RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Iodine-Mediated Synthesis of Benzopyridothiazines via Tandem C−H Thiolation and Amination

Liang Wei,[a,b] Li Xu[b] and Ri-Yuan Tang*[a,b]

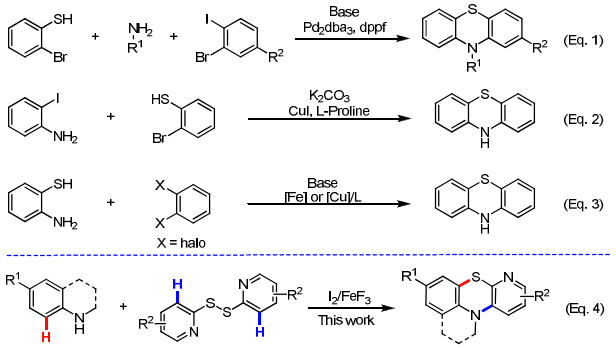
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

The first example of iodine-mediated tandem C−H thiolation/amination strategy for the synthesis of benzopyridothiazines by the reaction of secondary amine with pyridine disulfides is described.

Phenothiazines is one of the important heterocycles that exert numerous effects on biological systems.[1] These compounds have been widely used as antibacterial, antifungal, anticancer, antiviral, anti-inflammatory, antimalarial, and antifilarial agents.[1] Among this type of compounds, benzopyridothiazines are particularly effective for remedy of various diseases such as asthma, allergic coryza, atopic dermatitis, hives, and hay fever.[2] Additionally, phenothiazines are promising biosensor materials in bioelectrochemical system.[3] Despite the importance of phenothiazines, synthetic methods for the formation of phenothiazines are limited.[4−8] In recent years, great efforts are made to overcome some drawbacks such as poor regioselectivity, narrow substrate scope, multi-step procedure or harsh conditions in early works.[4] Presently, the tandem C–S/C–N bonds cross-coupling reaction strategy serves as a powerful tool for the synthesis of phenothiazines (Scheme 1, Eqs.1–3). For example, in 2008, Jørgensen's group demonstrated that palladium-catalyzed three-component coupling reaction of substituted 1-bromo-2-iodobenzenes with primary amines and 2-bromobenzenethiol can efficiently access to phenothiazines (Scheme 1, Eq. 1).[5] In 2010, Ma group reported that CuI/L-proline-catalyzed coupling of 2-iodoanilines with 2-bromobenzenethiols is an alternative route to phenothiazines, in which a good regioselectivity can be obtained by controlling the reaction temperature and time (Scheme 1, Eq. 2).[6] Recently, copper-(Zeng *et al.*)[7] or iron-catalyzed (Zhang *et al.*)[8] coupling of 2-aminobenzenethiol with 1,2-dihalobenzene is also an effective route to phenothiazines with good regioselectivity (Scheme 1, Eq. 3).

Although great progress has been made for the synthesis of phenothiazines, a long-standing challenge, namely exploring a protocol for tandem C–S/C–N bonds formation by C–H bond disconnection, remains to be addressed. To the best of our knowledge, synthesis of phenothiazines via tandem C−H thiolation/amination strategy has never been evaluated. Additionally, less attention is paid to the synthesis of benzopyridothiazines.[9] Guided by the principles of green chemistry,[10] the development of an inexpensive and environmental-friendly C−H functionalization strategy for tandem C–S/C–N bonds formation is highly desirable. In recent years, hypervalent iodine (III) reagents have been used in direct C−H amination,[11] whereas iodine-mediated nonreactive C−H bond amination remains scarce. Based on our own iodine-mediated C−H thiolation,[12] we reasoned that the intramolecular C(sp^2)−H amination followed by the *ortho* C−H thiolation of aniline with diaryl disulfides may be carried out in the presence of iodine, as iodine can react with pyridine to form *N*-iodopyridinium that may facilitate the amination.[13] Herein we report an iodine-mediated tandem C−S/C−N bond formation via C−H bond disconnection leading to a wide range of benzopyridothiazines by the reaction of *N*-methylanilines with pyridine disulfides (Scheme 1, Eq. 4).

