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SYNTHESIS OF 5-H THIAZOLES VIA THIOAMIDE DIANIONS WITH THIOFORMAMIDES: PYRIDYLMETHYL GROUP ON THE NITROGEN ATOM OF THIAZOLE PROMOTES THE FORMATION OF 5-H THIAZOLES

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Abstract – The reaction of *in situ*-generated thioamide dianions having a pyridylmethyl group on the nitrogen atom with thioformamides resulted in the formation of 5-H thiazoles as major products along with 5-*N*,*N*-dimethylaminothiazoles. The presence of a pyridylmethyl group plays an important role in the formation of 5-H thiazoles. A wide range of substituents at the 2-position of a thiazole ring tolerated the reaction conditions, and the intramolecular cyclization reaction proceeded smoothly. However, a phenyl substituent at the 4-position of a thiazole ring significantly reduced the yields of 5-H thiazoles.

INTRODUCTION

Organic compounds containing a five-membered ring have great advantages in the development of various materials, such as drugs,[1] liquid crystals,[2] and anti-leukemic agents.[3] Among five-membered ring compounds, thiazoles or 1,3-thiazoles are some of the most promising and worthwhile compounds and have attracted considerable interest due to their wide applicabilities. Thiazoles are aromatic five-membered rings containing nitrogen and sulfur atoms that have unique structures compared to other aromatic heterocycles. In nature, thiazole skeletons can be found in the structures of firefly oxyluciferin,[4] thiamin (vitamin B1),[5] and other bioactive molecules.[6] In research laboratories, thiazoles are often used as an important building block in the search for new fluorescent materials. As an example, 5-aminothiazoles possessing a highly twisted conformation lead to multi-stimuli fluorescent materials.[7] Moreover, other types of substituted thiazoles, 5-hydroxythiazoles, can be converted to thiazole dianions upon treatment with a base to result in a significant bathochromic shift and remarkable quantum yields.[8] Moreover,

thiazole derivatives such as diarylthiazoles (**i**),[9] 2-phenylthiazoles (**ii**)[10] and arylidenethiazole-hydrazine derivatives (**iii**)[11] are some beneficial compounds in the medicinal field due to their activity as anti-mycobacterial and anti-fungal compounds.

Recently, a series of Pt(IV)-thiazole complexes as an anti-tumor candidate (**iv**) have been reported and their spectral properties have been documented.[12] Moreover, Espinoza and co-workers[13] described the catalytic activity of palladium-thiazole complexes (**v**) for Suzuki-Miyaura C-C coupling (Figure 1).

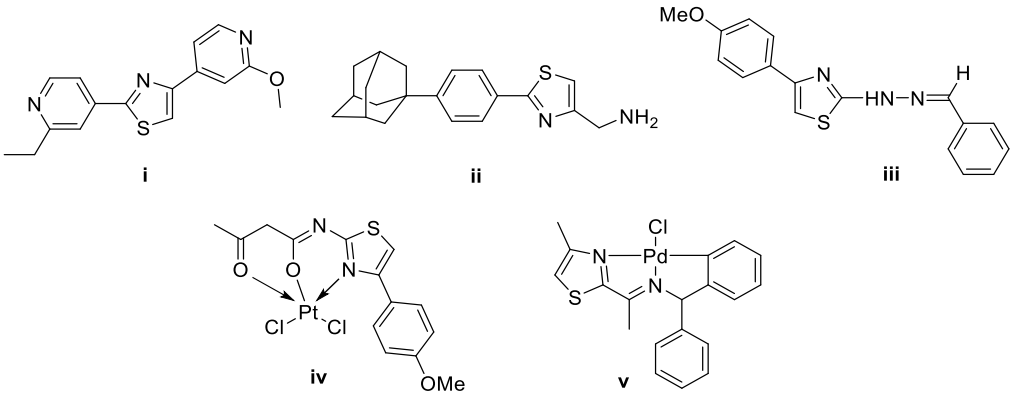
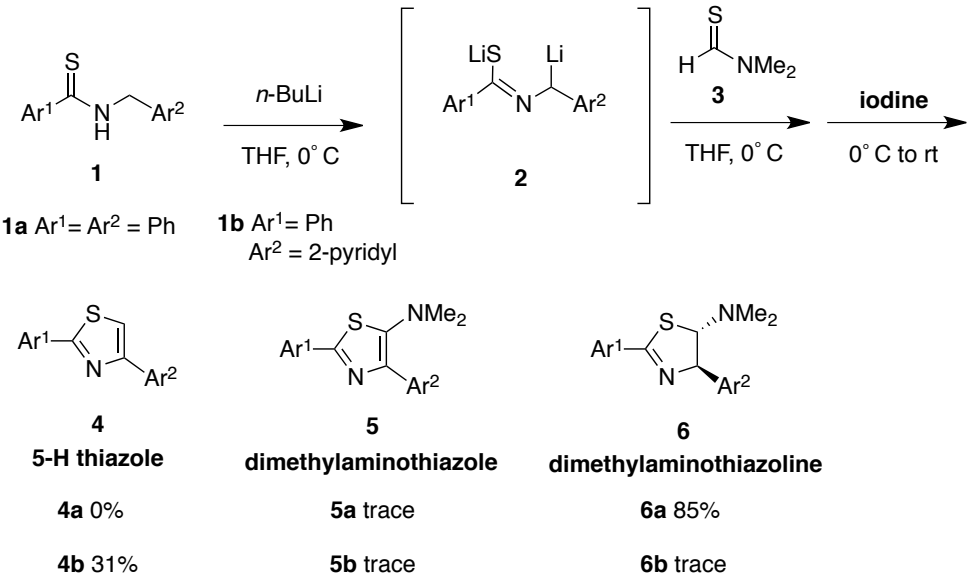


