Homogeneous Catalysis

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Assembly of Substituted Phenothiazines by a Sequentially Controlled CuI/L-Proline-Catalyzed Cascade C–S and C–N Bond Formation**

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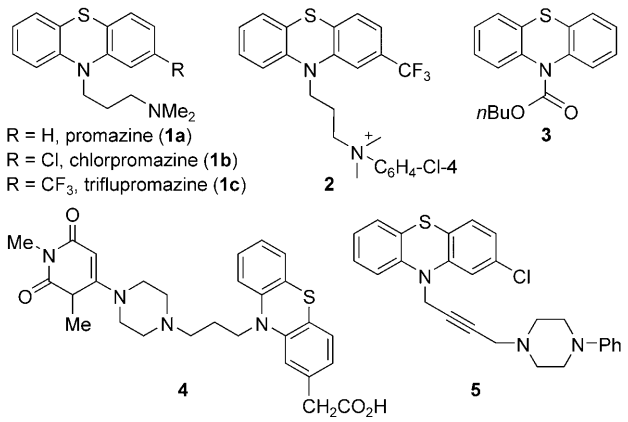
The phenothiazine structural motif has been successfully employed in the design of a variety of pharmaceuticals. Successful examples include promazine drugs (**1a–c**), which are clinically used for psychotropic medication;[1] quaternized trifluoropromazine derivative **2** that has antitubercular activity;[2] cholinesterase inhibitor **3**;[3] histamine H_1 antagonist **4**;[4] and MDR (multiple drug resistance) reverting agent **5**.[5] Substituted phenothiazines have also attracted interest



because of their optoelectrochemical and photophysical properties. Phenothiazines have been utilized as, for example, molecular wires,[6] electrogenerated chemiluminescene (ECL) emitters,[7] chemosensors for the selective fluorescence detection of flavins,[8] and intramolecular electron donors for the photoinduced reductive repair of thymine glycol.[9] As the substituents on the phenothiazine rings have a great influence on their properties, efficient methods for the preparation of a diverse range of substituted phenothiazines are highly desirable.

Traditionally, phenothiazines are synthesized using the iodine-catalyzed reaction of diphenylamines with sulfur.[10] When *meta*-substituted diphenylamines are employed, the thionation reaction proceeds at high temperatures to afford two regioisomers in a near 1:1 ratio. Because of their high structural similarity, separation of these regioisomers is difficult, and fractional crystallization has been frequently used to solve this problem. To overcome this drawback, a four-step procedure based on the Smiles rearrangement was developed to assemble substituted phenothiazines from 2-aminobenzenethiol and substituted 2-chloro-nitrobenzenes.[11a] However, the difficulty of this synthesis has limited the application of this protocol.[11b,c] Functionalization of unsubstituted phenothiazine is another commonly used approach,[12,13] although this suffers from a lack of regioselectivity in most cases. More recently, Jørgensen and coworkers reported an elegant method for preparing substituted phenothiazines that relied on the palladium-catalyzed three-component coupling reaction of substituted 1-bromo-2-iodobenzenes, primary amines and 2-bromo-benzenethiol.[14] However, in most cases substituted 2-iodoanilines are more readily available than substituted 1-bromo-2-iodobenzenes; therefore, we investigated the use of the former as the coupling partner in the reactions with 2-bromobenzenethiols. To our delight, this coupling reaction was effectively catalyzed by CuI/L-proline to produce substituted phenothiazines in high yields, thereby offering a general and efficient approach to these heterocycles.[15] Herein, we wish to present these results.

In our previous studies, we showed that CuI/L-proline can catalyze the N-arylation[16] of aryl amines, and the S-arylation[17] of aryl thiols. As both 2-haloanilines and 2-halobenzenethiols have two reaction centers that can undergo cross-coupling reactions, controlling the reaction sequence is essential for obtaining the desired products in good yields. Because aryl thiols are more reactive than aryl amines in CuI/L-proline-catalyzed coupling reactions,[18] we decided to employ the less reactive 2-bromobenzenethiols as the substrates in our investigation. We expected that these reagents would couple exclusively with 2-iodoanilines, and not undergo self-coupling to their corresponding dimerization products. Therefore, the reaction of 2-iodoaniline with 2-bromobenzenethiol in the presence of a CuI/L-proline catalyst (10 mol% and 20 mol%, respectively) in dimethoxyethane at 90 °C afforded only the simple S-arylation product **9a** in 90% yield (Table 1, entry 1), which indicated that the first coupling reaction proceeded smoothly and in accordance with our planned reaction sequence. Next, we heated the reaction mixture at 110 °C to attempt to facilitate the N-arylation cyclization step. However, in this case we observed a