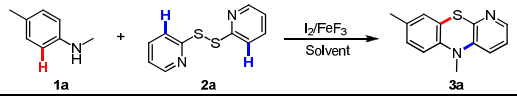


Scheme 1. Synthetic methods for phenothiazines.

After extensive study, the reaction of *N*,4-dimethylaniline **1a** with 1,2-di(pyridin-2-yl)disulfane **2a** was selected as a model reaction (Table 1). Several solvents including DMSO, acetone, MeCN, $MeNO_2$, DMF, and 1,4-dioxane were examined in the presence of I_2 (20 mol%) at 80 °C for 12 hours, respectively (entries 1–6). Among these solvents, acetone is ineffective for this reaction (entry 2); and $MeNO_2$ appears effective to give the target product **3a** in 45% yield (entry 4). In the presence of NIS (N-iodosuccinimide) instead of I_2, the reaction also proceeded smoothly to afford product **3a** in 40% yield (entry 7). We are expecting to improve the yield of **3a** by increasing the loading of I_2. However, the reaction with one equivalent of I_2 appears no change on the yield of **3a** (entry 8). Reducing the loading of I_2 to 10 mol% lowered the yield of **3a** to 31% (entry 9). To our delight, the addition of FeF_3 (20 mol%) enhanced the yield of **3a** to 56% in the presence of I_2 (20 mol%) at 80 °C for 12 hours (entry 10). Encouraged by this result, other iron salts such as $FeBr_3$, $FeCl_3$, $Fe(OAc)_2$, $Fe(OTf)_3$, and Fe_2O_3 were investigated (entries 11−15).

However, these iron salts were less effective than FeF_3. The reaction temperature evaluation indicates that either lower or higher temperature than 80 °C cannot improve the yield of **3a** (entry 16−18). It was pleasing to find that prolonging the reaction time to 24 hours would increase the yield of **3a** to 63% (entry 19). Finally, the amount of FeF_3 was examined. Loading 50 mol% of FeF_3 decreased the yield of **3a** to 50% (entry 20). No target product was observed when the reaction was conducted in the absence of I_2 (entry 21).

Table 1. Screening of optimal conditions [a]