Figure 1. Selected examples of 5-H thiazoles and their complex formations

The amount of research on the synthesis of 5-H thiazoles is rapidly increasing. Remarkable synthesis protocols for the preparation of 2,4-disubstituted thiazoles that use transition metal palladium catalysts have been reported by Tani[11] and Wang.[12] Very recently, Ni and his co-workers[13] proposed a different protocol to access 5-H thiazoles under metal-free conditions with comparable and satisfying results. Our research group has also been focusing on the development of thiazole derivatives for use as potential florescent materials. As part of our going work toward the development of thiazole chemistry, we describe here the effect of the substituent at the 4-position of a thiazole ring on the formation of 5-H thiazole via thioamide dianions with *N,N*-dimethylthioformamide.

RESULTS AND DISCUSSION

As described previously,[14] the reaction of *N*-benzylthiobenzamide **1a** with *N*,*N*-dimethylthioformamide (**3**) gave *N*,*N*-dimethylaminothiazoline **6a** as a major product along with a small amount of 5-aminothiazole **5a** (Scheme 1). The formation of 5-H thiazole was not observed at all. In contrast, we found that the reaction of *N*-(2pyridylmethyl)thiobenzamide **1b** with *N*,*N*-dimethylthioformamide (**3**) accommodates the formation of 5-H thiazole **4b** as a major product. Encouraged by this interesting result, we shifted our attention to evaluate the effect of the substituent at the 2-position of a thiazole ring on the formation of 5-H thiazoles.

