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Four-Component Approach to *N*-Substituted Phenothiazines under Transition-Metal-Free Conditions

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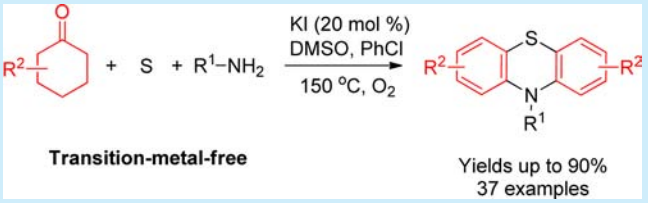
Supporting Information

ABSTRACT: An efficient synthesis of *N*-substituted phenothiazines has been developed from readily available amines, cyclohexanones, and elemental sulfur. The combination use of KI/DMSO in an oxygen atmosphere significantly improved the reaction yields.



Phenothiazines represent an important class of heterocyclic compounds and exhibit valuable bioactivities. Over 100 phenothiazine derivatives have been used as neuroleptics in clinical settings.[1] The phenothiazines have also been used as antitubercular agents, cholinesterase inhibitors, an MDR (multiple drug resistance) reverting agent, and antihistaminics (Figure 1).[2] Additionally, substituted phenothiazines have

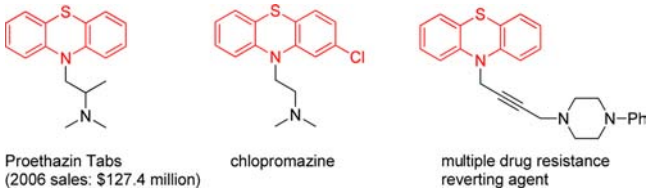


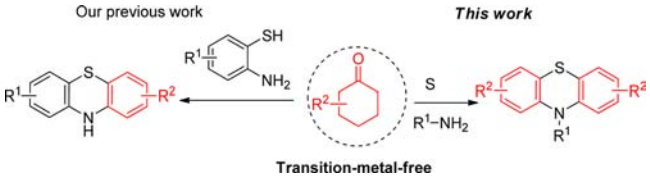
Figure 1. Important drugs containing phenothiazine core.

frequently been found in many functional materials such as polymerization inhibitors, optoelectronic materials, and dyes.[3] Conventionally, phenothiazines were synthesized from diarylamines and sulfur via iodine-catalyzed thionation reactions.[4] However, regioselective control of the thionation at high temperature is challenging when *meta*-substituted diarylamines are used. The Smiles rearrangement process could provide an alternative route to preparing them with good selectivity, but multiple steps are required.[5] Arylation or alkylation of the heterocyclic phenothiazine core could provide a different efficient method for substituted phenothiazine preparation.[6]

Transition-metal-catalyzed coupling reactions were proven to be versatile for the construction of substituted phenothiazines via the coupling of two aromatic substrates, with both having two reactive functional groups at the *ortho* position of the phenyl ring. In 2008, Jørgensen and co-workers developed a palladium-catalyzed three-component approach to synthesize *N*-substituted phenothiazines.[7] In 2010, Ma et al. developed the first copper-catalyzed substituted phenothiazine synthesis from 2-bromothiophenols and 2-iodoanilines via cascade C−S and C−N bond formation.[8] In 2012, Zeng et al. disclosed another efficient approach for phenothiazine synthesis from aryl *ortho*-dihalides and 2-aminobenzenethiols under copper catalysis conditions.[9] In these excellent protocols, the regioselectivity could be precisely controlled by choosing a different transition-metal catalysis system. However, the use of two *ortho* difunctionalized aromatic starting materials limited the reaction scope. Although a few other methods are available,[10] phenothiazine synthesis from readily available materials without the use of a metal catalyst is highly desirable, especially for pharmaceutical drug synthesis.[11]

Cyclohexanones are easily available, inexpensive, and widely used as organic synthetic intermediates. In 2011, Stahl and co-workers found that cyclohexanones could be converted into cyclohexenes or phenols using palladium as the catalyst and molecular oxygen as the hydrogen acceptor.[12] In recent years, we and other groups successfully utilized the dehydrogenation intermediates of cyclohexanones for the further construction of C−C[13] and C−hetero[14] bonds as well as heterocycles[15] in the presence or absence of transition metals.[16] Very recently, we also utilized this strategy for the construction of phenothiazine from 2-aminobenzenethiols and cyclohexanones (Scheme 1).[17] However, this method used highly functionalized and malodorous 2-aminobenzenethiols as the coupling partners and thus limited its substrate scope. As a part of our continuing effort to develop efficient methods for heterocycle formation from easily available starting materials, herein, we report a four-