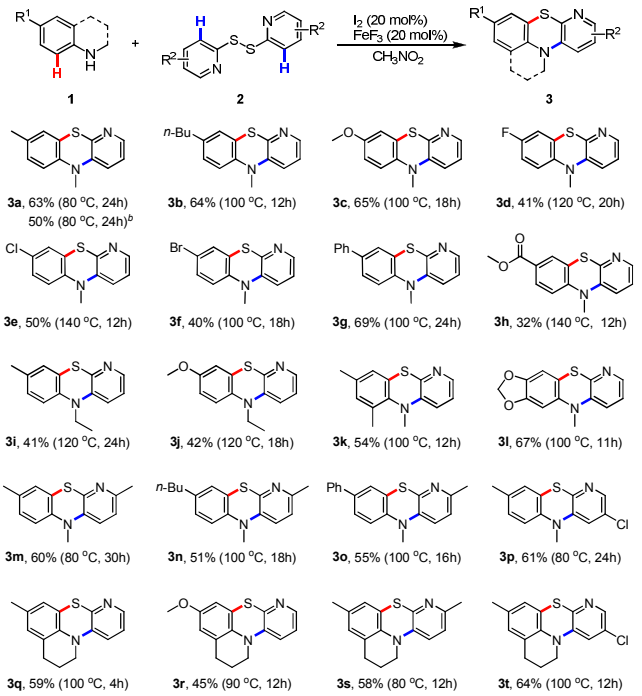
1a 2a 3a

Entry	Catalyst (eq)	Solvent	Isolated yield (%)
1	I_2 (20)	DMSO	26
2	I_2 (20)	Acetone	0
3	I_2 (20)	CH_3CN	37
4	I_2 (20)	CH_3NO_2	45
5	I_2 (20)	DMF	30
6	I_2 (20)	1,4-Dioxane	34
7	NIS (20)	CH_3NO_2	40
8	I_2 (100)	CH_3NO_2	47
9	I_2 (10)	CH_3NO_2	31
10	I_2 (20)/FeF_3 (20)	CH_3NO_2	56
11	I_2 (20)/$FeBr_3$ (20)	CH_3NO_2	49
12	I_2 (20)/$FeCl_3$ (20)	CH_3NO_2	44
13	I_2 (20)/$Fe(OAc)_2$ (20)	CH_3NO_2	46
14	I_2 (20)/$Fe(OTf)_3$ (20)	CH_3NO_2	50
15	I_2 (20)/Fe_2O_3 (20)	CH_3NO_2	52
16[b]	I_2 (20)/FeF_3 (20)	CH_3NO_2	51
17[c]	I_2 (20)/FeF_3 (20)	CH_3NO_2	55
18[d]	I_2 (20)/FeF_3 (20)	CH_3NO_2	53
19[e]	I_2 (20)/FeF_3 (20)	CH_3NO_2	63
20[e]	I_2 (20)/FeF_3 (50)	CH_3NO_2	50
21[e]	FeF_3 (20)	CH_3NO_2	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.15 mmol), solvent (2 mL) at 80 °C for 12 h. [b] at 60 °C. [c] at 100 °C. [d] at 120 °C. [e] for 24 h.

With the optimized reaction conditions in hand (Table 1, entry 19), the scope of the tandem C−H thiolation/amination of *N*-methylanilines with 1,2-di(pyridin-2-yl)disulfane was investigated (Table 2). *N*-methylanilines **1** bearing either an electron-withdrawing or -donating substituents on the benzene ring worked well to give the corresponding products in moderate yields (products **3a**–**3l**). Generally, the electron-donating groups favored the transformation and gave better yields. For example, the butyl-substituted substrate gave product **3b** in 64% yield at 100 °C for 12 hours. The substrate bearing a methoxy group afforded product **3c** in 65% yield at 100 °C for 18 hours. Whereas the halogen groups exhibit less effective for this transformation, giving the corresponding products in lower yields (products **3d**, **3e** and **3f**). Interestingly, the substrate with a phenyl group performed well to afford product **3g** in 69% yield at 100 °C for 24 hours. The substrate with an ester group was also tolerated, albeit in low yield (product **3h**). It is noteworthy that further modification can be easily made on the ester group. Replacing methyl with ethyl on the nitrogen atom of anilines leads to a decrease on the yield of products (e.g. **3i** vs **3a, 3j** vs **3c**). The dimethyl- and dioxyl-substituted substrates are also suitable for this reaction, giving the corresponding products **3k** and **3l** in 54% and 67% yields, respectively. Next, other pyridine disulfides such as 1,2-bis(6-methylpyridin-2-yl)disulfane and 1,2-bis(5-chloropyridin-2-yl)disulfane were also investigated. Both appear to have good tolerance with the reaction conditions to afford products **3m** and **3p** in 60% and 61% yields, respectively. Significantly, 1,2,3,4-tetrahydroquinolines were well tolerated to give novel benzopyridothiazines in moderate yields ranging from 45% to 64% (products **3q**−**3t**). These fused heterocycles, containing pyridine, thiazine and tetrahydroquinoline rings, were constructed for the first time. It was pleasing to find that pyridine-2-thiol can react with **1a** to afford product **3a** in 50% yield under the standard conditions. This because pyridine-2-thiol can be oxidized to 1,2-di(pyridin-2-yl)disulfane in situ for the next transformation.

