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A facile method for the synthesis of pyridazino[4,5-b][1,4]thiazine-diones via Smiles rearrangement

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ABSTRACT

An efficient one-pot tandem method for the synthesis of pyridazino[4,5-*b*][1,4]thiazine-diones via Smiles rearrangement was developed. A number of ideal products were obtained with high yields without any byproducts. More specifically, this transition metal-free process is an environmentally friendly, economical, and efficient method for preparation of mixture-based heterocyclic libraries.

Introduction

Small molecules play a key role in modern drug development, especially in the area of drug discovery, because of their inhibition of disease-associated molecular interactions and interaction with proteins.[1] For example, the discovery and development of small molecules that have been used as cancer drugs and have been revolutionized over the last decade.[2] Moreover, small mixture-based heterocyclic molecules and libraries have dramatically different physical and biological properties from the prime compounds used as starting materials.[3] Heterocyclic-fused thiomorpholin-3-ones have aroused a considerable interest due to their extensive range of biological activities, such as bacteriostatic,[4] antiarrhythmic[5], and antidiabetic.[6] Moreover, 4*H*-benzo[*b*][1,4]thiazin-3(4*H*)-ones are used as herbicides.[7] Pyridazinone derivatives are a kind of fused heterocyclic compounds that have a number of biological activities, such as antimicrobial,[8] antiarrhythmic,[9] bioavailable inhibitors of Aurora A kinase,[10] pesticides,[11] and anticancer activities.[12] However, pyridazino[4,5-*b*][1,4]thiazine-diones has been studied neither for biological activities nor its synthesis pathway. Therefore, it is a worthwhile study of pyridazino[4,5-*b*][1,4]thiazine-diones considering that dissimilar compounds generally produce dissimilar effects.

It is generally acknowledged that molecules whose properties obey 'Lipinski's rule of 5'[13] have a high propensity for penetration into cells and for oral absorption. So, we first calculated the physicochemical properties of fused pyridazino[4,5-*b*][1,4]thiazine-diones to find out if they can be considered as 'drug-like' molecules,[14] so that the risk of pointless synthesis could be avoided. All of the related properties such as log*P* (octanol/water partition co-efficient),[15] PSA (polar surface area),[16] and molecular volume were obtained using the Molinspiration online property calculator, based on group contribution.[17] Moreover, for the majority of compounds, the values of log*P* were between 2 and 3 and all of these data are provided in our Supporting information Table 2. As a result, none of these designed molecules violated Lipinski's rule of 5. Therefore, an efficient method for the synthesis of fused pyridazino[4,5-*b*][1,4]thiazine-diones is needed, in order to study their biological activities in detail.

Considering pressing environmental and energy problems, organic synthesis toward cleaner and greener chemical processes is becoming increasingly important today.[18] In addition, using a metal catalyst has some drawbacks in industrial applications as it is expensive, oxygen sensitive, and may leave toxic trace metal contaminants. We have been studying the development of economical syntheses of heterocyclic systems.[19] In continuation of our work, we describe a one pot metal-free synthesis of 7-(tetrahydro-2*H*-pyran-2-yl)-2*H*-pyridazino[4,5-*b*][1,4]thiazine-3,8(4*H*,7*H*)-ions at mild reaction conditions. The ideal products were obtained by the reaction of 4,5-dichloro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one with a variety of *N*-substituted mercaptoacetamides (Scheme 1).

Results and discussion

Optimized reaction conditions were found by systematically investigating the reaction parameters using 4,5-dichloro-2-(tetra-

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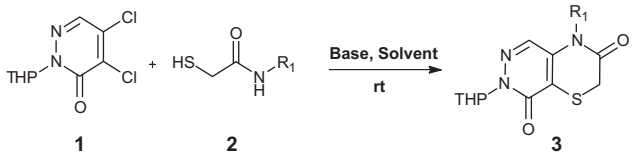


Scheme 1. One-pot synthesis of pyridazino[4,5-*b*][1,4]thiazine-diones.