Scheme 1. Phenothiazine Synthesis from Cyclohexanones



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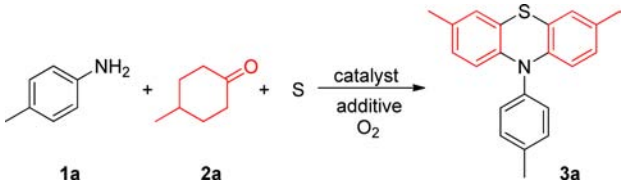
component strategy for *N*-substituted phenothiazine formation from inexpensive and readily available amines, cyclohexanones, and elemental sulfur without the aid of a transition-metal catalyst.

To obtain the optimized reaction conditions, we initiated our research by examining the reaction of *p*-toluidine (**1a**) with 4-methylcyclohexanone (**2a**) and elemental sulfur in chlorobenzene under an oxygen atmosphere at 150 °C. When 20 mol % of KI was used as the catalyst, the desired *N*-substituted phenothiazine **3a** was obtained in 37% yield (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



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

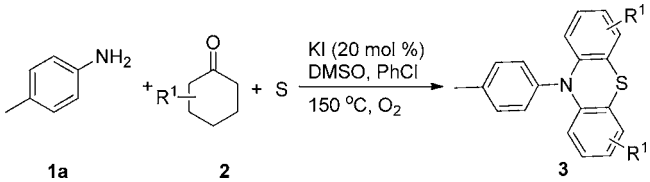
entry	catalyst	additive	solvent	yield (%)[b]
1	KI	none	PhCl	37
2	KI	TBHP	PhCl	52
3[c]	KI	DMSO	PhCl	75
4	KI	DMSO	PhCl	88
5	KI	benzylphenyl sulphone	PhCl	70
6	KI	diphenyl sulfoxide	PhCl	68
7	NH_4I	DMSO	PhCl	55
8	NIS	DMSO	PhCl	41
9	I_2	DMSO	PhCl	66
10	KI	DMSO	toluene	81
11	KI	DMSO	NMP	35
12	KI	DMSO	*o*-DCB	63
13	KI	DMSO	$C_2H_2Cl_4$	52
14[d]	KI	DMSO	PhCl	68
15[e]	KI	DMSO	PhCl	72
16[f]	KI	DMSO	PhCl	73
17[g]	KI	DMSO	PhCl	43

[a]Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), sulfur (0.8 mmol), catalyst (0.04 mmol), additive (0.8 mmol), solvent (0.6 mL), 150 °C, 14 h, under oxygen unless otherwise noted. [b]GC yield. [c]DMSO (0.4 mmol). [d]Sulfur (0.6 mmol). [e]Under air. [f]140 °C. [g]Under N_2.

The reaction yield of the desired product could be improved to 52% when *tert*-butyl peroxide (TBHP) was used as the oxidant (entry 2). Addition of organic additives containing a sulfone group could significantly increase the reaction yield (entries 3−6). Among the various additives screened, the combination use of KI/DMSO showed the best efficiency to give **3a** in 88% yield (entry 4). With DMSO as the organic additive, several iodide-containing chemicals were tested for this kind of transformation and were found to be less efficient (entries 7−9). Besides chlorobenzene, toluene is also a good reaction media for this kind of reaction to provide **3a** in 81% yield (entry 10). Other organic solvents such as NMP, 1,2-dichlorobenzene, and 1,1,2,2-tetrachloroethane all significantly reduced the reaction efficiency (entries 11−13). When 3 equiv of sulfur were used, the desired product was obtained in 68% yield (entry 14). A poor yield resulted when oxygen was replaced by air (entry 15). A high temperature is necessary to ensure good conversion of the starting materials (entry 16).

With these optimized conditions in hand, cyclohexanones with various substituents at different positions were used to react with *p*-toluidine (**1a**) and elemental sulfur (Table 2). In

Table 2. Reaction of 1a with Various Cyclohexanones (2)[a]



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

entry	cyclohexanone		product	yield (%)[b]
1	R^1 = 4-Me	**2a**	**3a**	86
2	R^1 = 4-Et	**2b**	**3b**	77
3	R^1 = 4-*n*-propyl	**2c**	**3c**	83
4	R^1 = 4-isopropyl	**2d**	**3d**	76
5	R^1 = 4-*tert*-butyl	**2e**	**3e**	72
6	R^1 = 4-*n*-pentyl	**2f**	**3f**	84
7	R^1 = 4-*tert*-pentyl	**2g**	**3g**	77
8	R^1 = 4-Ph	**2h**	**3h**	90
9	R^1 = 4-(C_6H_4-4-OH)	**2i**	**3i**	58
10	R^1 = 4-CO_2Et	**2j**	**3j**	59
11	R^1 = 2-Me	**2k**	**3k**	trace

