Ring-Enlargement Reaction of 3-Alkyl-2-(*N*-cyanoimino)thiazolidine 1-Oxide: Formation of Novel 5,6-Dihydro-2*H*-1,2,4-thiadiazin-3(4*H*)-one Derivatives

Tetsuaki Tanaka,[a] Wakako Takase,[a] Xie Fang,[a] Tsutomu Azuma,[a] Shuji Uchida,[b] Toshimasa Ishida,[c] Yasuko In,[c] and Chuzo Iwata[a,*]

Faculty of Pharmaceutical Sciences, Osaka University,[a] 1-6 Yamadaoka, Suita, Osaka 565, Japan, Faculty of Pharmaceutical Sciences, Setsunan University,[b] 45-1 Nagaotogecho, Hirakata, Osaka 573-01, Japan, Osaka University of Pharmaceutical Sciences,[c] 4-20-1 Nasahara, Takatsuku, Osaka 569-11, Japan

Fax 81 6 879 8214; E-mail iwata@phs.osaka-u.ac.jp

Received 19 November 1996

Abstract: The reaction of 3-alkyl-2-(*N*-cyanoimino)thiazolidine 1-oxides (**4**) with trifluoroacetic anhydride resulted in a ring-enlargement reaction to give novel 5,6-dihydro-2*H*-1,2,4-thiadiazin-3(4*H*)-one derivatives (**6**).

In our continuous investigation of the reactivity of 2-(*N*-cyanoimino)thiazolidine[1] (**1** : Y = H) derivatives, several interesting reactions toward nucleophiles have been developed.[2] However, there are very few reactions toward electrophiles.[3] We are interested in reactions in which the sulfur atom participates directly, especially ring-transformation reactions. The attempted formation of sulfonium salt **2** or ylide[4] **3** by reaction of the sulfur atom with several alkylating agents or carbene species such as diazomalonate or diazoacetate has failed. These results were contrary to our expectations from the considerably large HOMO coefficient value at the sulfur atom.[3] However, the oxidation reaction with *m*-CPBA occurred selectively on the sulfur atom to give a sulfoxide **4** along with a sulfone **5**[5] (Scheme 1). Although the sulfoxide itself is an attractive functionality, that conjugated with a cyanoimino group is also interesting, and the reactivity of such a functional group has not yet been investigated. Since the electrophilicity of the imino carbon (C2) would be increased more than that of the parent compound, the S-C(2) bond of **4** is expected to become more reactive. Therefore, we investigated the reactivity of this new functional system under Pummerer[6]-type reaction conditions as a typical reaction for sulfoxides. In this paper, we report the formation of unprecedented 5,6-dihydro-2*H*-1,2,4-thiadiazin-3(4*H*)-one derivatives (**6**) by the reaction of 3-alkyl-2-(*N*-cyanoimino)thiazolidine 1-oxides (**4**) with trifluoroacetic anhydride (TFAA), and a few reactions of **6**.

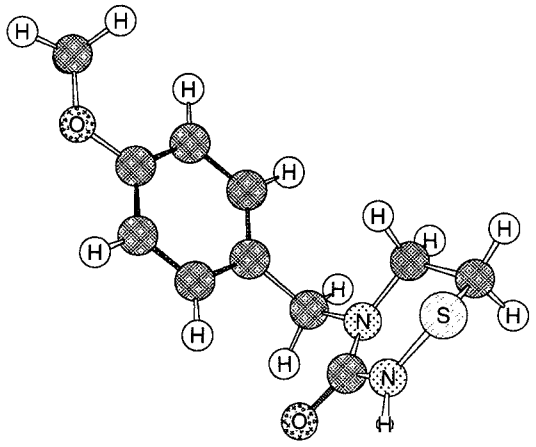
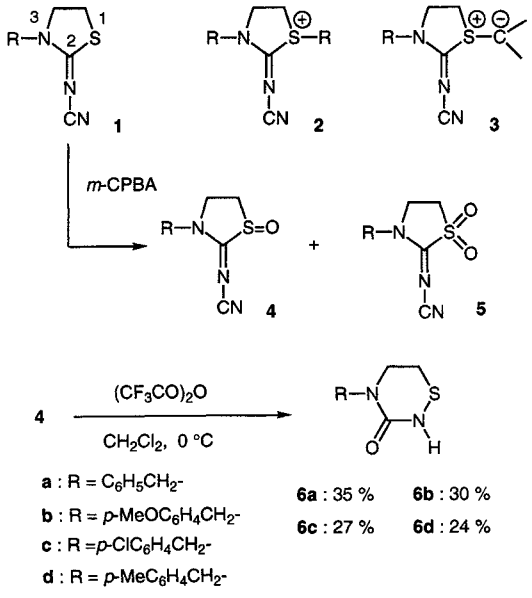