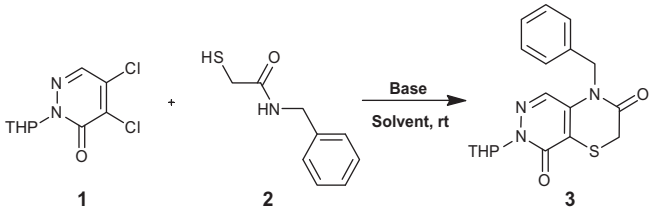
hydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one and *N*-benzyl-2-mercaptoacetamide (Table 1). First, different bases such as KOH, NaH, NaOH, and K_2CO_3 in DMF were tested at room temperature, which proved that Cs_2CO_3 was the most suitable base. Then we probed into the influence of different solvents on the reaction. DMF was found to be an effective solvent with a good result, but CH_3CN, DMSO, and THF were less effective.

Then, the optimized reaction conditions were used to explore the scope of synthesizing 7-(tetrahydro-2*H*-pyran-2-yl)-2*H*-pyridazino[4,5-*b*][1,4]thiazine-3,8(4*H*,7*H*)-diones (Table 2). The desired 7-(tetrahy dro-2*H*-pyran-2-yl)-2*H*-pyridazino[4,5-*b*][1,4] thiazine-3,8(4*H*,7*H*)-diones were obtained yielding from 78% to 95% (Table 2). As shown in Table 2, for the variation of R_1, comparing the yields of *N*-substrates alkyl (Table 2, entries 1–7) with those of *N*-aryl substrates (Table 2, entries 8–12), there was no difference. Additionally, according to the experiments, when the *N*-substrate of **2** is 2-propylamine or cyclohexylamine the reaction did not produce the expected product in spite of trying higher temperatures and longer reaction times. We believe steric hindrance is responsible for the results. It was also found that the *N*-aryl substrates with an electron-donating group (Table 2, entries 11 and 12) provided little higher yield than substrates with an electron-withdrawing group (Table 2, entries 8–10). The structures of desired compounds were shown in Figure 1. In addition, the molecular structure of the representative product **3j** was determined by X-ray crystallographic analysis (Fig. 2).

Based on reported Smiles rearrangement reaction and our experimental results, a plausible reaction mechanism was proposed in Scheme 2. The reaction of **1** with **2** yielded compound **4**. Compound **4** could proceed in two paths (I and II). Path II could produce the direct intramolecular nucleophilic substitution product **8**. Path I could lead to compound **3** via Smiles rearrangement. However, we only obtained compound **3**.

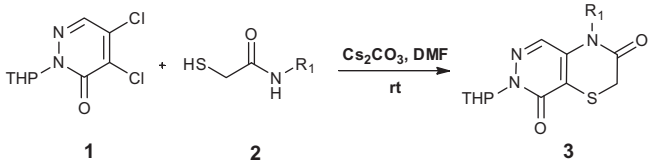
Imido nitrogen in compound **5** underwent intramolecular nucleophilic attack on the carbonium (*meta*-position to the carbonyl group). Migration of the spiro-sulfur, proceeding through

Table 1
Optimization of reaction conditions



Entry	Base	Solvent	Temp/°C	Time/h	Yield/%
1	Cs_2CO_3	DMF	rt	3	86
2	K_2CO_3	DMF	rt	7	83
3	NaOH	DMF	rt	3	79
4	NaH	DMF	rt	3	52
5	Cs_2CO_3	DMSO	rt	3	37
6	Cs_2CO_3	CH_3CN	80	7	32
7	Cs_2CO_3	THF	80	7	36

