Transition Metal free Synthesis of Phenothiazines from S-2-acetamidophenyl Ethanethioate and Ortho-Dihaloarenes

Yue Zhou[1], Qingle Zeng[1], Li Zhang[1]

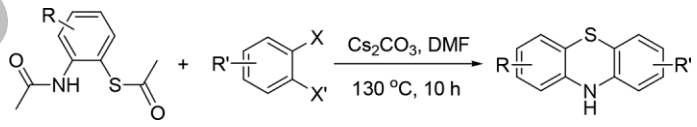
[1]State Key Laboratory of Geohazard Prevention and Geoenvironment Protection (Chengdu University of Technology), College of Materials, Chemistry & Chemical Engineering, Chengdu University of Technology, Chengdu, Sichuan, P. R. China.

Coresponding to author: Qingle Zeng State Key Laboratory of Geohazard Prevention and Geoenvironment Protection (Chengdu University of Technology), College of Materials, Chemistry & Chemical Engineering, Chengdu University of Technology, 1#, Dongsanlu, Erxianqiao, Chengdu 610059, Sichuan, P. R. China. E-mail: qinglezeng@hotmail.com

Abstract

An efficient cesium carbonate-mediated synthesis of phenothiazine derivatives from S-2-acetamidophenyl ethanethioates and ortho-dihaloarenes has been developed. This protocol affords an efficient approach for the construction of phenothiazine derivatives without the need of transition-metal catalyst or ligand. A plausible mechanism is proposed.

Graphical Abstact



KEYWORDS: Phenothiazines; cesium carbonate; S-2-acetamidophenyl ethanethioates; ortho-dihaloarenes; synthetic method

INTRODUCTION

Phenothiazines are extensively used in various fields, such as tricyclic antipycholic drugs, rubber solidation agents.[1] Thus synthesis of phenothiazines is becoming a hot research spot in recent years. In traditional methods, phenothiazines are prepared via heating diphenylamines and sulfur in high temperature,[2] or via Smiles rearrangement.[3] But the two reactions afford low yields, and have narrow substrate scopes, that is, the former is only suitable for some simple diphenylamines, and the latter are low atom economic and uses ortho-nitroaryl halides as the complex substrates. Derivatization of phenothiazine usually affords substituted phenothiazines with poor regioselectivity.[4]

In 2008 Jørgensen and coworkers discovered the synthesis of N-substituted phenothiazines via the palladium-catalyzed three component coupling of substituted 1-bromo-2-iodobenzenes, primary amines and 2-bromobenzenethiol.[5] Later Ma et al. reported CuI/L-proline-catalyzed cascade C-S and C-N coupling of 2-iodoanilines and 2-bromobenzenethiols.[6] In 2012 our group disclosed a copper-catalyzed tandem C-S/C-N coupling protocol, which avoids self-coupling reaction of the reactants via adopting ortho-aminothiophenols as bi-nucleophiles and ortho-dihalobenzenes as bi-electrophiles.[7] More recently Zhang et al. developed a greener iron-catalyzed protocol to construct the functionalized phenothiazines.[8]

Transition metal free synthetic method is beneficial for product purification and environment and becoming a research hotspot.[9] In 2012 Alok et al. developed a transition metal free synthetic protocol of phenothiazines via heating sulphur and the Schiff bases at high temperature (260-280 ^{o}C), which were prepared from cyclohexanone and diphenylamines.[10] In 2013 Deng and coworkers reported a new transition-metal-free synthesis of phenothiazines from cyclohexanones and 2-aminobenzenethiols via in situ condensation, addition and dehydrogenation.[11] Very recently Zhang reported an interesting transition-metal-free and ligand-free synthetic method of phenothiazines. They found potassium carbonate promoted tandem C–S and C–N coupling reaction between N-(2-iodophenyl)acetamides and 2-halo-benzenethiols.[12]

In view of the promising development of transition-metal-free arylation,[9] especially Bolm's transition-metal-free synthesis of N-substituted phenoxazines via the intramolecular N-arylations and Zhang's transition-metal-free and ligand-free synthesis of phenothiazines,[12] we envisioned that S-2-acetamidophenyl ethanethioate is possible to react with ortho-dihaloarenes at higher reaction temperature (Scheme 1), which is verified by our experiments.