Fig. 1. Crystal structure of **6b** drawn by Chem 3D

The reaction of 3-benzyl-2-(*N*-cyanoimino)thiazolidine 1-oxide (**4a**) with TFAA proceeded smoothly at 0 °C in dichloromethane. The main product did not exhibit a nitrile band in its IR spectrum. It was apparent that this reaction was not a normal Pummerer-type reaction.[7] The structure of 4-benzyl-2*H*-1,2,4-thiadiazin-3(4*H*)-one (**6a**) was based on elemental and spectral analyses.[8] It was finally confirmed by an X-ray crystallographic analysis of **6b** (Fig. 1).[9] Two other substituted benzyl compounds, **6c** and **6d**, were also obtained in similar yields (Scheme 1). Monocyclic 1,2,4-thiadiazin-3-one derivatives are very uncommon, and only a few such compounds have been reported.[10] Moreover, the sulfur atom in each previously reported compound is in a sulfone state, and there has been no report of a compound bearing a divalent sulfur. Thus, this is the first synthesis for this type of compound. The yields are fairly good as a crude product, but the isolation yield is not high due to decomposition upon purification. Although the proper isolation method remains to be determined, this may lead to the discovery of new biologically active compounds related to diuretic and antihypertensive benzothiadiazine derivatives.[10f,11] Therefore, not only the reaction mechanism, but also the reactivity of this novel compound are of interest.

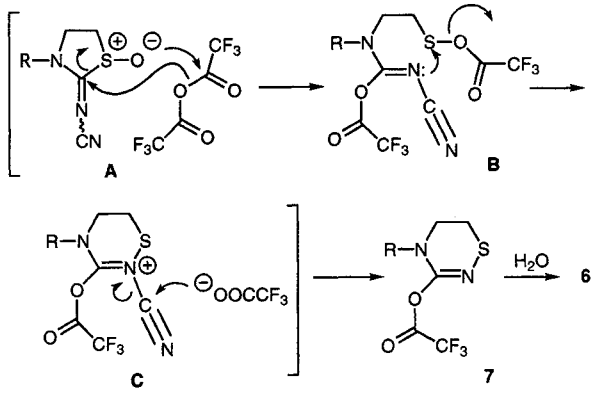


Scheme 1

The reaction mechanism is speculated to be as follows (Scheme 2). Beginning with the addition of a trifluoroacetyl group to the sulfinyl oxygen of **4**, the resulting trifluoroacetoxy anion concertedly attacks the highly electrophilic imino carbon (C2), and C(2)-S bond cleavage then takes place (**A**→**B**). Since the concurrently formed functional group, C-S-OCOCF$_3$ of **B**, has the same structure as a mixed anhydride composed of a sulfenic acid and trifluoroacetic acid, it is so highly reactive that the S-O bond is easily cleaved. Next, the imino nitrogen intramolecularly attacks the electron-deficient sulfur atom to cleave the S-O bond, thereby creating a thiadiazine skeleton, which is followed by elimination of the nitrile group (**B**→**C**→**7**). The resulting enol trifluoroacetate (**7**) is readily hydrolyzed upon aqueous workup to give **6**. Although **7** was so unstable that it was decomposed in $CDCl_3$ after a few hours, it could be detected spectroscopically by quick measurement of the ^{1}H-NMR, IR, and Mass spectra of the crude product [8] after careful evaporation of volatile materials from the reaction mixture. Furthermore, it could also be chemically detected by reacting it with benzylamine to give *N*-benzyl trifluoroacetamide in addition to **6**.