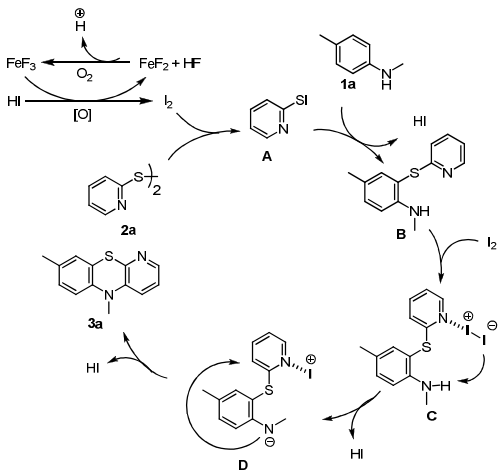
Table 2. Substrates scope.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.15 mmol), I_2 (20 mol%), FeF_3 (20 mol%), $MeNO_2$ (2 mL) at indicated temperature for indicated time. [b] Reaction of **1a** with pyridine-2-thiol: **1a** (0.2 mmol), pyridine-2-thiol (0.3 mmol), I_2 (20 mol%), FeF_3 (20 mol%), $MeNO_2$ (2 mL) at 80 °C for 24 h.

To gain insight into the mechanism, several control experiments were conducted (see the Supporting Information). During the development of this reaction, a thiolated intermediate **B** (Scheme 2) was observed on GC−MS.[14] It was shown that intermediate **B** could undergo an intramolecular amination to provide product **3a** in 65% yield under the standard conditions. In the absence of I_2, the amination did not take place. Whereas the treatment of intermediate **B** with I_2 alone gave product **3a** in 53% yield. The NMR study demonstrated that I_2 could interact with intermediate **B** in CD_3CN at room temperature. In comparison

with the ^{1}H NMR of intermediate **B** in CD_3CN without I_2, The addition of I_2 led the proton peaks shift to low field, but the proton peak of the amino disappeared (see the Supporting Information). These results suggest that I_2 may be chelated with pyridine to form pyridine-iodine complexes **C**.[13] After stirring for 24 hours, the mixture of intermediate **B** and I_2 in CD_3CN at room temperature was also detected on a HRMS instrument (ESI-Q-TOF). Unfortunately, only the intermediate **B** was observed under the electrospray ionization conditions. According to the present results, I_2 may play two roles in the amination step: 1) activate the reactivity of the pyridine ring; 2) help to abstract the hydrogen atom and enhance the nucleophilicity of the amino group. According to the present results and previous reports,[12, 13] a possible mechanism is proposed (Scheme 2). Disulfide **2a** first reacts with I_2 to yield intermediate **A** in situ, followed by a thiolation with compound **1a** to generate an intermediate **B**. Intermediate **B** was then reacted with I_2 to produce intermediate **C**. Intermediate **C** undergoes an hydrogen iodide elimination to afford an intermediate **D**. Finally, intermediate **D** undergoes an amination process to afford target product **3a**. Hydrogen iodide can be oxidized by FeF_3 or CH_3NO_2 to regenerate I_2 for next cycle.



Scheme 2 A possible mechanism.

Conclusions

In summary, we have developed an iodine-mediated tandem C–H thiolation/amination strategy for the synthesis of benzopyridothiazines. Significantly, this unprecedented protocol allows 1,2,3,4-tetrahydroquinolines to give novel benzopyridothiazines with unique structure (products **3q**−**3t**) that may attract great attention in medicine chemistry. Although the progress of C−H functionalization strategy for the formation of thiazine ring is made, the direct synthesis of phenothiazines by tandem C−H thiolation/amination of anilines with common diaryldisulfides remains to be addressed.

Notes and references

[a] *College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, China.*
[b] *Department of Applied Chemistry, College of Materials and Energy, South China Agricultural University, Guangzhou 510642, China. E-mail: rytang@scau.edu.cn*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

This work was supported by the National Natural Science Foundation of China (No. 21202121).