As our on-going research on the cross coupling reactions,[13] especially on our synthesis of phenothiazines,[7] we discovered a novel transition metal free and ligand-free cesium

carbonate-promoted synthesis of phenothiazines from S-2-acetamidophenyl ethanethioate and ortho-dihaloarenes (Scheme 1).

RESULTS AND DISCUSSION

S-2-acetamidophenyl ethanethioates was facilely prepared via acetylation of ortho-aminothiophenols.[14]

With S-2-acetamidophenyl ethanethioates in hand, we tried a reaction of S-2-acetamidophenyl ethanethioate and ortho-bromoiodobenzene in DMF at 130 ^{o}C. To our surprise, this reaction gave 81% yield (Table 1, entry 1).

This promising result encouraged us to further study this new type reaction. To improve the reaction yield, the reaction conditions were examined (Table 1). Potassium carbonate gave lower yield than that of Cs_2CO_3 (Entry 2 vs. 1). The strong non-nucleophilic base sodium tert-butoxide afforded moderate yield (Entry 3), but KOH gave only 20% yield (Entry 4). The reason should be that nucleophilic base KOH causes the reagent S-2-acetamidophenyl ethanethioate saponification. The strong polar aprotic solvents DMSO and DMA gave poorer results (Entries 5 to 6). It seems that the reaction temperature highly influenced this reaction (Entries 7 to 9). Lower temperature of less than 110 ^{o}C resulted in little product (Entries 7 to 8), but high temperature of 150 ^{o}C was even not beneficial to this reaction (Entry 9). Shorter time afforded lower yield (Entries

10-11), but prolonging the reaction time under the conditions is not necessary (Entry 12). After screening bases, solvents, temperature and reaction time, the original conditions was still the best one (Entries 1-12).

With the optimized conditions in hand, we next explored S-2-acetamidophenyl ethanethioate and various aryl dihalides (Table 2). The lower reactive reagent 1-chloro-2-iodobenzene produced phenothiazine with lower yield (Entries 2 vs. 1). 1,2-Diiodobenzene with higher activity achieved high yield up to 91% (Entry 3).
It is obvious that one additional electron-withdrawing group on aryl dihalides, such as halo, trifluoromethyl, enhanced the reaction reactivity. Ortho-chloroiodobenzenes with an additional CF_3, Cl or Br group gave higher yields than ortho-chloroiodobenzene (Entries 4-6 vs 2). Similarly, ortho-bromoiodobenzene with an additional Cl or F group afforded better results (Entries 7-8 vs. 1). 1,4-Difluoro-2-iodobenzene with an ortho fluoro group of lower activity also offered a good yield (Entry 9).

A complicated substrate 1,3-dibromo-2-iodo-5-fluorobenzene with multiple reaction points gave lower yield (Entry 10). Although 2,3,5-triiodobenzoic acid afforded good yield with 2.0 mmol and 3.0 mmol (Entry 11-12), perhaps due to saponification, methyl 3-bromo-4-iodobenzonate gave much poorer yield (Entry 13). In order to avoid saponification, fresh distilled DMF (dried over CaH_2) was used to perform this reaction. Actually the saponification during the reaction was effectively inhibited, and the yield

was increased to 65% (Entry 14). With the fresh distilled DMF at hand, the reaction of S-2-acetamidophenyl ethanethioate and ortho-bromoiodobenzene was tried again. And higher yield of 86% was obtained, as means this type reaction is not promoted by trace water.

