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Intramolecular Cyclization of in Situ Generated Adducts Formed between Thioamide Dianions and Thioformamides Leading to Generation of 5-Amino-2-thiazolines and 5-Aminothiazoles, and Their Fluorescence Properties

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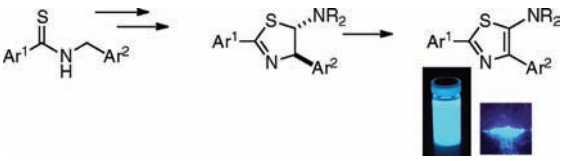
ABSTRACT



Reactions of thioamide dianions, derived from secondary *N*-arylmethyl thioamides using BuLi, with thioformamides followed by the addition of iodine to yield 5-amino-2-thiazolines are described. Treatment of the 5-amino-2-thiazolines with iodine leads to a highly efficient production of 5-aminothiazoles. When *N,N*-diarylthioformamides are employed in this process, fluorescent 5-*N,N*-diarylthiazoles are obtained.

Owing to their unique biological[1] and optical properties,[2] 2-thiazolines[3] and thiazoles[4] are among the most important classes of nitrogen-containing heterocylces. As a result, a large number of protocols have been devised for their synthesis over the past century. Nevertheless, all types of derivatives of these substances are not readily accessed by employing the existing preparative methods. For example, in contrast to the dramatic developments made in the chemistry of 2-aminothiazoles[5] as a consequence of their utility as pharmaceuticals, much less attention has been paid to 5-aminothiazoles.[6] Meanwhile, we have recently reported that tertiary thioformamides react with two different carbon nucleophiles at the thiocarbonyl carbon atom in one operation to form a wide range of tertiary amines.[7] In the course of these studies,[8] we also

(1) For reviews, see: (a) Adams, A.; Kimpe, N. D. *Chem. Rev.* **2006**, *106*, 2299. (b) Sansinenea, E.; Ortiz, A. *Mini-Rev. Org. Chem.* **2009**, *6*, 120. (c) Meroni, G.; Rajabi, M.; Santaniello, E. *Arkivoc* **2009**, 265.

(2) For a review, see: Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548.

(3) For a review, see: Gaumont, A.-C.; Gulea, M.; Levillain, J. *Chem. Rev.* **2009**, *109*, 1371.

(4) For a review, see: Wu, Y.-J.; Yang, B. V. *Prog. Heterocycl. Chem.* **2007**, *18*, 247.

(5) For recent examples, see: (a) Sakai, R.; Nakamura, T.; Kamiya, H. *Curr. Bioact. Compd.* **2006**, *2*, 395. (b) Chimenti, F.; Bizzarri, B.; Maccioni, E.; Secci, D.; Bolasco, A.; Fioravanti, R.; Chimenti, P.; Granese, A.; Carradori, S.; Rivanera, D.; Lilli, D.; Zicari, A.; Distinto, S. *Biorg. Med. Chem. Lett.* **2007**, *17*, 4635. (c) Salvador, M. A.; Reis, L. V.; Almeida, P.; Santos, P. F. *Tetrahedron* **2008**, *64*, 299. (d) Siméon, F. G.; Wendahl, M. T.; Pike, V. W. *J. Org. Chem.* **2009**, *74*, 2578. (e) Thomae, D.; Perspicace, E.; Xu, Z.; Henryon, D.; Schneider, S.; Hesse, S.; Kirsch, G.; Seck, P. *Tetrahedron* **2009**, *65*, 2982. (f) Rossignol, J.-F. *Exp. Opin. Drug Metab. Toxicol.* **2009**, *5*, 667. (g) Kitas, E.; Mohr, P.; Kuhn, B.; Hebeisen, P.; Wessel, H. P.; Haap, W.; Ruf, A.; Benz, J.; Joseph, C.; Huber, W.; Sanchez, R. A.; Paehler, A.; Benardeau, A.; Gubler, M.; Schott, B.; Tozzo, E. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 594. (h) Tsukada, T.; Takahashi, M.; Takemoto, T.; Kanno, O; Yamane, T.; Kawamura, S.; Nishi, T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1004. (i) Bursavich, M. G.; Parker, D. P.; Willardsen, J. A.; Gao, Z.-H.; Davis, T.; Ostanin, K.; Robinson, R.; Peterson, A.; Cimbora, D. M.; Zhu, J.-F.; Richards, B. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1677. (j) Nefzi, A.; Arutyunyan, S. *Tetrahedron Lett.* **2010**, *51*, 4797.