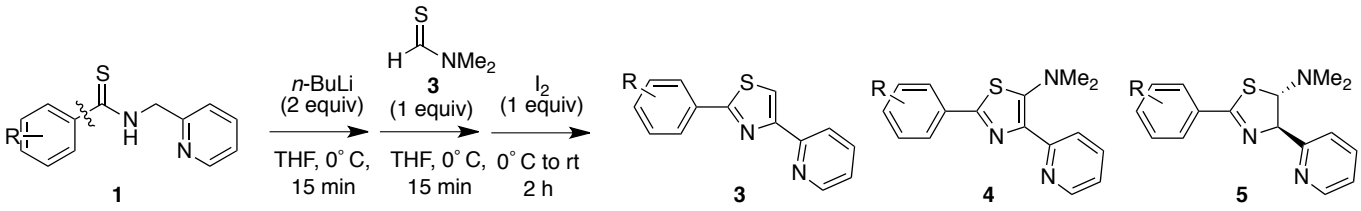


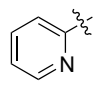
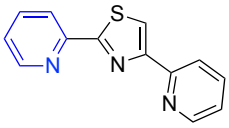
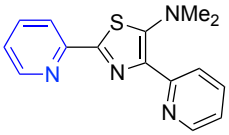
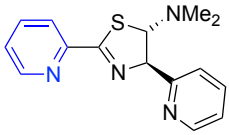
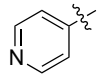
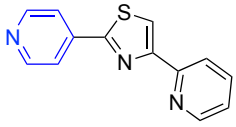
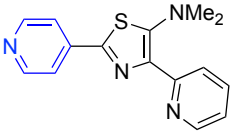
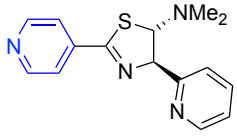
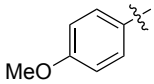
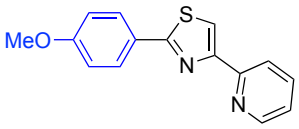
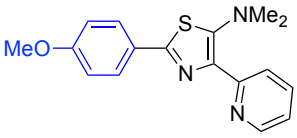
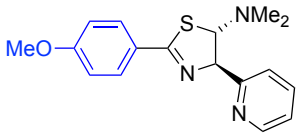
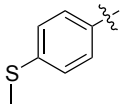
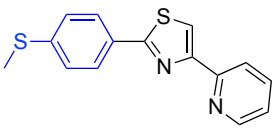
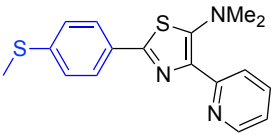
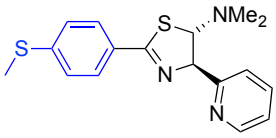
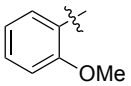
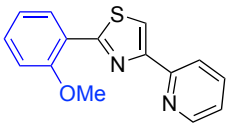
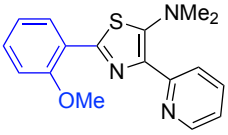
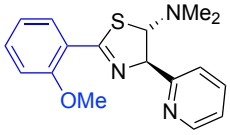
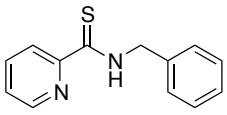
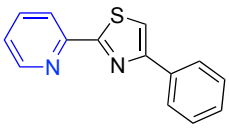
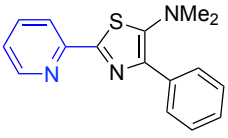
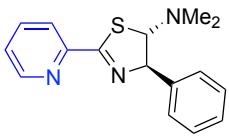
Scheme 1. Reaction of *N*-(arylmethyl)thiobenzamide with *N*,*N*-dimethylthioformamide

We then extended our reaction to secondary thioamides having electron-deficient substituents such as 2-pyridyl (**7a**) and 4-pyridyl (**7b**) groups. The reaction with *N*,*N*-dimethylthioformamide (**3**) resulted in the formation of 5-H thiazoles in up to 55% yields (Table 1). Moreover, thioamides with 4-methoxyphenyl (**7c**) and 4-methylthiophenyl (**7d**) groups gave comparable results (60% and 56% yields, respectively). These experimental results show that the substituents at the 2-position of a thiazole ring do not affect the reaction efficiency. Thioamide with a 2-methoxyphenyl group (**7e**) gave the desired 5-H thiazole **8e** in only 20% yield. On the other hand, the introduction of a phenyl substituent to the 4-position of a thiazole ring significantly reduced the yield to 3% (**7f**). In addition to 5-H thiazoles **8**, *N*,*N*-dimethylaminothiazoles **9a-f** were also obtained in moderate yields. These results confirm that the pyridyl moiety at the 4-position of a thiazole ring predominantly facilitates deamination reactions. However, no formation of thiazolines **10** was observed after reaction completion, except for thioamide having *N*-benzyl group **7f**, which gave a trace amount of the corresponding thiazoline **10f**.

A plausible reaction pathway to 5-H thiazoles **8** is shown in Scheme 2. Deprotonation from secondary thioamides with *n*-BuLi may generate thioamide dianions **I**, which then react with thioformamide **3** to form **II** as an intermediate. In the reaction of the dianion derived from *N*-benzylthiobenzamide **1a**, a LiS group acts as a leaving group to give 5-aminothiazoline **10**.