Dihalobenzene with an amino group 4-chloro-3-iodobenzenamine produced nothing (Entry 16), because amidation, a by-reaction occurred between the amino group of 4-chloro-3-iodobenzenamine and S-2-acetamidophenyl ethanethioate.

Substituted S-2-acetamidophenyl ethanethioates are also effective substrates for this reaction. 4-Chloro-S-2-acetamidophenyl ethanethioate with a chloro substituent also gave good yield (Entry 17).

These products are key intermediates of clinic tricyclic antidepressants, for example, phenothiazine (Entries 1-3), 3-(trifluoromethyl)-10H-phenothiazine (Entry 4) and 2-chloro-10H-phenothiazine (Entries 7-8) are the core structures of promethazine, trifluoperazine, chlorpromazine, respectively.

About the mechanism of this reaction, it is not very clear now. Some preliminary experiments were performed. This reaction cannot be carried out under acid condition or under neutral condition. The common radical scavenger

2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 3.0 equiv.) reacted with ortho-bromoiodobenzene, so much lower yield (18%) was obtained. Since the alkalic condition is necessary for this reaction, it probably is a base-promoted reaction.

Lee reported synthesis of symmetrical and unsymmetrical aryl sulfides by Pd-catalyzed couplings of aryl halides and thioacetates.[15] For example, in the presence of palladium catalyst and the base K_3PO_4, reaction of S-phenyl thioacetate and 4-tolyl bromide afforded phenyl tolyl thioether.[15] As means S-phenyl thioacetate will be turned into potassium benzenethiolate, which is the really nucleophile to couple with bromobenzene. With the same rule, acetyl group of N-acetylphenothiazine may be removed. A plausible mechanism is proposed as shows in Scheme 2.

S-2-acetamidophenyl ethanethioate **1a** is attacked by Cs_2CO_3, and turned into cesium 2-acetamidobenzenethiolate **4**, which attacks ortho-bromoiodobenzene via aromatic nucleophilic reaction to give an intermediate **5**. The intermediate **5** is deprotonated by Cs_2CO_3 to give cesium salt **6**. An intramolecular aromatic nucleophilic substitution of cesium salt **6** produces N-acetylphenothiazine **7**. Due to strong alkalinity and the higher temperature, acetyl group of N-acetylphenothiazine **7** is removed by Cs_2CO_3 to give phenothiazine's cesium salt **8**, which grasps a proton from $CsHCO_3$ or other proton sources and produces phenothiazine **3a**.

CONCLUSION

We discovered an efficient, transition metal free synthesis of phenothiazines via reaction of S-2-acetamidophenyl ethanethioate and ortho-dihaloarenes. This new protocol is simple, operation easy, ligand free and transition metal free. The products phenothiazines may be used in drug synthesis and in fine chemical industries. A plausible mechanism is proposed.

EXPERIMENTAL

Transition Metal Free Synthesis Of Phenothiazine From S-2-Acetamidophenyl Ethanethioate

To an oven-dried 25 mL ground mouth test tube equipped with a stir bar was added S-2-acetamidophenyl ethanethioate (0.5 mmol), 1-bromo-2-iodobenzene (0.6 mmol), Cs_2CO_3 (2.0 mmol), DMF (3 mL). The test tube was sealed with a sleeve rubber stopper and evacuated and refilled with argon for three cycles. The mixture was stirred 130 ^oC for 10 hours. After cooling to room temperature, the reaction mixture was quenched with water (20 mL), and extracted with ethyl acetate (20 mL) for three times. The combined organic layer was dried with anhydrous $MgSO_4$, and condensed in vacuum on a rotary evaporator. The residual was purified on a silica gel chromatograph column by means of gradient elution (eluent: petroleum ether / ethyl acetate) to give a white solid, mp 179-182 ^oC. ^1H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.04 (td, J = 7.8, 1.5 Hz, 2H), 6.97 (dd, J = 7.6, 1.3 Hz, 2H), 6.81 (td, J = 7.5, 1.2 Hz, 2H), 6.74 (dd, J = 7.9, 1.1 Hz,

2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 142.57 (s), 128.03 (s), 126.72 (s), 122.25 (s), 116.78 (s), 114.89 (s).