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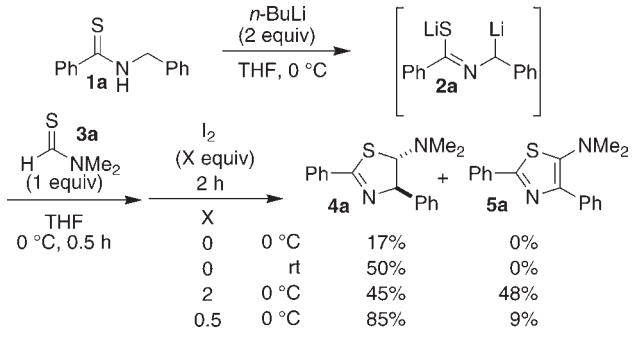
found that thioamide dianions, generated from secondary *N*-arylmethyl thioamides, can be used as equivalents of α-nitrogen carbanions. Below, we describe the results of an investigation of addition reactions of thioamide dianions to thioformamides that highly stereoselectively yield new classes of 2-thiazolines and thiazoles in which dialkyl- and diaryl-amino groups are present at their C5-positions. In addition, results obtained from studies of the fluorescence properties of 5-diarylaminothiazoles are summarized.

Treatment of *N*-benzylthiobenzamide (**1a**) with BuLi (2 equiv) at 0 °C was found to generate the thioamide dianion **2a**, which undergoes addition to *N*,*N*-dimethylthioformamide (**3a**) to give *trans*-5-amino-2-thiazoline **4a** in a 17% yield (Scheme 1). The yield of **4a** is improved to 50% when the reaction is conducted at room temperature and even more when iodine is employed as an additive. For example, reaction of the dianion of **1a** with *N*,*N*-dimethylthioformamide followed by the addition of 2 equiv of I_2 gave **4a** and 5-aminothiazole **5a** in a combined 93% yield. The aminothiazole product **5a** is formed by oxidation of **4a**. In accord with this proposal is the finding that the reaction carried out in the presence of 0.5 equiv of I_2 gives **4a** in high yield (85%) along with a small amount (9%) of **5a**.

Scheme 1. Addition of Thioamide Dianion to Thioformamide



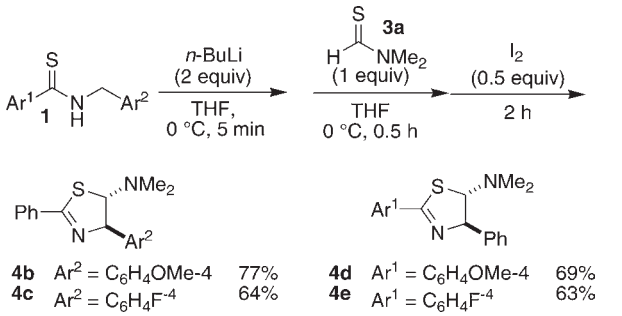
X		4a	5a
0	0 °C	17%	0%
0	rt	50%	0%
2	0 °C	45%	48%
0.5	0 °C	85%	9%

Finally, this methodology was applied to reactions of a range of secondary *N*-arylmethylthioamides **1** (Scheme 2). The results show that the presence of electron-withdrawing and -donating groups on the aromatic rings of these substances both adjacent to the thiocarbonyl and on the *N*-benzyl group does not influence the efficiency of the reaction.

A plausible mechanism for the reaction described above involves the addition of the carbanion adjacent to the nitrogen atom in dianion **2** to the thiocarbonyl carbon of **3a** to form intermediate **6** (Scheme 3).

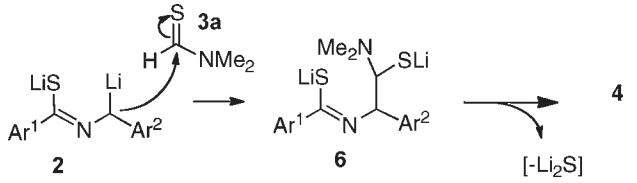
Intramolecular cyclization of **6** accompanied by elimination of Li_2S then takes place to give 5-amino-2-thiazoline **4**. In this step, one of the two LiS groups in **6** plays the role of a nucleophile and the other serves as a leaving group. The effect of I_2 on this process may be a consequence of its ability to convert the LiS group in **6** to an IS group that may be a better leaving group.