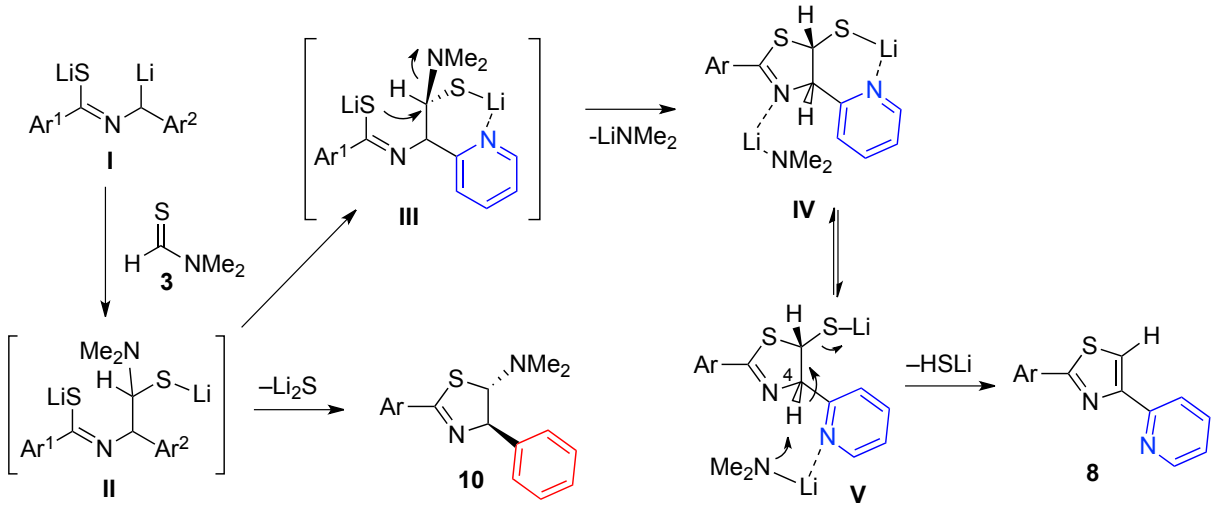
Tabel 1. Product distribution of the reaction between thioamides and *N*,*N*-dimethylthioformamide[a]



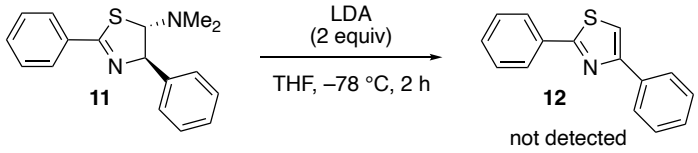
 **1a**	 **3a** 52%[b]	 **4a** 18%[b]	 **5a** 0%[b]
 **1b**	 **3b** 55%	 **4b** 18%	 **5b** 0%
 **1c**	 **3c** 41% 60%[c]	 **4c** 35% 24%[c]	 **5c** 0%
 **1d**	 **3d** 56%	 **4d** 28%	 **5d** 0%
 **1e**	 **3e** 20%	 **4e** 16%	 **5e** 0%
 **1f**	 **3f** 3%	 **4f** 27%	 **5f** trace

[a]All reactions were carried out in 2.0 mmol scale unless otherwise noted;
[b]Carried out in 3.0 mmol scale
[c]Carried out in 1.0 mmol scale

In contrast, a pyridyl group such as Ar^2 in **II** may coordinate to lithium to generate intermediate **III**, which may reduce the leaving ability of the LiS group, and thus a dimethylamino group in **III** may act as a leaving group to form **IV** and lithium dimethylamide ($LiNMe_2$). Finally, $LiNMe_2$ acts as a base to deprotonate from the 4-position of the thiazoline ring to lead to the formation of **8**. As in intermediate **V**, coordination of the nitrogen atom of the pyridyl group to lithium may enhance the basicity of $LiNMe_2$. In fact, attempted deprotonation from thiazoline **11** with LDA failed to give 5-H thiazole **12**, as shown in Scheme 3.