Table 2
Synthesis of Pyridazino[4,5-*b*][1,4]thiazine-3,8(4*H*,7*H*)-diones



Entry	R_1	Time/h	Product	Yield/%
1	**2a** Me	4	**3a**	92
2	**2b** Et	4	**3b**	89
3	**2c** Pr	4	**3c**	90
4	**2d** Bu	4	**3d**	95
5	**2e** Bn	6	**3e**	87
6	**2f** β-Phenethyl	6	**3f**	83
7	**2g** 3,4-MeOphenethyl	6	**3g**	81
8	**2h** 4-FC_6H_4	10	**3h**	78
9	**2i** 4-ClC_6H_4	10	**3i**	87
10	**2j** Ph	10	**3j**	87
11	**2k** 4-MeC_6H_4	10	**3k**	92
12	**2l** 4-$MeOC_6H_4$	10	**3l**	87

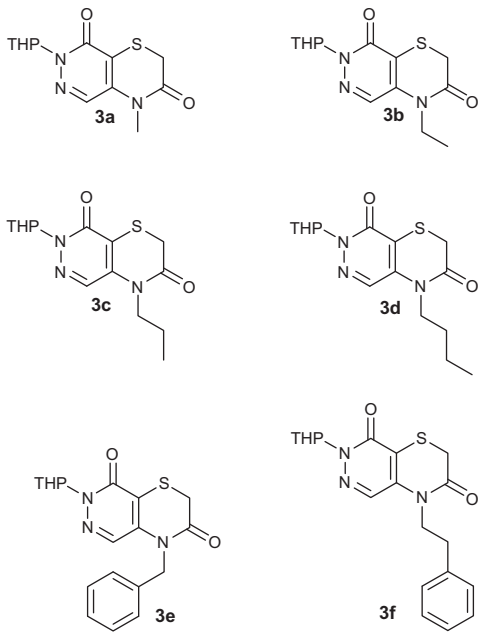


Figure 1. Structures of desired compounds of **3a–l**.

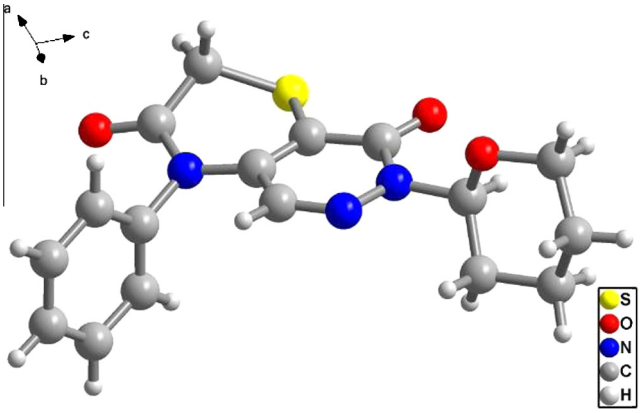
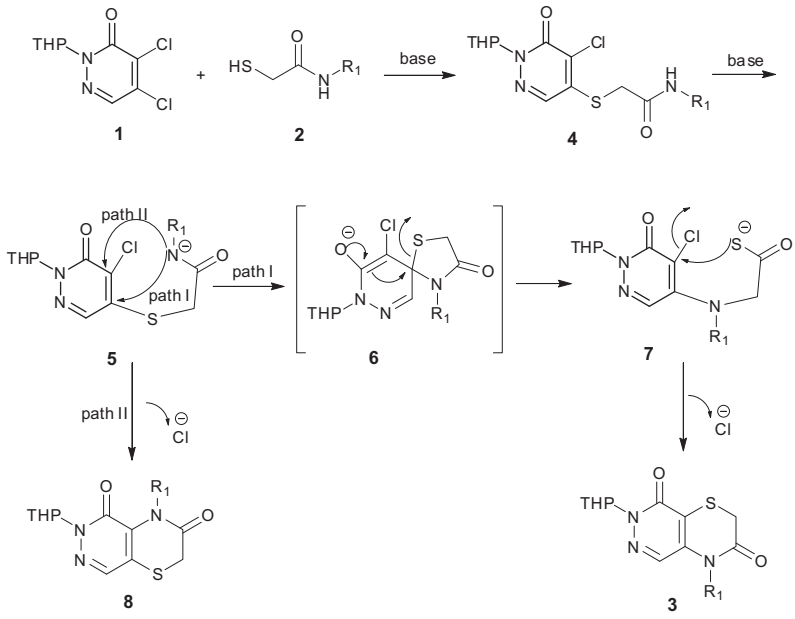


Figure 2. X-ray structure of compound **3j** with atomic numbering scheme.