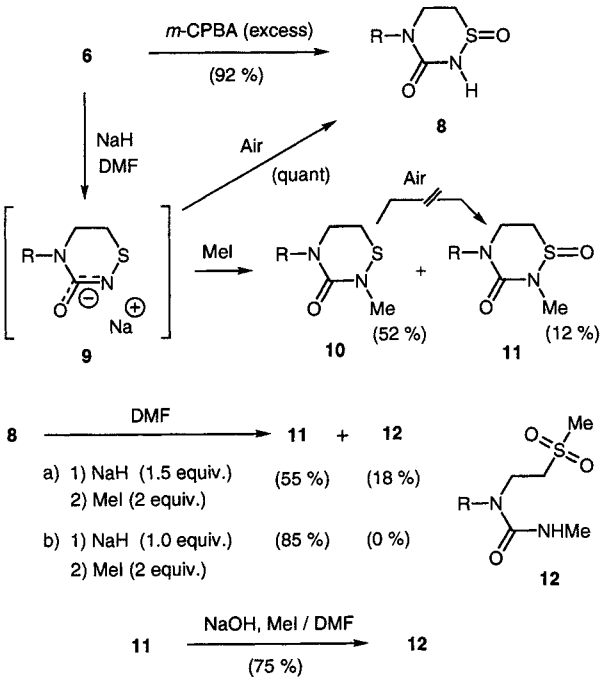
Next, we investigated the reactivity of these novel compounds **6** to prepare various derivatives (Scheme 3). To our surprise, oxidation of **6** with *m*-CPBA gave only sulfoxide **8** and not sulfone compounds, even with excess reagent for a prolonged reaction time.[12] This is a curious

result because the sulfur atoms of the known compounds are only in the sulfone state.[10]



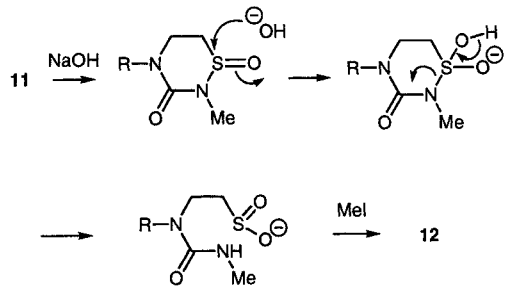
Scheme 2

To introduce various substituents at *N*(2), a methylation reaction was tried. Upon treatment of the sodium salt **9**, prepared from **6** and NaH (1.5 equiv.) in DMF, with MeI (2.0 equiv.), an unpredicted *N*-Me-sulfoxide **11**[8] (12 %) was obtained along with the anticipated *N*-Me derivative **10**[8] (52 %). Since compound **10** was not oxidized to **11** by air in DMF solution, the sulfoxide **11** should be obtained *via* methylation of the sodium salt of the sulfoxide **8**, which would be generated through oxidation of the anion **9** by the dissolved oxygen in DMF. This notion may be supported by the result that the sulfoxide **8** was obtained in a quantitative yield with stirring of the DMF solution of **9** in air without MeI. The ambident nature of the anion **9** may play a role in the competitive *N*-methylation and oxidation prior to methylation.



Scheme 3

We next attempted the methylation reaction of **8**. Treatment of **8** with NaH (1.5 equiv.) followed by MeI (2.0 equiv.) in DMF (conditions a) gave **11** (55 %) and a sulfone **12**[8] (18 %). The mechanism for the formation of **12** was also interesting. Sulfone **12** was not observed in the reaction mixture and the use of 1 equiv. of NaH (conditions b) gave **11** (85 %), but no sulfone **12**, even in the presence of excess MeI. Sulfone **12** was apparently produced during aqueous workup with the use of more than 1 equiv. of NaH. This means that a ring-opening reaction of **11** and methylation of the sulfur atom occurred concurrently during aqueous workup in the presence of excess base and MeI. In fact, treatment of **11** with aqueous sodium hydroxide, which would be generated during aqueous workup, in DMF in the presence of MeI gave **12** in good yield (Scheme 3). It was clear that sulfone **12** was produced *via* hydrolysis of **11** followed by methylation of a resulting sulfinate anion[13] with excess MeI, as shown in Scheme 4.