FUNDING

We thank the National Natural Science Foundation of China (No. 21372034), the Department of Science and Technology of Sichuan Province (No. 2016HH0074), the Education Department of Sichuan Province (No. 16ZA0084) for financial support.

SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

REFERENCES

1. (a) Korth, C.; May, B. C. H.; Cohen, F. E.; Prusiner, S. B. *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98*, 9836-9841; (b) Melvin, J. Y.; Jefferson, R. M. *J. Med. Chem.* **1992**, *35*, 716-724; (c) Kataria, V. B.; Solanki, M. J.; Trivedi, A. R.; Shah, V. H. *Lett. Drug Des. Discov.* **2013**, *10*, 951-956.

2. Mayer, M.; Lang, P. T.; Gerber, S.; Madrid, P. B.; Pinto, I. G.; Guy R. K.; James, T. L. *Chem. Biol.* **2006**, *13*, 993-1000.

3. (a) Rathore, R. S.; Jain, M.; Gupta, A.; Saraswat, V.; Gupta, V.; Gupta, R. R. *Pharmazie* **1992**, *47*, 945-946; (b) Sharma, N.; Gupta, R.; Kumar, M.; Gupta, R. R. *J. Fluorine Chem*. **1999**, *98*, 153-157.

4. (a) Lai, R. Y.; Kong, X.; Jenekhe, S. A.; Bard, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 12631-12639; (b) Sailer, M.; Franz, A. W.; Müller, T. J. J. *Chem. Eur. J.* **2008**, *14*, 2602-2614.

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

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

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

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

9. (a) Roopan, S. M.; Palaniraja, J. *Res. Chem. Intermed.* **2015**, *41*, 8111-8146; (b) Zhao, J.; Zhao, Y.; Fu, H. *Angew. Chem.* **2011**, *123*, 3853-3857; (c) Thomé, I.; Bolm, C. *Org. Lett*. **2012**, *14*, 1892-1895.

10. Alok, M.; Debobrata, S.; Jayanta, D.; Pranab, G. *J. Pharm. Sci. Innov.* **2012**, *1*, 41-42.

11. Liao, Y.; Jiang, P.; Chen, S.; Xiao, F.; Deng, G.-L. *RSC Adv.* **2013**, *3*, 18605-18608.

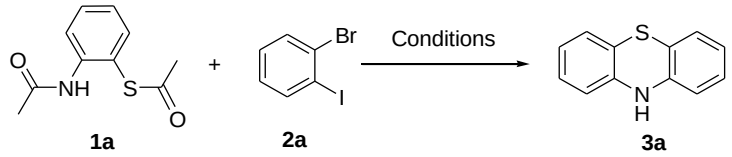
12. Wu, S.; Hu, W.-Y.; Zhang, S.-L. *RSC Adv*. **2016**, *6*, 24257-24260.

13. (a) Dong, J.; Wang, Y.; Xiang, Q.; Lv., X.; Weng, W.; Zeng, Q. *Adv. Synth. Catal.* **2013**, *355*, 692-696; (b) Wang, Y.; Tu, X.; Lv, X.; Zhou, L.; Zeng, Q. *Tetrahedron Lett*. **2013**, *54*, 6045-6048.