Scheme 2. A plausible reaction mechanism.

the 'Meisenheimer complex' **6**, with intramolecular nucleophilic displacement of the chlorine anion by a sulfur anion of compound **7** yielded the desired cyclization product **3** (Scheme 2).

Also, a theoretical study of this S–N type Smiles rearrangement process was done to rationalize the experimental observations.[19b] By performing quantum chemical calculations, the molecular mechanism for the S–N type Smiles rearrangement was shown. The theoretical results showed that the Smiles rearrangement pathway was energetically more favorable than the direct nucleophilic substitution pathway.

Conclusions

In conclusion, we developed an operationally simple and economic synthesis of a number of pyridazino[4,5-*b*][1,4]thiazinediones based on the Smiles rearrangement. Furthermore, this metal-free method accords with the development of the current organic synthesis trend toward cleaner and greener chemical processes which is due to pressing environmental and energy problems. Therefore, this transition-metal-free process has potential applications in the synthesis of biologically and medicinally relevant compounds.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures, physicochemical properties of **3a–l**, and spectral data of compounds **3a–l**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.026.

References and notes

1. (a) Knudsen, L. B.; Kiel, D.; Teng, M., et al *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*(3), 937; (b) Sloop, K. W.; Willard, F. S.; Brenner, M. B., et al *Diabetes* **2010**, *59*(12), 3099; (c) Hann, M. M.; Leach, A. R.; Harper, G. J. *Chem. Inf. Comput. Sci.* **2001**, *41*, 856.
2. Hoelder, S.; Clarke, P. A.; Workman, P. *Mol. Oncol.* **2012**, *6*, 155.
3. (a) Eichler, J.; Houghten, R. A. *Mol. Med. Today* **1995**, *1*(4), 174; (b) Dooley, C. T.; Houghten, R. A. J. *Perspect. Drug. Disc. Design.* **1995**, *2*, 287.
4. Guarda, V. L. M.; Perrissin, M.; Thomasson, F.; Ximenes, E. A.; Galdino, S. L.; Pitta, I. R.; Luu-Duc, C.; Barbe, J. *Eur. J. Med. Chem.* **2003**, *38*, 769.
5. Fujita, M.; Ito, S.; Ota, A.; Kato, N.; Yamamoto, K.; Kawashima, Y.; Yamauchi, H.; Iwao, J. *J. Med. Chem.* **1990**, *33*, 1898.
6. Kawashima, Y.; Ota, A.; Mibu, H. W.O. Patent 9,405,647, 1994.
7. Wuemachu, T.; Oshi, H. K.R. Patent 8,200,849, 1982.
8. Sridhara, A. M.; Reddy, K. R. V.; Keshavayya, J.; Goud, P. S. K.; Somashekar, B. C.; Bose, P.; Peethambar, S. K.; Gaddam, S. K. *Eur. J. Med. Chem.* **2010**, *45*, 4983.
9. (a) Mátyus, P. *J. Heterocycl. Chem.* **1998**, *35*, 1075; (b) Bidló-Iglóy, M.; Mátyus, P. *J. Pharm. Biomed. Anal.* **1999**, *19*, 487.