Scheme 4

As described above, the reaction of 3-alkyl-2-(*N*-cyanoimino)thiazolidine 1-oxide (**4**) with TFAA gave novel 4-alkyl-2*H*-1,2,4-thiadiazin-3(4*H*)-one derivatives (**6**) as the result of a ring-expansion reaction, and **6** and its monoxide **8** both showed interesting reactivity. Further investigation of the reactivity of these new compounds is now underway.

Acknowledgment: The authors are grateful to the Ministry of Education, Science, Sports and Culture of Japan for financial support (Grant No. 05671751).

References and Notes

(1) Neidlein, R.; Reuter, H. *Arch. Pharm.* **1972**, *305*, 731-737.

(2) Iwata, C.; Watanabe, M.; Okamoto, S.; Fujimoto, M.; Sakae, M.; Katsurada, M.; Imanishi, T. *Heterocycles* **1988**, *27*, 323-326; Iwata, C.; Watanabe, M.; Okamoto, S.; Fujimoto, M.; Sakae, M.; Katsurada, M.; Imanishi, T. *Synthesis* **1988**, 261-262; Iwata, C.; Fujimoto, M.; Okamoto, S.; Nishihara, C.; Sakae, M.; Katsurada, M.; Watanabe, M.; Kawakami, T.; Tanaka, T.; Imanishi, T. *Heterocycles* **1990**, *31*, 1601-1604; Iwata, C.; Fujimoto, M.; Watanabe, M.; Kawakami, T.; Maeda, N.; Imanishi, T.; Tanaka, T. *Heterocycles* **1991**, *32*, 2471-2478; Iwata, C.; Fujimoto, M.; Watanabe, M.; Kawakami, T.; Nakamoto, Y.; Sakae, M.; Katsurada, M.; Imanishi, T.; Tanaka, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1379-1381; Tanaka, T.; Watanabe, M.; Nakamoto, Y.; Okuno, K.; Maekawa, K.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1994**, 2301-2302; Tanaka, T.; Nakamoto, Y.; Maekawa, K.; Watanabe, M.; Nishihara, C.; Iwata, C. *Heterocycles* **1996**, *42*, 265-272.

(3) Iwata, C.; Kawakami, T.; Fujimoto, M.; Nakamoto, Y.; Tanaka, T. *Heterocycles* **1993**, *36*, 55-62.

(4) For a review of sulfur ylides, see Trost, B. M.; Melvin Jr., L. S. "Sulfur Ylides", Academic Press, New York, 1975.

(5) Yields of sulfoxides (**4**) and sulfones (**5**): **4a** (47 %), **5a** (35 %); **4b** (61 %), **5b** (30 %); **4c** (60 %), **5c** (27 %); **4d** (56 %), **5d** (36 %).

(6) For reviews, see Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717-1760; Marino, J. P. *Pure Appl. Chem.* **1993**, *65*, 667-674; De Lucchi, O.; Miotti, U.; Modena, G. "Organic Reactions," ed. by Paquette, L. A. John Wiley & Sons, Inc., New York, 1991, Vol. 40, pp. 157-405; Kennedy, M.; McKervey, M. A. "Comprehensive Organic Synthesis", ed. by Trost, B. M.; Fleming, I. Pergamon Press, Oxford, 1991, Vol. 7, pp. 193-206.

(7) *Cf.* Tokitoh, N.; Igarashi, Y.; Ando, W. *Tetrahedron Lett.* **1987**, *28*, 5903-5906; McIntosh, J. M.; Leavitt, R. K. *Can. J. Chem.* **1985**, *63*, 3313-3316.

