Stereoselective Synthesis of 4,5-Dihydro-1,3-thiazole and 4*H*-5,6-Dihydro-1,3-thiazine Derivatives

Nobuyuki Yasuda, Michinori Karikomi,† and Takashi Toda*†
Tokyo Tanabe Co., Ltd. Research Laboratories, R&D Division, Akabanekita, Kita-ku, Tokyo 115
†*Department of Applied Chemistry, Faculty of Engineering, Utsunomiya University, Ishiicho, Utsunomiya 321*

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4-Bromomethyl-4,5-dihydro-1,3-thiazoles and 5-bromo-4*H*-5,6-dihydro-1,3-thiazines were synthesized by intramolecular cyclization of allylthioimidates by the reaction with *N*-bromosuccinimide (NBS) or bromine in dichloromethane at room temperature.

Recently, many 4,5-dihydro-1,3-thiazole derivatives have been found in nature,[1] and those compounds show interesting biological activities.[2] Also, some 4*H*-5,6-dihydro-1,3-thiazine derivatives are known as pharmaceuticals and to have physiologically active feature.[3,4] Several reports have been appeared on the syntheses of those compounds.[4,5]

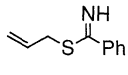
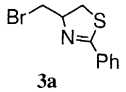
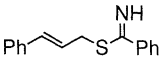
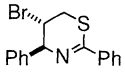
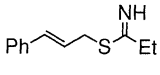
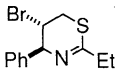
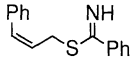
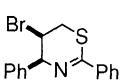
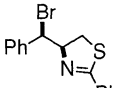
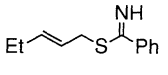
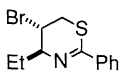
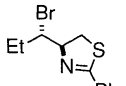
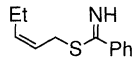
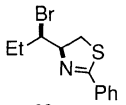
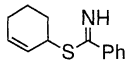
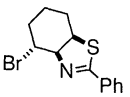
Intramolecular iodo-cyclization reactions have been applied for synthesis of analogous heterocyclic compounds; typicals are iodo-lactonization,[6] iodo-lactamization,[7] iodo-carbamation,[8] and so far. Appropriate allyl- or homo-allyl compounds are choice of the starting substances for those intramolecular cyclization reactions. For example, allyl- and homoallyl-thiourea derivatives were reported to give corresponding thiazole and thiazine derivatives, respectively, by treatment with iodine.[9] Similar reactions have been reported that cyclization of allylimidates gave oxazole and oxazine derivatives with *N*-iodosuccinimide (NIS).[10]

We applied this methodology for the synthesis of 4,5-dihydro-1,3-thiazole and 4*H*-5,6-dihydro-1,3-thiazine derivatives. Allylthioimidates **1** were chosen for the starting substrates which were readily prepared from corresponding allyl alcohols by the known procedure.[11] The reaction of the (*E*)-cinnamylthioimidates **1b** with NIS gave iodothiazoline and iodothiazine derivatives, but the yields were low and formed iodine derivatives were fairly unstable. Investigation by NMR spectra revealed that those iodoine derivatives disappered by the subsequent reaction.[12a] So that, we chose NBS and bromine as the halogenation reagents. The results are shown in Table 1.[13]

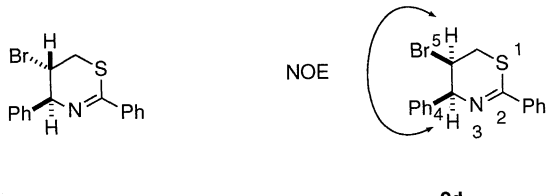
The cyclization of allylbenzothioimidate **1a** with NBS in dichloromethane at room temperature gave only 4-bromomethyl-2-phenyl-4,5-dihydrothiazole **3a** (entry 1). On the other hand, (*E*)-cinnamyl derivatives **1b** and **1c** with NBS or bromine gave *trans*-thiazine derivatives **2b** and **2c** (entry 2-4). However, the reaction of (*E*)-2-penten-1-yl-benzothioimidate **1e** afforded as the mixture of *trans*-thiazine **2e** and *anti*-thiazole **3e** in 50 : 50 ratio (entry 6).[14] (*Z*)-Allylic derivatives **1d**, **1f**, and **1g** gave mainly *syn*-thiazoles **3d**, **3f**, and **3g** (entry 5,7,8, and 9). The yields of entry 5 and 6 were low, because separation and purification of the products were difficult, and some *trans*-thiazines **2** are unstable.[12b]