Scheme 2. Addition of a Range of Thioamide Dianions to Thioformamide



4b $Ar^2 = C_6H_4OMe$-4 77%
4c $Ar^2 = C_6H_4F$-4 64%
4d $Ar^1 = C_6H_4OMe$-4 69%
4e $Ar^1 = C_6H_4F$-4 63%

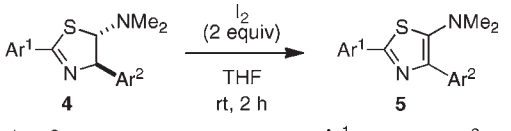
Scheme 3. Plausible Reaction Pathway to **4**



Because of the novelty of 5-dialkylamino-2-thiazoles **5**, procedures for their efficient synthesis were explored. As expected, reactions of the isolated thiazolines **4** with 2 equiv of I_2 proceed smoothly to give the corresponding thiazoles **5** (Scheme 4). Substituents, such as methoxy and fluorine, present on the aromatic rings of **4** do not affect the courses of these reactions, but thiazoles containing a methoxy group are obtained in slightly reduced yields.

N-Arylthioformamides **3b**–**3d**[9] were also employed in reactions with the thioamide dianions **2** (Table 1). Unlike reactions with **3a**, when I_2 (0.5 equiv) is used as an additive large amounts of unreacted starting thioformamides **3** are recovered. However, in all cases where 2 equiv of I_2 are

Scheme 4. Oxidation of 5-Aminothiazoline



	Ar^1	Ar^2	
5a	Ph	Ph	86%
5b	Ph	C_6H_4OMe-4	87%
5c	Ph	C_6H_4F-4	98%
5d	4-$MeOC_6H_4$	Ph	74%
5e	4-FC_6H_4	Ph	92%

(7) (a) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780. (b) Murai, T.; Asai, F. *J. Org. Chem.* **2008**, *73*, 9518. (c) Murai, T.; Ui, K.; Narengerile *J. Org. Chem.* **2009**, *74*, 5703.

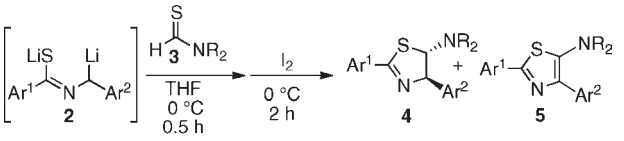
(8) Murai, T. *Pure Appl. Chem.* **2010**, *82*, 541 and references cited therein.

(9) *N*-Aryl thioformamides were prepared by the thionation of the corresponding *N*-aryl formamides with $HSiCl_3$ and elemental sulfur in the presence of amines; see: Shibahara, F.; Sugiura, R.; Murai, T. *Org. Lett.* **2009**, *11*, 3064.

used, 5-amino-2-thiazolines **4** are obtained as major products along with 5-aminothiazoles **5**. Reaction of thioamide dianions **2a** and **2d** with *N*,*N*-diphenylthioformamide (**3b**) gives **4f** and **5f** and **4g** and **5g** in 81% and 80% combined yields, respectively (entries 1 and 2), but the selectivities of the reactions are only moderate. Reactions of thioamide dianions **2e**−**2g** give thiazolines **4** in reduced yields along with little to no thiazoles **5** (entries 3−5). *N*-Methyl-*N*-phenyl- (**3c**) and *N*,*N*-dimethoxyphenyl-thioformamides (**3d**) participate in the addition-intramolecular cyclization reaction (entries 6 and 7) with the latter process providing the corresponding 5-aminothiazoline in higher yield. In reactions that produce **4** and **5** in reduced yields, arylamines originating from thioformamides **3** are also generated to variable extents. Reactions, aimed at the direct one-pot syntheses of 5-aminothiazoles **5** starting from **2** and **3**, carried out in the presence of large excesses of I_2 have not been successful, but treatment of the isolated 5-aminothiazolines **4** with I_2 (2−3 equiv) yields the corresponding 5-aminothiazoles **5** with high efficiency.[10]

The molecular structures of 5-amino-2-thiazolines and

Table 1. Reaction of a Range of Thioamide Anions **2** with Thioformamides **3**[a]