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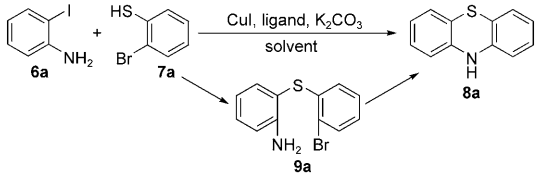
Table 1: CuI-catalyzed coupling of 2-iodoaniline and 2-bromobenzenethiol under different reaction conditions.[a]



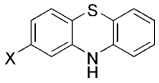
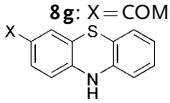
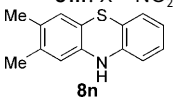
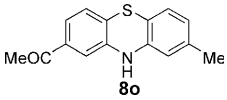
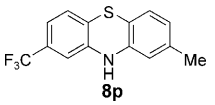
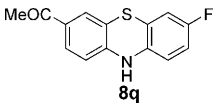
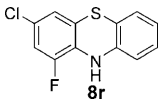
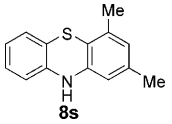
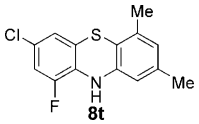
Entry	Ligand[b]	Solvent	Product	Yield [%][c]
1	A	dimethoxyethane	**9a**	90[d,e]
2	A	DMSO	**8a**	66
3	A	*N*-methylpyrrolidone	**8a**	48
4	A	dioxane	**8a**	22
5	A	1,3-dimethoxypropane	**8a**	18
6	A	2-methoxyethanol	**8a**	77
7	A	2-methoxyethanol	**8a**	62[d]
8	B	2-methoxyethanol	**8a**	36
9	C	2-methoxyethanol	**8a**	52
10	D	2-methoxyethanol	**8a**	32

[a] Reaction conditions: **6a** (0.5 mmol), **7a** (0.55 mmol), CuI (0.1 mmol), ligand (0.2 mmol), K_2CO_3 (2.5 mmol), solvent (2 mL), 90 °C, 48 h; then 110 °C, 72 h. [b] Ligand: A = L-proline, B = *trans*-4-hydroxy-L-proline, C = *N*,*N*-dimethylglycine, D = 1,10-phenanthronine. [c] Yield of isolated product. [d] 0.05 mmol of CuI and 0.1 mmol of L-proline were added. [e] The reaction was carried out at 90 °C for 48 h.

complicated mixture containing the desired product **8a**. Changing the solvent to DMSO and increasing the catalytic loading afforded the isolated product **8a** in 66% yield, although some unidentified side products were also formed (Table 1, entry 2). These results demonstrated that the solvent plays a key role in this cascade reaction process; therefore, other polar solvents were then examined. The reaction in *N*-methylpyrrolidone gave **8a** in moderate yield (Table 1, entry 3), whereas dioxane and 1,3-dimethoxypropane both gave phenothiazine **8a** in low yields (Table 1, entries 4 and 5); the best result was obtained using 2-methoxyethanol (Table 1, entry 6). Reducing the loading of the CuI catalyst to 10 mol% caused the reaction yield to drop to 62% (Table 1, entry 7). Under these reaction conditions, three other ligands gave **8a** in relatively low yields (Table 1, entries 8–10). Thus, we established our optimized reaction conditions to be using L-proline as a ligand and 2-methoxyethanol as the solvent.

After the optimized reaction conditions were established, we examined the scope and the limitations of our cascade process for the assembly of substituted phenothiazines (Table 2). Using 2-bromobenzenethiol **7a** as a coupling partner, we tested a number of substituted 2-iodoanilines. It was found that 5-substituted 2-iodoanilines containing both electron-rich and electron-deficient substituents worked well, giving their corresponding 2-substituted 10*H*-phenothiazines in good yields (Table 2, entries 1–7). However, the electronic influence of the substituent has a marked effect on the reaction rate of both the S-arylation and the N-arylation steps. In the S-arylation step, 2-iodoanilines bearing an electron-withdrawing group generally reacted faster than those with an electron-donating group (Table 2, compare entries 1 and 2 with 3–7). However, this trend was inverted in the N-arylation step, made evident by the longer reaction times required by