1 (*a*) K. Pluta, B. Morak-Młodawska and M. Jeleń, *Eur. J. Med. Chem.*, 2011, **46**, 3179–3189. (*b*) L. Rodrigues, J. A. Ainsa, L. Amaral and M. Viveiros, *Recent Pat. Anti-Infective Drug Discov.*, 2011, **6**, 118–127. (*c*) J. J. Aaron, M. D. G. Seye, S. Trajkovska and N. Motohashi, *Top. Heterocycl. Chem.*, 2009, **16**, 153–231.

2 M. Miyamoto, T. Yoshiuchi, K. Sato, M. Soejima, T. Sato, K. Kikuchi, H. Yoshimura, K. Moriya, Y. Sakuma, S. Akasofu, K. Yamada, S. Yamada and R. Yamada, US Pat. 6583138, 2003.

3 (*a*) M. Ma, Z. Miao, D. Zhang, X. Du, Y. Zhang, C. Zhang, J. Lin and Q. Chen, *Biosens. Bioelectron.*, 2015, 64477−64484. (*b*) H. Puzanowska-Tarasiewicz, J. Karpinska and L. Kuzmicka, *Anal. Chem.*, 2011, 63−77.

4 (*a*) M. Mayer, P. T. Lang, S. Gerber, P. B. Madrid, I. G. Pinto, R. K. Guy and T. L. James, *Chem. Biol.*, 2006, **13**, 993–1000. (*b*) N. Sharma, R. Gupta, M. Kumar and R. R. Gupta, *J. Fluorine Chem.*, 1999, **98**, 153–157. (*c*) M. Sailer, A. W. Franz and T. J. J. Müller, *Chem.–Eur. J.*, 2008, **14**, 2602–2614; (*d*) R. Y. Lai, X. Kong, S. A. Jenekhe and A. J. Bard, *J. Am. Chem. Soc.*, 2003, **125**, 12631–12639.

5 T. Dahl, C. W. Tornøe, B. Bang-Andersen, P. Nielsen and M. Jørgensen, *Angew. Chem., Int. Ed.*, 2008, **47**, 1726–1728.

6 D. Ma, Q. Geng, H. Zhang and Y. Jiang, *Angew. Chem., Int. Ed.*, 2010, **49**, 1291–1294.

7 C. Dai, X.-F. Sun, X.-Z. Tu, L. Wu, D. Zhan and Q.-L. Zeng, *Chem. Commun*., 2012, **48**, 5367–5369.

8 W.-Y. Hu and S.-L. Zhang, *J. Org. Chem.*, 2015, **80**, 6128−6132.

9 B. Morak-Młodawska, K. Pluta, M. Zimecki, M. Jeleń, J. Artym and M. Kocięba, *Med. Chem. Res.*, 2015, **24**, 1408–1418.

10 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, NY, 1998.

11 Reviews for hypervalent iodine(III)-mediated amination, see: (*a*) R. Narayan, S. Manna and A. P. Antonchick, *Synlett*, 2015, **26**, 1785–1803, and references therein cited. (*b*) P. Finkbeiner and B. J. Nachtsheim, *Synthesis*, 2013, **45**, 979–999, and references therein cited.

12 (*a*) X.-M. Ji, S.-J. Zhou, F. Chen, X.-G. Zhang and R.-Y. Tang, *Synthesis*, 2015, **47**, 659−671. (*b*) X.-L. Fang, R.-Y. Tang, P. Zhong and J.-H. Li, *Synthesis*, 2009, 4183−4189.

13 (*a*) E. M. Karlsen and J. Spanget-Larsen, *Chem. Physics Lett.,*2009, **473**, 227–232. (*b*) S. Aronson, S. B. Wilensky, T.-I. Yeh, D. Degraff and G. M. Wieder, *Can. J. Chem*, 1986, **64**, 2060−2063.

14 Reaction conditions for intermediate **B**: **1a** (1 mmol), **2a** (1.5 mmol), I_2 (20 mol%), FeF_3 (20 mol%), in DMF (2 mL) at 90 °C for 24 h; yield: 48%.

Tandem C-H thiolation/amination for benzopyridothiazines