Iodo-cyclization of *N*-Homoallyl Thioamides Leading to 2,4-Diaryl-5,6-dihydro-4*H*-1,3-thiazines

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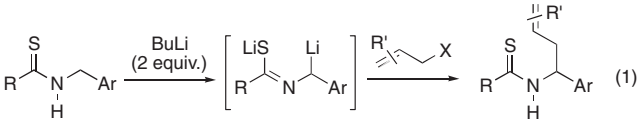
Iodo-cyclization of *N*-homoallyl thioamides was carried out in the presence of Et_3N to form 2,4-diaryl-5,6-dihydro-4*H*-1,3-thiazines in good to high yields. The reaction of thioamides bearing 1-naphthyl or 2-methoxyphenyl group at the carbon atom adjacent to the nitrogen atom showed high diastereoselectivity. The relative stereochemistry was confirmed by X-ray molecular structure analyses. The obtained thiazines were converted to 6-alkylidene-1,3-thiazines by treating with pyrrolidine.

Because of highly broad utility of 5,6-dihydro-2,4-diaryl-4*H*-1,3-thiazines[1,2] as intermediates in the productions of drugs and pesticides, a variety of their synthetic methods have been reported. The retero Diels–Alder reaction of 2-phenyl-1-thia-3-azabuta-1,3-diene and *N*-thioacylformamidines with dienophiles was reported to form 4-amino derivatives.[3] Cyclization of *N*-3-hydroxyalkyl amides and thioamides[4] with Lawesson's reagent and Burgess, reagent has been developed. Bromo-cyclization of allylthioimidates has led to 5-bromo derivatives along with 4,5-dihydro-1,3-thiazoles.[5] Very recently, we have found that the deprotonation of secondary *N*-benzylic thioamides with Bu-Li efficiently gives thioamide dianions and the subsequent allylation selectively takes place at the carbon atom adjacent to the nitrogen atom. (Eq 1).[6]



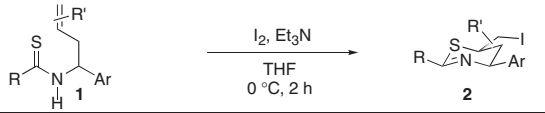
(1)

We report here iodo-cyclization of *N*-homoallyl thioamides obtained by the reaction in Eq 1 leading to 2,4-diaryl-5,6-dihydro-4*H*-1,3-thiazines.[7]

The reaction of *N*-3-butenyl thioamides **1a–1f** with iodine in the presence of Et_3N was carried out with THF as a solvent at 0 °C. The results are shown in Table 1.[8,9] The use of thioamide **1a** gave 1,3-thiazine **2a** in 77% yield with a ratio of 75:25 of two diastereomers (Entry 1). Highly diastereo-selective iodo-cyclization proceeded when thioamides **1b** and **1c**, where 1-naphthyl or 2-methoxyphenyl group was introduced, were employed as a starting material (Entries 2 and 3). The efficiency of the reaction was dependent on the substituents attached to the thiocarbonyl group. The reaction of thioamide having *tert*-butyl group **1d** gave the product **2d** in a reduced yield (Entry 4). Iodo-cyclization of 2-methoxythiobenzamide **1e** did not proceed at all, and **1e** was recovered quantitatively (Entry 5),[10] whereas the reaction of 4-methoxythiobenzamide **1f** proceeded with high efficiency to give the product **2f** with better diastereoselectivity (Entry 6).

A similar iodo-cyclization of thioamides bearing the internal alkenyl or trisubstituted alkenyl group **1g–1j** proceeded smoothly to give the corresponding 1,3-thiazines **2g–2j** (Entries 7–10). The 1,3-thiazines **2g–2j** involving secondary and tertiary iodide structures were also isolated, and the prospective elimination of hydrogen iodide from the products did not take place under the reaction conditions, although they showed reduced stability. Notably, high diastereoselective iodo-cyclization was achieved with *N*-3-methyl-3-butenyl thioamide **1k** to give exclusively **2k** where aryl and iodomethyl groups are located in a *cis*-position. Thioamide possessing cyclohexenyl group **1l** also reacted with iodine in the presence of Et_3N to give two diastereomers **2l** among eight possible isomers. X-Ray molecular structure analyses of **2l** were carried out. Ortep drawings of **2l** are shown in Figure 1.[11,12]