The stereochemistry of **2** and **3** is predictable on the basis of mechanistic considerations. Since the electrophilic addition to olefins occurs antiperiplanar mode, cyclization of (*E*)-olefins **1** gave *trans*-thiazines **2** and/or *anti*-thiazoles **3**, and (*Z*)-olefins **1** gave *cis*-thiazines **2** and/or *syn*-thiazoles **3**, respectively. These predictions were supported by NOE experiment. For example,

Table 1. Synthesis of 1,3-Thiazine and 1,3-Thiazole Derivatives

Entry	Substrates	Reagents	Yields[a] (relative ratio)[b]	
1	 **1a**	NBS		 **3a** 77% (100)
2	 **1b**	NBS	 **2b** 53% (100)	
3	**1b**	Br_2	**2b**[c] 78% (100)	
4	 **1c**	NBS	 **2c** 53% (100)	
5	 **1d**	NBS	 **2d** 10% (20)	 **3d** 23% (80)
6	 **1e**	NBS	 **2e** 15% (50)	 **3e** 23% (50)
7	 **1f**	NBS		 **3f** 55% (100)
8	**1f**	Br_2		**3f** 54%(100)
9	 **1g**	NBS		 **3g** 72%(100)

[a]The yields indicate the isolated products after usual workup. [b]Relative ratio was estimated by ^{1}H NMR before purification. [c]Obtained as HBr salt.



2b **2d**

Figure 1.

the NOE between 4-H and 5-H of *cis*-**2d** was observed, but not for *trans*-**2b** (Figure 1).

Similarly, stereochemistry of *anti*-thiazole **3e** and *syn*-thiazole **3f** was determined by the measurement of NOE of the corresponding *exo* olefinic compounds **4e** and **4f** which derived from **3e** and **3f** by dehydrobromination reaction with DBU *via trans* elimination, respectively (Figure 2).

4e **4f**

Figure 2.

This result shows cyclization of (*E*)-olefins **1** gave *anti*-thiazoles **3** and the reaction of (*Z*)-olefins **1** afforded *syn*-thiazoles **3**.

As a conclusion, we have found the stereo selective synthetic method of 5-bromo-4*H*-5,6-dihydro-1,3-thiazines **2** and 4-bromomethyl-4,5-dihydro-1,3-thiazole **3** under mild conditions.

References and Notes

1 R. Jansen, B. Kunze, H. Reichenbach, E. Jurkiewicz, G. Hunsmann, and G. Höfle, *Liebigs Ann. Chem.*, **1992**, 357; K. Shindo, A. Takenaka, T. Noguchi, Y. Hayakawa, and H. Seto, *J. Antibiotics.*, **42**, 1526 (1989); M. Aoki, T. Ohtsuka, M. Yamada, Y. Ohba, H. Yoshizaki, H. Yasuno, T. Sano, J. Watanabe, and K. Yokose, *J. Antibiotics.*, **44**, 582 (1991).

2 H. Seto and T. Noguchi, *Jpn. Kokai*, 181998 (1988).

3 A. G. Tarasenko, S. V. Krasavtseva, L. F. Dement'eva, and V. M. Fedoseev, *Mekh. Prir. Modif. Radiochuvstvitel'nosti*, **3**, 102 (1977); *Chem. Abstr.*, **93**, 442r (1980).

4 B. J. Dominique, C. Claude, G. Claude, and P. Philippe, *Eur. Pat. Appl.* EP 367678 (1990).

5 S. E. Tkachenko, A. N. Pushin, and V. M. Fedoseev, *Zh. Obshch. Khim.*, **57**, 2400 (1987); *Chem. Abstr.*, **109**, 6469a (1988).

6 E. E. van Tamelen and M. Shamma, *J. Am. Chem. Soc.*, **76**, 2315 (1954); J. Klein, *J. Am. Chem. Soc.*, **81**, 3611 (1959); H. O. House, R. G. Carlson, and H. Babad, *J. Org. Chem.*, **28**, 3359 (1963).