3b NR_2 = NPh_2, **3c** NR_2 = NPhMe
3d NR_2 = $N(C_6H_4OMe\text{-}4)_2$

	2			3		yield of 4[b]		yield of 5[b]
entry		Ar^1	Ar^2					
1	**2a**	Ph	Ph	**3b**	**4f**	54%	**5f**	27%
2	**2d**	4-$MeOC_6H_4$	Ph	**3b**	**4g**	54%	**5g**	26%
3	**2e**	4-FC_6H_4	Ph	**3b**	**4h**	45%	**5h**	4%
4[c]	**2f**	4-ClC_6H_4	Ph	**3b**	**4i**	52%	**5i**	trace
5	**2g**	Ph	4-ClC_6H_4	**3b**	**4j**	47%	**5j**	trace
6	**2d**	4-$MeOC_6H_4$	Ph	**3c**	**4k**	30%	**5k**	19%
7[d]	**2f**	4-ClC_6H_4	Ph	**3d**	**4l**	63%	**5l**	8%

[a] The reaction was carried out as follows unless otherwise noted: To a THF solution of thioamide dianions (1.0 mmol) were added thioformamides **3** (1.0 mmol) at 0 °C, and the reaction mixtrue was stirred for 0.5 h. I_2 (2.0 equiv) was then added to the reaction mixture, and the reaction was continued for 2 h at that temperature. [b] Isolated yields. [c] I_2 (3 equiv) was added. [d] I_2 (2.5 equiv) was added.

5-aminothiazoles were unequivocally proven by using X-ray crystallographic analyses of **4f** and **5f** (Figures 1 and 2). The structures show that the phenyl rings at the 2-positions of **4f** and **5f** lie almost in the same plane of those of the thiazoline and thiazole rings, respectively, and that **4f** possesses a *trans* relationship between the 4-phenyl and 5-NPh_2 groups. In **5f** the aromatic substituent at the

(10) See Supporting Information for the detail.

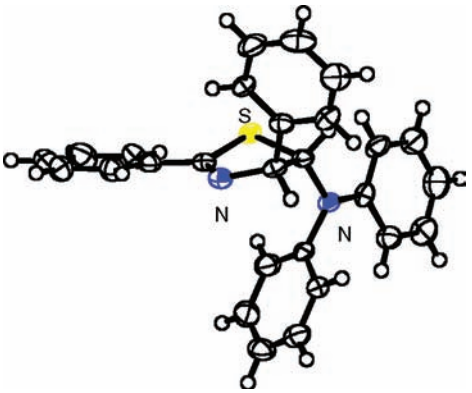


Figure 1. Ortep drawing of **4f** with 50% probability for thermal ellipsoids.

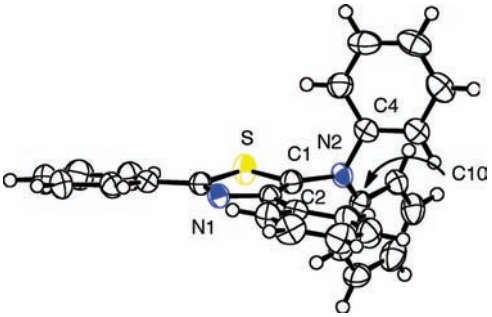


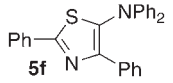
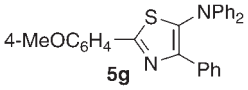
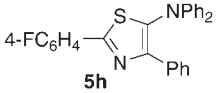
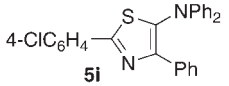
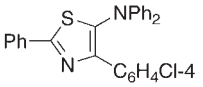
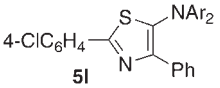
Figure 2. Ortep drawing of **5f** with 50% probability for thermal ellipsoids.

4-position is oriented in nearly the same plane as that of the thiazole ring whereas the diphenylamino group is twisted toward the thiazole ring. (The C4−N2−C1−C2 and C10−N2−C1−C2 dihedral angles are −76.9(3)° and 125.6(2)°, respectively.)

Finally, the photophysical properties of the 5-aminothiazoles **5** were explored (Table 2).