14. Sabitha, G.; Reddy, B.V. S.; Srividya, R.; Yadav, J. S. *Synth. Commun.* **1999**, *29*, 2311-2315.

15. Park, N.; Park, K.; Jang, M.; Lee, S. *J. Org. Chem.* **2011**, *76*, 4371-4378.

Table 1. Optimization of reaction conditions of S-2-acetamidophenyl ethanethioate and 1-bromo-2-iodobenzene

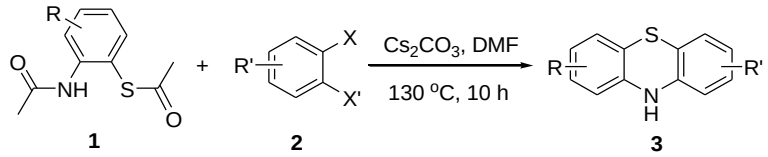


1a **2a** **3a**

Entry	Base	Solvent	Temp. (^{o}C)	Time (h)	Yield (%)
1	Cs_2CO_3	DMF	130	10	81
2	K_2CO_3	DMF	130	10	72
3	t-BuONa	DMF	130	10	60
4	KOH	DMF	130	10	25
5	Cs_2CO_3	DMSO	130	10	67
6	Cs_2CO_3	DMA	130	10	39
7	Cs_2CO_3	DMF	90	10	18
8	Cs_2CO_3	DMF	110	10	25
9	Cs_2CO_3	DMF	150	10	78
10	Cs_2CO_3	DMF	130	6	53
11	Cs_2CO_3	DMF	130	8	68
12	Cs_2CO_3	DMF	130	12	80

Reaction conditions: S-2-acetamidophenyl ethanethioate (0.5 mmol), 1-bromo-2-iodobenzene (0.6 mmol), base (2.0 mmol), solvent (3 mL), temperature, time, argon.

Table 2. Evaluation of S-2-acetamidophenyl ethanethioate and various aryl dihalides under catalyst-free conditions.[a]



1 **2** **3**

Entry	R	X	X′	R′	**3**	Yield (%)
1	H	1-Br	2-I	H	**3a**	81
2	H	1-Cl	2-I	H	**3a**	54
3	H	1-I	2-I	H	**3a**	91
4	H	1-Cl	2-I	4-CF_3	**3b**	65
5	H	2-Cl	3-I	1-Cl	**3c**	64
6	H	1-I	2-Cl	4-Br	**3d**	70
7	H	1-I	2-Br	4-Cl	**3e**	88
8	H	1-I	2-Br	4-F	**3f**	82
9	H	1-F	2-I	4-F	**3g**	80
10	H	1-Br	2-I	3-Br, 5-F	**3h**	65
11	H	2-I	3-I	5-I, 1-COOH	**3i**	73
12[c]	H	2-I	3-I	5-I, 1-COOH	**3i**	75
13	H	3-Br	4-I	1-$COOCH_3$	**3j**	42
14[d]	H	3-Br	4-I	1-$COOCH_3$	**3j**	65
15[d]	H	1-Br	2-I	H	**3a**	86

16	H	4-Cl	3-I	1-NH_2	--	0
17	4-Cl	1-Br	2-I	H	**3c**	81

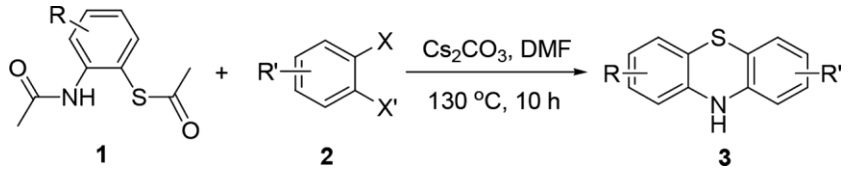
[a] Reaction conditions: S-2-acetamidophenyl ethanethioate (0.5 mmol), 1-bromo-2-iodobenzene (0.6 mmol), Cs_2CO_3 (2.0 mmol), DMF (3 mL), 130 ^oC, 10 h, argon.

[b] Isolated yield.

[c] Cs_2CO_3 (3.0 mmol) was added.

[d] Fresh distilled DMF (dried over CaH_2) as solvent.

Scheme 1. Cesium carbonate-promoted synthesis of phenothiazines from S-2-acetamidophenyl ethanethioate and ortho-dihaloarenes



Scheme 2. A plausible mechanism