Table 1. Iodo-cyclization of *N*-homoallyl thioamides **1**[a]



Entry	*N*-Homoallyl thioamide			Product Ratio			Yield/%
1	Ar	1a	Ph	2a	75	: 25	77
2		1b	1-naphthyl	2b	>99	: <1	55
3		1c	C_6H_4-OCH_3-2	2c	>99	: <1	83
4	R	1d	*t*-Bu	2d	75	: 25	47
5		1e	C_6H_4-OCH_3-2	2e			0
6		1f	C_6H_4-OCH_3-4	2f	90	: 10	71
7	Ar	1g	1-naphthyl	2g[b]			83
8		1h	C_6H_4-OCH_3-2	2h[c]			92
9	Ar	1i	Ph	2i	78	: 22	45
10		1j	C_6H_4-OCH_3-2	2j	97	: 3	55
11	Ar	1k	C_6H_4-OCH_3-2	2k	93	: 7	91
12	Ar	1l[d]	C_6H_4-OCH_3-2	2l	60	: 40	75

[a]*N*-Homoallyl thioamides **1** reacted with iodine (1.5 equiv.) in the presence of Et_3N (1 equiv.) in THF for 2 h. [b]Three diasteromers were obtained in a ratio of 81:14:5. [c]Three diastereomers were obtained in a ratio of 86:7:7. [d]A mixture of diastereomers (64:36) was used.

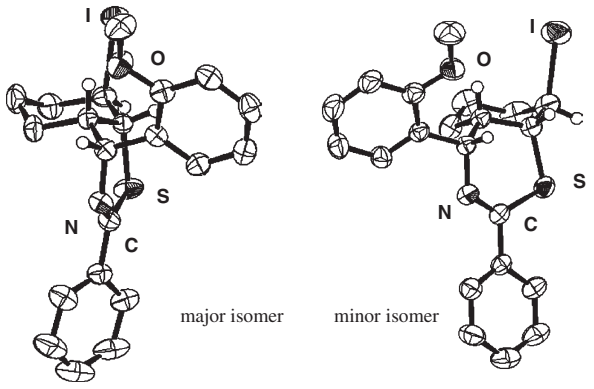
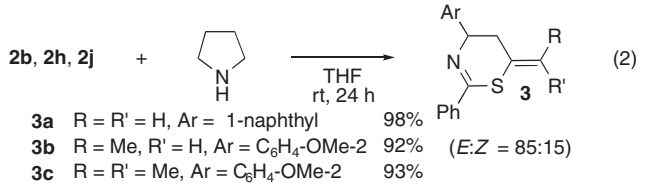


Figure 1. ORTEP drawings of two diastereomers of **21**.

They have indicated that the relative stereochemistry at the carbon atom bearing 2-methoxyphenyl group in the 1,3-thiazine ring is only different. It is ascribed to the use of the diatereomers **1l** as a starting material. Accordingly, iodo-cyclization of **1l** proceeded in a *trans*-manner with high stereoselectivity.

Finally, 1,3-thiazines **2** were converted to 6-alkylidene-1,3-thiazines[13] (Eq 2). Although no elimination occurred with Et_3N as a base, the treatment of **2b**, **2h**, and **2j** with pyrrolidine (3 equiv.) gave the corresponding products **3** in high yields.



In summary, we successfully provided a new synthetic route to 2,4-diaryl-5,6-dihydro-4*H*-1,3-thiazines from *N*-homoallyl thioamides. Further studies on applications of thioamides are in progress.

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References and Notes

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2 For a recent application as starting materials for the synthesis of cepham analogues, see: S. D. Sharma, A. Saluja, and S. Bhaduri, *Indian J. Chem.*, **39b**, 156 (2000).

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7 Iodo-cyclization of *N*-3-butenyl thiourea has been reported to form 2-amino-5,6-dihydro-5-iodoalkyl-4*H*-1,3-thiazine, but the reaction conditions have not been shown: P. I. Creeke and J. M. Mellor, *Tetrahedron Lett.*, **30**, 4435 (1989).

8 Typical experimental procedure for the synthesis of 2,4-diaryl-5,6-dihydro-4*H*-1,3-thiazines **2**: To a THF (10 mL) solution of *N*-homoallyl thioamides **1** (1 mmol) was added iodine (0.38 g, 1.5 mmol), and subsequently Et_3N (1 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. Et_2O (20 mL) was poured onto the reaction mixture, and the organic layer was washed with saturated $Na_2S_2O_3$ aqueous solution and hydrochloric acid (about 5% aqueous solution, 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to give **2**.