7 S. Knapp and A. T. Levorse, *J. Org. Chem.*, **53**, 4006 (1988).

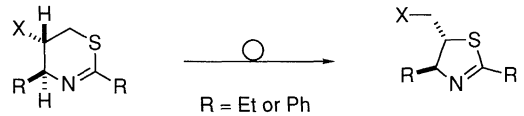
8 M. Hirama, M. Iwashita, Y. Yamazaki, and S. Ito, *Tetrahedron Lett.*, **25**, 4963 (1984); S. Kobayashi, T. Isobe, and M. Ohno, *Tetrahedron Lett.*, **25**, 5079 (1984).

9 P. I. Creeke and J. M. Mellor, *Tetrahedron Lett.*, **30**, 4435 (1989).

10 A. Bongini, G. Cardillo, M. Orena, S. Sandri, and C. Tomasini, *J. Org. Chem.*, **51**, 4905 (1986).

11 S. R. Sandler and W. Karo, in "Organic Functional Group Preparations," Academic (1972), Vol. III, Chap. 8, p. 268.

12 a) The rearrangement reaction has occured from iodo-thiazine **2** to a thiazole derivative **4** (not **3** type). The iodo-thiazine **2** was unstable and only crude product **4** was observed in ^{1}H NMR. b) Thiazole **4** was isolated as pure form. The detail will be reported near future.



2 **4**

13 Spectral data of the typical thiazines **2** are as follow. *trans*-5-bromo-2,4-diphenyl-4*H*-5,6-dihydro-1,3-thiazine **2b**: colorless crystals ; mp 71.0-72.5 °C; IR (KBr) 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.37 (1H, dd, *J* = 13.4, 6.7, H-6), 3.44 (1H, dd, *J* = 13.4, 4.7, H-6), 4.43 (1H, ddd, *J* = 4.3, 6.7, 6.7, H-5), 5.32 (1H, d, *J* = 6.7, H-4), 7.20-7.50 (8H, m, Ph), 7.80-7.90 (2H, m, Ph); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 31.67 (C-6), 46.45 (C-5), 66.97 (C-4), 126.53 (Ph), 127.52 (Ph), 127.83 (Ph), 128.30 (Ph), 128.56 (Ph), 130.85 (Ph), 138.33 (Ph), 140.96 (Ph), 157.31 (C-2); MS (70 eV, rel.intensity) *m/z* 333 (M^+, 8), 331 (M^+, 8), 252 (45), 225 (38), 193 (14), 149 (100).
cis-5-bromo-2,4-diphenyl-4*H*-5,6-dihydro-1,3-thiazine **2d**: paleyellow crystals ; mp 99.0-101.0 °C; IR (KBr) 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.45 (1H, dd, *J* = 12.8, 7.3 Hz, H-6), 3.71 (1H, ddd, *J* = 12.8, 3.7, 1.2 Hz, H-6), 4.70 (1H, ddd, *J* = 7.3, 3.7, 3.1 Hz, H-6), 5.10 (1H, d, *J* = 3.1, 1.2 Hz, H-4), 7.20-7.50 (8H, m, Ph), 7.80-7.95 (2H, m, Ph); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 32.74 (C-6), 46.09 (C-5), 62.97 (C-4), 126.43 (Ph), 127.79 (Ph), 128.03 (Ph), 128.32 (Ph), 130.83 (Ph), 138.43 (Ph), 139.29 (Ph), 158.05 (C-2); MS (70 eV, rel.intensity) *m/z* 333 (M^+, 37), 331 (M^+, 37), 252 (14), 225 (100).

14 The main chain is drawn in zig-zag fashion, and two substituted heteroatoms on the same side are designed "*syn*", and those which are not, "*anti*". The definition of stereochemisty, see S. Masamune, S. A. Ali, L. Snitman, and D. S. Garvey, *Angew. Chem. Int. Ed. Engl.*, **19**, 557 (1980); S. Masamune, T. Kaiho, and D. S. Garvey, *J. Am. Chem. Soc.*, **104**, 5521 (1982).