[a]Conditions: **1a** (0.2 mmol), **2** (0.6 mmol), KI (0.04 mmol), DMSO (0.8 mmol), sulfur (0.8 mmol), PhCl (0.6 mL), 150 °C, 14 h, under oxygen. [b]Isolated yields based on **1a**.

general, good yields were achieved when alkyl substituents were presented at the *para* position of cyclohexanone (entries 1−7). From comparison with linear alkyl substituents, lower yields were obtained when branched alkyls were presented. When 4-phenylcyclohexanone (**2h**) was treated with **1a** and sulfur powder, the desired product **3h** was isolated in 90% yield (entry 8). However, a much lower yield was observed when a hydroxy group was presented at the phenyl ring of 4-phenylcyclohexanone (entry 9). An ester group was tolerated to give **3j** in moderate yield (entry 10). When 2-methylcyclohexanone (**2k**) was used as the substrate, no desired product was obtained as detected by GC analysis (entry 11).

Subsequently, a range of amines were subjected to this transition-metal-free system (Table 3). The reactions with aromatic amines bearing electron-donating substituents at C4 of the amino group proceeded efficiently to afford various *N*-arylated phenothiazines in moderate yields (entries 2−4). When strong electron-withdrawing groups were employed, much lower yields were obtained (entries 8 and 9). Active functional groups including chloro, bromo, acetyl, and hydroxy were tolerated under the optimal conditions (entries 6−7, 10−11). No significant change was observed when the substituents were located at the *meta* or *ortho* position of amines (entries 12−17). Interestingly, aliphatic octan-1-amine also could smoothly react with **2a** and sulfur to give the *N*-alkylated phenothiazine **3ag** in 68% yield (entry 22).

To acquire unsymmetrical *N*-substituted phenothiazines, the reaction of *p*-toluidine (**1a**) with two different cyclohexanones was investigated. When **1a** reacted with 4-methylcyclohexanone (**2a**) and 4-phenylcyclohexanone (**2h**), the corresponding unsymmetrical product **4a** was obtained in 28% yield (Scheme 2). A better yield was achieved when **2a** was replaced by ethyl 4-oxocyclohexanecarboxylate (**2j**). Interestingly, the reaction of benzene-1,4-diamine (**1x**) with **2a** afforded the corresponding product **3xa** in 68% yield (Scheme 3). In this transformation, four C−N and four C−S bonds were assembled in one pot. Similarly, aromatic benzidine (**1y**) and aliphatic hexane-1,6-diamine (**1z**) both could be smoothly reacted with **2a** and sulfur.

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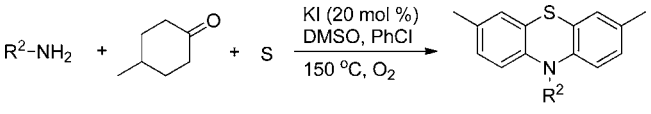
Table 3. Reaction of 2a with Various Amines (1)[a]

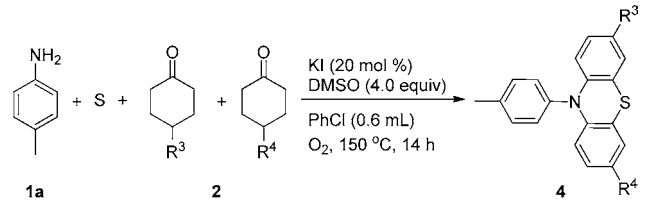


1 2a 3

entry	R^2		product	yield (%)[b]
1	Ph	**1b**	**3l**	74
2	4-isopropyl-C_6H_4	**1c**	**3m**	64
3	4-^{t}Bu-C_6H_4	**1d**	**3n**	56
4	4-MeO-C_6H_4	**1e**	**3o**	71
5	4-Ph-C_6H_4	**1f**	**3p**	63
6	4-Cl-C_6H_4	**1g**	**3q**	78
7	4-Br-C_6H_4	**1h**	**3r**	65
8	4-O_2N-C_6H_4	**1i**	**3s**	40
9	4-CF_3O-C_6H_4	**1j**	**3t**	54
10	4-MeOC-C_6H_4Et	**1k**	**3u**	66
11	4-HO-C_6H_4	**1l**	**3v**	54
12	3-Me-C_6H_4	**1m**	**3w**	57
13	3-Cl-C_6H_4	**1n**	**3x**	62
14	3-O_2N-C_6H_4	**1o**	**3y**	52
15	2-Me-C_6H_4	**1p**	**3z**	61
16	2-Cl-C_6H_4	**1q**	**3qa**	57
17	2-Br-C_6H_4	**1r**	**3ra**	52
18	2,4-dimethyl-C_6H_3	**1s**	**3sa**	65
19	4-Br,2-Me-C_6H_3	**1t**	**3ta**	64
20	2,4,6-trimethyl-C_6H_2	**1u**	**3ua**	62
21	2,6-diisopropyl-C_6H_3	**1v**	**3va**	43
22	*n*-C_8H_{17}	**1w**	**3wa**	68