9 Representative spectroscopic data: **2c** ^{1}H NMR (400 MHz) $\delta = 1.17$ (dt, $J = 13.2$, 11.0 Hz, 1H), 2.62 (dt, $J = 13.2$, 2.7 Hz, 1H), 3.27 (dd, $J = 9.7$, 6.9 Hz, 1H), 3.33 (dd, $J = 9.7$, 6.9 Hz, 1H), 3.84–3.90 (m, 4H), 5.01 (dd, $J = 11.0$, 2.7 Hz, 1H), 6.91–7.03 (m, 2H), 7.25–7.29 (m, 1H), 7.37–7.49 (m, 4H, Ar), 7.92–7.95 (m, 2H); ^{13}C NMR (100 MHz) $\delta = 9.90$, 35.6, 43.1, 55.4, 57.6, 110.3, 120.9, 126.6, 127.8, 128.0, 128.3, 130.6, 132.5, 138.5, 156.1, 158.7; MS *m/z*: 423 (M^+); Anal. Calcd for $C_{18}H_{18}INOS$: C, 51.07; H, 4.29; N 3.31. Found: C, 50.91; H, 4.29; N, 3.28%; **2j** ^{1}H NMR (400 MHz) δ 1.32 (dt, $J = 13.2$, 11.7 Hz, 1H), 2.00 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.70 (ddd, $J = 13.2$, 3.9, 2.4 Hz, 1H), 3.78 (dd, $J = 11.7$, 3.9 Hz, 1H), 3.89 (s, 3H), 4.98 (dd, $J = 10.8$, 2.4 Hz, 1H), 6.93 (d, $J = 7.9$ Hz, 1H), 7.04 (t, $J = 7.3$ Hz, 1H), 7.28 (dt, $J = 7.8$, 1.9 Hz, 1H), 7.37–7.44 (m, 3H), 7.57 (dd, $J = 7.8$, 2.0 Hz, 1H), 7.96–7.99 (m, 2H); ^{13}C NMR (100 MHz) δ 33.6, 33.8, 35.1, 52.9, 55.4, 57.4, 57.9, 110.3, 120.9, 126.7, 126.8, 127.9, 128.3, 130.5, 132.7, 138.7, 156.1, 159.7; MS *m/z* 451 (M^+); Anal. Calcd for $C_{20}H_{22}INOS$: C, 53.22; H, 4.91, N, 3.10. Found: C, 53.05; H, 4.84; N, 3.08%.

10 Although the result in Entry 5 is not completely understood at the present stage, the interaction of the iodine atom with the oxygen atom of MeO group may be present in the iodonium ion intermediate.

11 Crystallographic data for major diastereomer **2l**: $C_{21}H_{22}INOS$, M_r 463.38, triclinic, space group $\bar{P}$ (no. 2), $a = 6.5567(6)$, $b = 12.3147(5)$, $c = 12.7989(5)$ Å, $\alpha = 70.26(1)°$, $\beta = 87.42(1)°$, $\gamma = 88.29(19)°$ $V = 971.6(1)$ Å^3, $Z = 2$, $D_{calcd} = 1.584$ g cm^{-3}, $T = 300$ K, $R = 0.047$, $R_w = 0.096$, 7800 reflections ($I > 2\sigma(I)$).

12 Crystallographic data for minor diastereomer **2l**: $C_{21}H_{22}INOS$, fw 463.38, monoclinic, space group $P2_1/n$, $a = 11.922(7)$, $b = 8.298(5)$, $c = 20.26(1)$ Å, $\beta = 101.786(6)°$, $V = 1938(1)$ Å^3, $Z = 4$, $D_{calcd} = 1.588$ g cm^{-3}, $T = 300$ K, $R = 0.064$, $R_w = 0.142$, 4352 reflections ($I > 2\sigma(I)$).

13 Only one example of 6-alkylidene-5,6-dihydro-4*H*-1,3-thiazines is reported. T. Hirayama, S. Fukatsu, A. Seki, H. Goi, and Y. Yamada, JP 53111080; *Chem. Abstr.*, **90**, 103982.

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