(8) Satisfactory elemental analyses and/or high resolution mass spectra were obtained for all new compounds except for **7**. Selected physical and spectroscopic data for **6a**: mp 145-146 °C; FT-IR cm^{-1}: 3135, 1625; MS *m/z*: 208 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.03 (2H, t-like), 3.63 (2H, t-like), 4.61 (2H, s), 4.94 (1H, m), 7.22-7.40 (5H, m). For **6b**: mp 148-150 °C; FT-IR cm^{-1}: 3140, 1628; MS *m/z*: 238 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.00 (2H, t-like), 3.62 (2H, t-like), 3.80 (3H, s), 4.54 (2H, s), 4.72 (1H, br), 6.84-7.27 (4H, AA'BB'). **7a** (crude): FT-IR cm^{-1}: 1770, 1683, 1221, 1161; MS *m/z*: 304 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.34 (2H, t-like), 3.61 (2H, t-like), 4.72 (2H, s), 7.20-7.45 (5H, m). **10c:** mp 69 °C; FT-IR cm^{-1}: 1628; MS *m/z*: 256 (M^+), 258 (M^++2); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.07 (2H, t-like), 3.11 (3H, s), 3.59 (2H, t-like), 4.56 (2H, s), 7.20-7.24 (4H, m). **11a:** colorless oil; FT-IR cm^{-1}: 1655, 1094; MS *m/z*: 238 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.83 (1H, ddd), 2.99 (1H, ddd), 3.31 (3H, s), 3.45 (1H, ddd), 4.28 (1H, ddd), 4.44 (1H, d), 4.88 (1H, d), 7.26-7.36 (5H, m). **12a:** colorless oil; FT-IR cm^{-1}: 3425-3367, 1635; MS *m/z*: 270 (M^+); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.77 (3H, d), 2.94 (3H, s), 3.31 (2H, t), 3.82 (2H, t), 4.49 (2H, s), 4.60 (1H, br), 7.18-7.42 (5H, m).

(9) Crystal data for **6b**: $C_{11}H_{14}N_2O_2S$, M = 238.305, triclinic, space group P1, Cell constant *a* (Å) = 9.363(1), *b* (Å) = 11.060(1), *c* (Å) = 6.208(1), α (°) = 96.82(1)°, β (°) = 102.23(1)°, γ (°) = 66.82(1)°, Volume ($Å^3$) = 577.1(1), Z = 2, Dx = 1.371 g cm^{-3}, F(000) = 252, μ(Cu-Kα) (mm^{-1}) = 2.40, R_F = 0.072, R_{WF} = 0.229.

(10) a) Andreasch, R. *Monatsh. Chem.* **1883**, *4*, 131-148; b) Wolfbauer, H. *Monatsh. Chem.* **1904**, *25*, 682-686; c) Hoogenboom, B. E.; Abbott, R.; Locatell Jr., L.; Hinman, R. L. *J. Org. Chem.* **1959**, *24*, 1983-1986; d) Hasegawa, K.; Hirooka, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1893-1896. For a review of thiadiazine derivatives, see e) Lawson, A.; Tinkler, R. B. *Chem. Rev.* **1970**, *70*, 593-618; f) Busby, R. E. *Advances in Heterocyclic Chemistry*; Katrizky, A. R., Ed.; Academic Press; New York; 1990; Vol. 50; pp. 255-320.

(11) Novello, F. C.; Sprague, J. M. *J. Am. chem. Soc.* **1957**, *79*, 2028-2029; Rubin, A. A.; Roth, F. E.; Winbury, M. M.; Topliss, J. G.; Sherlock, M. H.; Sperber, N.; Black, J. *Science*, **1961**, *133*, 2067; Landquist, J. K. *Comprehensive Organic Chemistry*; Barton, D.; Ollis, W. D. Ed.; Pergamon Press; Oxford; 1979; Vol. 4; p.1114-1121.

(12) We later found that *N*-Me-sulfoxide (**11**) was easily oxidized to a sulfone by *m*-CPBA in good yield.

(13) *S*-Alkylation has been noted previously in the alkylation reaction of sulfinate anion with a soft alkylating agent such as MeI to give a sulfone instead of an ester. See, Meek, J. S.; Fowler, J. S. *J. Org. Chem.* **1968**, *33*, 3422-3424.