[a]Conditions: **1** (0.2 mmol), **2a** (0.6 mmol), KI (0.04 mmol), DMSO (0.8 mmol), sulfur (0.8 mmol), PhCl (0.6 mL), 150 °C, 14 h, under oxygen. [b]Isolated yields based on **1**.

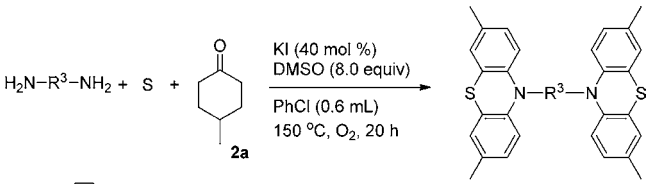
Scheme 2. Unsymmetrical Substituted Phenothiazine Synthesis



1a 2 4

R^3 = Me R^4 = Ph **4a** 28%
R^3 = Me R^4 = COOEt **4b** 48%

Scheme 3. Reaction of Diamines with 2a and Sulfur

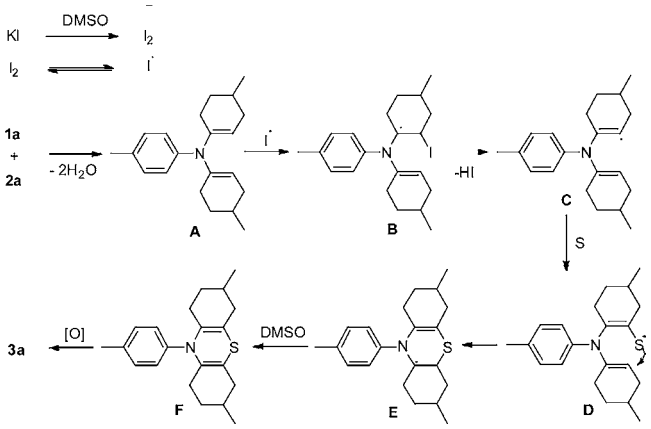


2a

R^3 = **1x** **3xa** 68%
R^3 = **1y** **3ya** 31%
R^3 = $-C_6H_{12}-$ **1z** **3za** 53%

Based on the observations and the literature, a plausible mechanism is outlined in Scheme 4. Oxidation of KI with DMSO generates I_2 which can be further converted into an iodine radical.[18] Condensation of **1a** with two equiv of **2a**

Scheme 4. Proposed Mechanism



affords an enamine intermediate **A** which then reacts with an iodine radical to give intermediate **B**. Elimination reaction of **B** generates a radical intermediate **C** which can react with elemental sulfur affording a sulfur radical **D**.[19] Intramolecular addition of a sulfur radical with C=C bond generates compound **E**.[20] Subsequent reaction of **E** with DMSO generates compound **F**.[21] Oxidative dehydrogenation of intermediate **F** affords the final product **3a**.[14i,17,20a]

In summary, we have disclosed a concise procedure for *N*-substituted phenothiazine formation from amines, cyclohexanones, and elemental sulfur. Both of the aryl rings in the phenothiazine moiety came from cyclohexanones via a condensation−dehydrogenation sequence. The condensation, dehydrogenation, tautomerization, and double C−S bond formation were achieved in one pot with the aid of a KI/DMSO/O_2 system. Active substitutents such as nitro, hydroxy, chloro, bromo, and ester groups all survived under the current reaction systems. Since amines, cyclohexanones, and sulfur were inexpensive and readily available starting materials, this four-component procedure affords an efficient method for the rapid construction of *N*-substituted phenothiazines without the use of a noble metal catalyst.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03058.

General experimental procedure and characterization data of the products (PDF)

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Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

The toc/abs graphic and Scheme 1 contained an error in the version published November 23, 2015. An R_2 was corrected to R^2 and the correct version reposted later on November 23, 2015.

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