Scheme 2. Plausible reaction pathway for 5-H thiazoles **8**



Scheme 3. Reaction of thiazoline **11** with LDA

The structure of **8a**[15] was confirmed by X-ray crystallography (Figure 2). A single crystal suitable for X-ray crystallography of **8a** was obtained by the slow diffusion method. The crystal contains three independent molecules and the sulfur atom and C-H group are disordered. Nevertheless, the molecular structure shows that two 2-pyridyl rings are in the same plane as the thiazole ring. Moreover, the nitrogen atom of the pyridyl group attached at the 2- and 4-positions is oriented close to the sulfur atom on the thiazole ring.

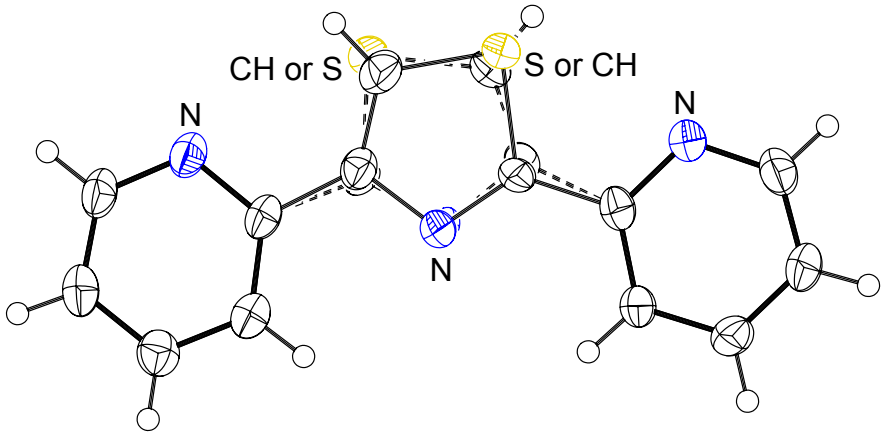


Figure 2. ORTEP Drawing of **8a**; thermal ellipsoids are shown at 50% probability

CONCLUSION

In summary, we have disclosed the synthesis of 5-H thiazoles via thioamide dianions, especially those with a pyridymethyl group on the nitrogen atom with *N,N*-dimethylthioformamide. The substituents attached at the 2-position of a thiazole ring do not significantly affect the formation of 5-H thiazoles. In contrast, the introduction of a phenyl group at the 4-position of the thiazole ring greatly decreases the formation of 5-H thiazoles. Further applications of 5-H thiazoles as metal ligands and fluorescent molecules are in progress.

EXPERIMENTAL

Characterization: The IR spectra were obtained on a JASCO FT-IR 410 spectrophotometer. ^{1}H NMR, and ^{13}C NMR spectra were measured on JNM-ECS400 (392 MHz), JNM-AL400 (396 MHz), JNM ECX-400P (400 MHz), JNM ECA-500 (500 MHz) in a deuterated solvent. Chemical shifts of ^{1}H and ^{13}C are reported in δ values referred to tetramethylsilane or $CDCl_3$ as an internal standard, respectively. All spectra were acquired in the proton-decoupled mode. The mass spectra (MS) and high resolution mass spectra (HRMS) were taken on a JMS-700 mass spectrometers. Melting points were determined by using a OptiMelt MPA100 melting point system.

Typical procedure for the preparation of 5-H thiazoles 8. **2,4-Di(pyridin-2-yl)thiazole** (**8a**). To a solution of *N*-(pyridin-2-ylmethyl)pyridine-2-carbothioamide (0.68 g, 3.0 mmol) in THF (10 mL) was added slowly a 1.25 M *n*-butyllithium in hexane (4.6 mL, 6.0 mmol), and the mixture was stirred for 15 min at 0 °C. To this mixture was added *N,N*-dimethylthioformamide (0.25 mL, 3.0 mmol) at 0 °C, and the mixture was stirred at this temperature for 30 min. Then, I_2 (0.76 g, 3.0 mmol) in THF (5 mL) was added at 0 °C, and the mixture was continuously stirred at room temperature for 3 h. The resulting mixture was poured into saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The organic layer was then

dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, hexane : EtOAc = 5 : 1) to give the corresponding thiazole **8a** in 52% yield as an orange solid; mp 132-135 ^oC; IR (KBr) 3180, 3034, 2998, 1586, 1567, 1506, 1464, 1436, 1057, 1001, 781, 751, 736, 694, 672, 619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.25 (m, 2H), 7.34-7.43 (m, 1H), 7.82-7.86 (td, 1H), 8.02 (s, 1H), 8.30-8.32 (d, *J* = 7.7 Hz, 1H), 8.41-8.43 (d, *J* = 7.9 Hz, 1H), 8.63-8.64 (d, *J* = 3.6 Hz, 1H), 8.70 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 119.5, 119.8, 121.1, 122.9, 124.6, 137.0, 149.5, 151.3, 152.5, 156.5, 169.0 ; MS (EI) *m/z* 239(M^+); HMRS (EI) calcd for $C_{13}H_9N_3S$, 239.0517. Found: 239.0505.

4-(Pyridin-2-yl)-2-(pyridin-4-yl)thiazole (8b): a yellow brownish solid; mp 143-145 ^oC: IR (KBr) 3108, 2923, 1586, 1464, 1421, 1296, 1275, 1057, 1001, 782, 736, 693, 620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.37 (m, 2H), 7.81-7.85 (td, 2H), 8.30-8.32 (m, 1H), 8.62-8.64 (m, 2H), 8.68-8.69 (d, *J* = 4.5 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 119.9, 120.0, 121.3, 123.0, 124.7, 137.1, 137.5, 149.1, 149.6, 151.3, 152.3; MS (EI) *m/z* 239(M^+); HMRS (EI) calcd for $C_{13}H_9N_3S$: 239.0517. Found: 239.0503.

2-(4-Methoxyphenyl)-4-(pyridin-2-yl)thiazole (8c): an ocher solid; mp 100-103 ^oC: IR (KBr) 3085, 3000, 2934, 1606, 1588, 1567, 1518, 1476, 1417, 1305, 1246, 1180, 1060, 1025, 834, 778, 714, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 6.96-6.99 (m, 2H), 7.25-7.32 (m, 3H), 7.89-7.98 (m, 2H), 8.34 (s, 1H), 8.64-8.65 (d, *J* = 4.1 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.5, 114.3, 116.2, 121.4, 122.8, 126.7, 128.1, 137.1, 149.4, 152.7, 155.8, 161.3, 168.0 ; MS (EI) *m/z* 268(M^+); HMRS (EI) calcd for $C_{15}H_{12}N_2OS$: 268.0670. Found: 268.0663.

2-(4-(Methylthio)phenyl)-4-(pyridin-2-yl)thiazole (8d): an ocher solid; mp 98-100 ^oC: IR (KBr) 3082, 1590, 1424, 1397,1239, 1092, 1064, 994, 810, 772, 737, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.53 (s, 3H), 7.25-7.32 (m, 5H), 7.93-7.95 (m, 2H), 8.19-8.39 (m, 1H), 8.66-8.67 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 15.4, 116.7, 121.4, 122.9, 126.2, 126.9, 130.3, 137.1, 141.5, 149.4, 152.6, 156.0, 167.7; MS (EI) *m/z* 284(M^+); HMRS (EI) calcd for $C_{15}H_{12}N_2S$, 284.0442. Found: 284.0440.

2-(2-Methoxyphenyl)-4-(pyridin-2-yl)thiazole (8e): a yellow brownish solid; mp 105-106 ^oC: IR (KBr) 3126, 1586, 1569, 1497, 1465, 1418, 1332, 1289, 1267, 1251, 1180, 1161, 1117, 1059, 1019, 751, 714, 673, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 3H), 6.82-7.13 (m, 3H), 7.38-7.43 (m, 2H), 7.81-7.85 (m, 1H), 8.34-8.36 (m, 1H), 8.53-8.56 (dd, 1H), 8.63-8.64 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 55.6, 111.4, 118.1, 121.1, 121.3, 122.3, 122.6, 128.5, 130.7, 137.0, 149.4, 153.1, 154.1, 156.5, 162.3; MS (EI) *m/z* 268(M^+); HMRS (EI) calcd for $C_{15}H_{12}N_2OS$: 268.0670. Found: 268.0676.

