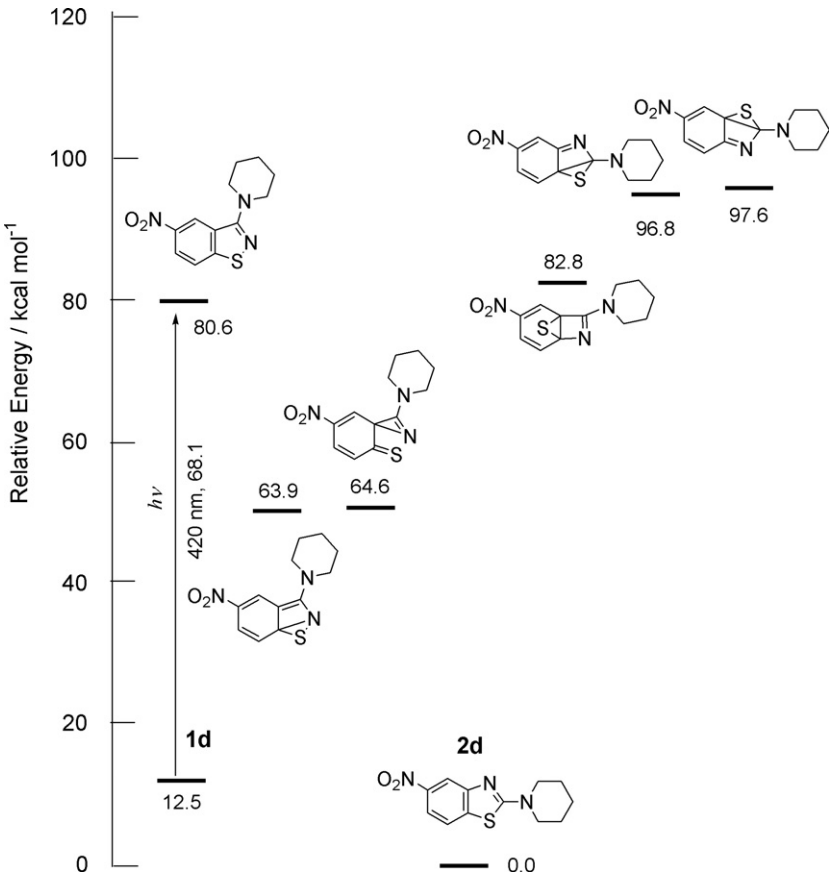

Fig. 6. Relative energies calculated by DFT method for the reactant, product, and intermediates considered in the photoisomerization of **1d**.

Dewar isomer and azirine. The ground state energy of **2d** is calculated to be 12.6 kcal mol^{-1} lower than **1d**.[16]

Figure 1 summarizes the substituent effects on the photochemistry of the benzisothiazole derivatives examined in this study. The reaction between nitrobenzisothiazole to nitrobenzothiazole was not reversible, however, the isomerization mechanism of the 3-piperidino-derivative (**1d**, R = piperidino) was elucidated, as shown in Figure 5. This study thus revealed the usefulness and limitations of nitrobenzisothiazole to nitrobenzothiazole photochemistry.

Acknowledgments

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9. 5-Nitro-1,2-benzisothiazole **1a**. 3-cyano-5-nitro-1,2-benzisothiazole **1b**, and 3-methoxy-5-nitro-1,2-benzisothiazole **1c**, were synthesized by the methods reported in Ref. 17. 3-Amino-5-nitro-1,2-benzisothiazole **1f** was prepared by the methods reported in Ref. 18.
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12. **3a** was identified by comparison of spectral data to those of standard sample prepared by the method reported; Hartmans, H.M.A., *Rec. Trav. Chim.*, **1946**, 65, 468. ^{1}H NMR 400 MHz ($CDCl_3$/DMSO-d_6 was used because of low solubility) $\delta = 8.52$ (1H, d, $J = 2.2$ Hz), 8.41 (1H, dd, $J = 8.0$, 2.2 Hz,), 8.32 (1H, d, $J = 7.6$ Hz), IR (KBr) 2240 cm^{-1} (CN). Mp 138–139 °C. Unfortunately, M^+ signal could not be detected by FAB-MS using NBA (*m*-nitrobenzyl alcohol) matrix.
13. Preparation of 3-piperidiono-5-nitro-1,2-benzisothiazole, **1d**. A mixture of piperidine (6 ml, 101 mmol) and 3-chloro-5-nitrobenziso-