The UV−visible spectra of these substances contain two intense absorption maxima at 252 ± 5 and at 375 ± 18 nm, along with shoulders at *ca.* 285 nm. The presence of a chlorine substituent on the C2 aromatic rings results in a shift of the absorption maxima to longer wavelengths, whereas the substituents on the C4 aromatic ring do not affect the position of the longest wavelength absorption bands. All of the 5-aminothiazoles listed in Table 2 fluoresce even in the solid state (see Figure 3). The observation that *N*-Phenyl-*N*-methyl-5-aminothiazole **5k** fluoresces only weakly suggests that two phenyl groups are important for efficient singlet excited state emission. Finally, the 5-aminothiazoles display a Stokes shift of *ca.* 100 nm (5900 cm^{-1}). The fluorescence results displayed in Table 2 clearly show that electron-donating and -withdrawing groups on the aromatic groups at C2 and on the amino

Table 2. Photophysical Data for **5** in $CHCl_3$

thiazole	absorption[a] λ_{abs} [nm]	absorption[a] ε [$M^{-1}cm^{-1}$]	fluorescence[a] λ_{em}[b] [nm]	fluorescence[a] Φ_F[c]
 **5f**	249 286 367	37400 25500 10500	463	0.43
 **5g**	262 289 357	35300 28400 13400	457	0.16
 **5h**	247 283 363	43000 30300 12200	461	0.25
 **5i**	256 281 371	42100 31300 11300	474	0.56
 **5j**	255 284 366	47800 33900 10700	463	0.33
 **5l** Ar = C_6H_4OMe-4	257 285 393	42000 24800 9900	509	0.29

[a] Measured at a concentration of 1.0×10^{-5} mol dm^{-3} at 25 °C. [b] Emission maxima upon excitation at 350 nm. [c] Determined with reference to quinine sulfate in 0.1 M aqueous sulfuric acid.

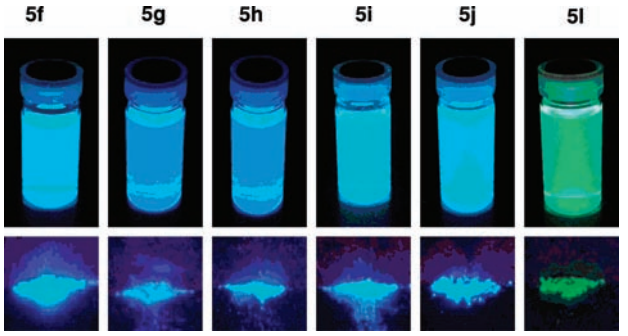


Figure 3. Visualized fluororescence of **5**: upper in $CHCl_3$; lower in the solid state.

moiety at the 5-positions can be used to govern the positions of fluorescence wavelength maxima.

In summary, the observations made in this effort show that reactions of thioamide dianions, derived from secondary *N*-arylmethyl thioamides, with thioformamides can be used in a new route for the preparation of 5-aminothiazolines and 5-aminothiazoles, substances whose syntheses have not been fully explored previously. The use of secondary thioamides in this process, which leads to thiazolines via an intramolecular cyclization of in situ generated adducts, is in marked contrast to similar well-established reactions of primary thioamides that lead to thiazoles.[11,12] The application of *N*,*N*-diarylthioformamides in these processes enables formation of members of a new class of fluorescent thiazoles, whose syntheses and applications currently hold great interest.[13] Further studies on the reactivity of thioamides and applications of fluorescent thiazoles are underway and will be described in due course.

Acknowledgment. This study was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The X-ray crystallographic analysis of **5f** was conducted by Professor Kiyohiko Nakajima in the Department of Chemistry at Aichi University of Education.

Supporting Information Available. Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) For recent examples of Hantzsch thiazole syntheses, see: (a) Alajarin, M.; Cabreta, J.; Pastor, A.; Sánchez-Andrada, P.; Bautista, D. *J. Org. Chem.* **2007**, *72*, 2097. (b) Legeay, J. C.; Eynde, J. J. V.; Bazureau, J. P. *Tetrahedron* **2008**, *64*, 5328. (c) Menche, D.; Hassfeld, J.; Li, J.; Mayer, K.; Rudolph, S. *J. Org. Chem.* **2009**, *74*, 7220. (d) Cummings, C. G.; Ross, N. T.; Katt, W. P.; Hamilton, A. D. *Org. Lett.* **2009**, *11*, 25. (e) Tang, S.; Xu, Z.; Ye, T. *Tetrahedron: Asymmetry* **2009**, *20*, 2027. (f) Popsavin, M.; Spaic, S.; Svircev, M.; Kojic, V.; Bogdanovic, G.; Pejanovic, V.; Popsavin, V. *Tetrahedron* **2009**, *65*, 7637.

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