4-Phenyl-2-(pyridin-2-yl)thiazole (8f): a pale brown solid; mp 67-69 ^oC: IR (KBr) 3113, 1582, 1565, 1501, 1465, 1434, 1229, 1276, 1075, 1057, 998, 785, 743, 732, 693, 675, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.37 (m, 2H), 7.43-7.46 (t, 2H), 7.59 (s, 1H), 7.79-7.84 (td, 1H), 7.98-8.00 (m, 2H), 8.31-8.33 (d, *J* = 7.7 Hz, 1H), 8.61-8.62 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 115.3, 120.0,

124.6, 126.4, 128.3, 128.8, 134.5, 137.1, 149.4, 151.5, 156.7, 168.7; MS (EI) *m/z* 238 (M^+); HMRS (EI) calcd for $C_{14}H_{10}N_2S$: 238.0565. Found: 238.0566.

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This paper is dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday.

REFERENCES AND NOTES

1 N. A. Meanwell, *Adv. Heterocycl. Chem.*, 2017, **123**, 245.

2 S. Y. Kotian, C. D. Mohan, A. A. Merlo, S. Rangappa, S. C. Nayak, K. M. L. Rai, and K. S. Rangappa, *J. Mol. Liq.*, 2020, **297**, 111686.

3 T. Ling, J. Maier, S. Das, A. Budhraja, R. Bassett, M. B. Potts, A. Shelat, Z. Rankovic, J. T. Opferman, and F. Rivas, *Eur. J. Med. Chem.*, 2019, **164**, 391.

4 A. Ghose, M. Rebarz, O. V. Maltsev, L. Hintermann, C. Ruckebusch, E. Fron, J. Hofkens, Y. Mély, P. Naumov, M. Sliwa, and P. Didier, *J. Phys. Chem. B*, 2014, **119**, 2638.

5 A. Chatterjee, C. T. Jurgenson, F. C. Schroeder, S. E. Ealick, and T. P. Begley, *J. Am. Chem. Soc.*, 2007, **129**, 2914.

6 P. Arora, R. Narang, S. K. Nayak, S. K. Singh, and V. Judge, *Med. Chem. Res.*, 2016, **25**, 1717.

7 K. Yamaguchi, T. Murai, S. Hasegawa, Y. Miwa, S. Kutsumizu, T. Maruyama, T. Sasamori, and N. Tokitoh, *J. Org. Chem.*, 2015, **80**, 10742.

8 S. Schramm and D. Weiß, *Adv. Heterocycl. Chem.*, 2019, **128**, 103.

9 I. Althagafi, N. M. El-Metwaly, and T. Farghaly, *Appl. Organomet. Chem.*, 2019, **33**, 1.

10 M. Camacho-Espinoza, A. Reyes-Deloso, R. A. Toscano, J. G. Penieres-Carrillo, J. G. López-Cortés, M. C. Ortega-Alfaro, and F. Ortega-Jiménez, *New J. Chem.*, 2019, **43**, 12967.

11 S. Tani, T. N. Uehara, J. Yamaguchi, and K. Itami, *Chem. Sci.*, 2014, **5**, 123.

12 Z. J. Wang, W. T. Chen, C. He, H. F. Luo, G. L. Zhang, and Y. P. Yu, *Tetrahedron*, 2020, **76**, 130953.

13 P. Ni, J. Tan, R. Li, H. Huang, F. Zhang, and G. J. Deng, *RSC Adv.*, 2020, **10**, 3931.

14 T. Murai, F. Hori, and T. Maruyama, *Org. Lett.*, 2011, **13**, 1718.

15 **8a:** $C_{13}H_9N_3S$, MW = 239.29, monoclinic, *C2/c*, a = 16.7618(19) Å, b = 11.9433(8) Å, c = 23.653(3) Å, β = 108.151(12)°, V = 4499.5(9) $Å^3$, T = 123 K, Z = 16, μcalcd = 1.413 g cm^{-3}, 5186

unique reflections out of 19766 with I > 2σ(*I*), 398 parameters, R_1 = 0.0835, wR_2 = 0.1358, GOF = 1.026. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: deposition number CCDC-1991123.