thiazole (310 mg, 1.4 mmol) prepared by the method reported in Ref. 16 was refluxed overnight, and removed excess piperidine under vacuum. Purification by crystallization (dichloromethane:hexane) after the column chromatography gave orange crystals, 121 mg, yield 32.8%. ^{1}H NMR 400 MHz ($CDCl_3$), $\delta = 8.79$ (1H, d, $J = 2.4$ Hz, H4), 8.30 (1H, dd, $J = 9.0$, 2.0 Hz, H6), 7.89 (1H, d, $J = 9.0$ Hz, H7), 3.53 (4H, t, $J = 5.4$ Hz, –NCH_2–), 1.86–1.84 (4H, m, –CH_2–), 1.74–1.71 (2H, m, –CH_2–). GC–MS *m*/*z*: 263. Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.56; H, 4.83; N, 16.03. Compound **1e** was prepared by a similar method with **1d**, 310 mg reactant gave, 311 mg, 84.4%. ^{1}H NMR 400 MHz ($CDCl_3$), $\delta = 8.60$ (1H, d, $J = 1.9$ Hz, H4), 8.31 (1H, dd, $J = 9.0$, 1.9 Hz, H6), 7.87 (1H, d, $J = 9.0$ Hz, H7), 5.14 (1H, br s, NH), 3.63–3.58 (2H, m, –NCH_2–), 1.78–1.70 (2H, quin, $J = 7.3$ Hz, –CH_2–), 1.53–1.44 (2H, sex, $J =$ 7.3 Hz, –CH_2–), 1.00 (3H, t, $J = 7.3$ Hz, –CH_3). GC–MS *m*/*z*: 251. Anal. Calcd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72. Found: C, 52.60; H, 5.23; N, 16.56.

14. Preparation of 3-piperidiono-5-nitro-1,2-benzothiazole, **2d**. A mixture of piperidine (4 ml, 68 mmol) and 2-chloro-5-nitro-1,3-benzothiazole (420 mg, 1.9 mmol) prepared by the method reported[19] was refluxed 3 h, and removed excess piperidine under vacuum. Purification by crystallization (CH_2Cl_2/hexane) after the column chromatography gave yellow crystals, 408 mg, yield 81.5%. ^{1}H NMR 400 MHz ($CDCl_3$) $\delta = 8.31$ (1H, d, $J = 2.2$ Hz, H4), 7.91 (1H, dd, $J = 8.6$, 2.2 Hz, H6), 7.65 (1H d, $J = 8.6$ Hz, H7), 3.65 (4H, m, NCH_2–), 1.73 (6H, m, –CH_2–). GC–MS *m*/*z*: 263. Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.66; H, 4.88; N, 15.75. Compound **2e** was prepared by a similar method with **2d**, 310 mg reactant gave 207 mg **2e**, 58.8%. ^{1}H NMR 400 MHz ($CDCl_3$) $\delta = 8.32$ (1H, d, $J = 2.2$ Hz, H4), 7.96 (1H, dd, $J = 9.0$, 2.2 Hz, H6), 7.67 (1H, d, $J = 9.0$ Hz, H7), 5.91 (1H, br s, NH), 3.48–3.44 (2H, t, $J = 7.3$ Hz, NCH_2–), 1.75–1.67 (2H, quin, $J = 7.3$ Hz, –CH_2–), 1.51–1.42 (2H, qt, $J = 7.3$, 7.3 Hz –CH_2–), 0.98 (3H, t, $J = 7.3$ Hz, –CH_3). GC–MS, *m*/*z*: 251. Anal. Calcd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21; N, 16.72. Found: C, 52.54; H, 5.15; N, 16.53.
15. **3f** Yield 81%; ^{1}H NMR 400 MHz (DMSO-d_6) $\delta = 6.87$ (1H, d, $J = 9.4$ Hz), 7.50 (2H, br s), 8.13 (1H, dd, $J = 2.7$ Hz, 9.4 Hz), 8.39 (1H, d, $J = 2.7$ Hz), IR (KBr) 2260 (CN). Manh, G. T.; Bakkali, H.; Maingot, L.; Pipelier, M.; Joshi, U.; Pradere, J. P.; Sabelle, S.; Tuloup, R.; Dubreuil, D. *Tetrahedron Lett.* **2004**, *45*(30), 5913–5916.
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