10. (a) Verhelst, T.; Verbeeck, S.; Ryabtsova, O.; Depraetere, S.; Maes, B. U. W. *Org. Lett.* **2011**, *13*, 272; (b) Li, Y. X.; Luo, Y. P.; Xi, Z.; Niu, C. W.; He, Y. Z.; Yang, G. F. *J. Agric. Food Chem.* **2006**, *54*, 9135.
11. (a) Schwartz, A.; Beke, G.; Kovári, Z.; Böcskey, Z.; Farkas, Ö.; Mátyus, P. J. *Mol. Struct: Theochem.* **2000**, *49*, 528; (b) Monsieurs, K.; Krajsovszky, G.; Dunkel, P.; Maes, B. U. W.; Tapolcsányi, P.; Egyed, O.; Boros, S.; Mátyus, P.; Pieter, L.; Lemière, G. L. F.; Hajós, G. L. F.; Hajós, G. *Tetrahedron* **2006**, *62*, 121.
12. Del Olmo, E.; Barboza, B.; Ybarra, M. I.; Lopez-Perez, J. L.; Carron, R.; Sevilla, M. A.; Boselli, C.; San Feliciano, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2786.
13. (a) Lipinsky, C. et al *Adv. Drug Delivery Rev.* **1997**, *23*, 2; (b) Kubinyi, H. et al *J. Med. Chem.* **1998**, *41*, 3325; (c) Murko, M. et al *J. Med. Chem.* **1998**, *41*, 3314; (d) Proudfood, J. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1647.
14. (a) Uetrecht, J. *Curr. Opin. Drug Disc. Dev.* **2001**, *4*, 55; (b) Uetrecht, J. *Chem. Res. Toxicol.* **2008**, *21*, 84; (c) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *ACS Comb. Sci.* **1999**, *1*, 55; (d) Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Disc.* **2007**, *6*(11), 881.
15. Mannhold, R.; Rekker, F. P. *Perspect. Drug Discovery Des.* **2000**, *18*, 1.
16. (a) Ertl, P.; Rohde, B.; Selzer, P. *J. Med. Chem.* **2000**, *43*, 3714; (b) Ertl, P. In *Molecular Drug Properties*; Mannhold, R., Ed.; Wiley-VCH, 2007; pp 111–126.
17. http://www.molinspiration.com.
18. (a) Pereira, C. J. *Chem. Eng. Sci.* **1959**, *1999*, 54; (b) Jin, Y.; Wang, D. Z.; Wei, F. *Chem. Eng. Sci.* **2004**, *59*, 1885; (c) Jin, Y.; Wang, D. Z.; Wei, F. J. *Chem. Eng. Sci.* **1885**, *2004*.
19. (a) Zhao, Y. M.; Dia, Q. L.; Chen, Z.; Zhang, Q. H.; Bai, Y. C. *ACS Comb. Sci.* **2013**, *15*, 130; (b) Zhao, Y. M.; Wu, Y.; Jia, J.; Zhang, D. J.; Ma, C. A. *J. Org. Chem.* **2012**, *77*, 8501; (c) Zhang, X. H.; Jia, J.; Ma, C. *Org. Biomol. Chem.* **2012**, *10*, 7944; (d) Zhan, C. J.; Jia, J.; Yang, B. C.; Huang, A. P.; Liu, Y. L.; Ma, C. *RSC Advances* **2012**, *2*(19), 7506; (e) Liu, Y. L.; Ma, Y.; Zhan, C. J.; Huang, A. P.; Ma, C. *Synlett* **2012**, *23*, 255; (f) Huang, A. P.; Qiao, Z.; Zhang, X. H.; Yu, W.; Zheng, Q. Q.; Ma, Y.; Ma, C. *Tetrahedron* **2012**, *68*, 906; (g) Huang, A. P.; Liu, F.; Zhan, C. J.; Liu, Y. L.; Ma, C. *Org. Biomol. Chem.* **2011**, *9*, 7351; (h) Liu, Y. L.; Chu, C. X.; Huang, A. P.; Zhan, C. J.; Ma, Y.; Ma, C. *ACS Comb. Sci.* **2011**, *13*, 547.