Table 2: CuI/L-proline-catalyzed coupling of 2-iodoanilines and 2-bromobenzenethiols for the assembly of substituted phenothiazines.[a]

Entry	Product	*t* 1 [h]	*t* 2 [h]	Yield [%][b]
1	 **8b**: X = OMe	40	50	71
2	**8c**: X = Me	40	60	75
3	**8d**: X = F	24	72	85
4	**8e**: X = Cl	28	72	85
5	**8f**: X = CF_3	28	72	83
6		48	96	70[c]
7	**8g**: X = COMe	30	70	79
8	 **8h**: X = OMe	40	48	73
9	**8i**: X = CF_3	26	72	86
10	**8j**: X = COMe	30	67	77
11	**8k**: X = CN	30	72	82
12	**8l**: X = CO_2Me	35	68	85
13	**8m**: X = NO_2	30	72	84
14	 **8n**	48	60	64
15	 **8o**	28	70	88[d]
16	 **8p**	26	72	85[d]
17	 **8q**	40	60	77[e]
18	 **8r**		48[f]	80
19	 **8s**		70[f]	46[g]
20	 **8t**		48[f]	81[g]

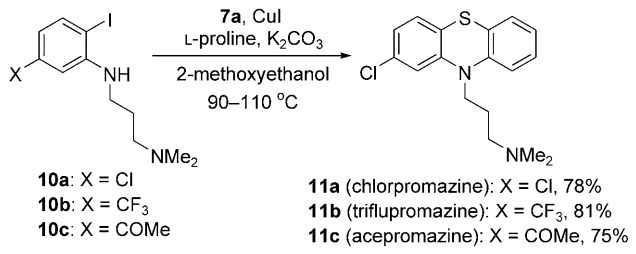
[a] Reaction conditions: 2-iodoaniline (0.50 mmol), **7a** (0.55 mmol), CuI (0.10 mmol), L-proline (0.20 mmol), K_2CO_3 (2.5 mmol), 2 mL of 2-methoxyethanol, 90 °C, *t* 1; then 110 °C, *t* 2. [b] Yield of isolated product. [c] The reaction was carried out in DMSO with 4 mmol of 2-iodo-4-trifluoromethylaniline. [d] 2-Bromo-4-methylbenzenethiol was used as the coupling partner. [e] 2-Bromo-5-fluorobenzenethiol was used as the coupling partner. [f] DMSO, 90 °C, for the indicated time. [g] 2-Bromo-4,6-dimethylbenzenethiol was used as the coupling partner.

the more electron-deficient anilines to complete the cyclization. This phenomenon is consistent with previous studies on CuI/L-proline-catalyzed reactions,[16,17] and can be rationalized by comparing the different nucleophilicities caused by their substituents. A similar reactivity trend was also noted when 4-substituted 2-iodoanilines were utilized as substrates.

Their reaction with **7a** afforded 3-substituted phenothiazines **8h–m** in yields ranging from 73% to 86% (Table 2, entries 8–13). Furthermore, the reaction could be scaled up to the gram-scale without any problems (Table 2, entry 6).

2,3-Dimethyl-10*H*-phenothiazine **8n** was obtained from 4,5-dimethyl-2-iodoaniline in 64% yield (Table 2, entry 14). To further demonstrate the capability of this process for the elaboration of polysubstituted phenothiazines, we attempted the coupling reactions between substituted 2-bromobenzenethiols and substituted 2-iodoanilines, and were pleased to isolate 2,8-disubstituted phenothiazines **8o** and **8p**, the 3,7-disubstituted phenothiazines **8q**, the 1,3-disubstituted phenothiazine **8r**, the 6,8-disubstituted phenothiazine **8s**, and the 1,3,6,8-tetrisubstituted phenothiazine **8t** in satisfactory yields (Table 2, entries 15–20). These results demonstrated that we would be able to introduce functional groups at the 1, 2, 3, 6, 7, and/or 8-positions of the phenothiazine ring by employing suitable coupling partners. A wide range of functional groups, such as fluoro, nitro, keto, methoxy, ester, and cyano groups were well-tolerated under these reaction conditions, which, along with the ability to decorate the phenothiazine ring at a variety of positions, makes this process very promising for synthesizing phenothiazines of great diversity. Importantly, 2-bromobenzenethiols were essential for this reaction as low yields were observed when 2-chlorobenzenethiol was used as the coupling partner.

Next, we moved our attention to employing N-substituted 2-iodoanilines to synthesize N-substituted phenothiazines. The coupling reactions of diamines **10a–10c** with **7a** worked well, providing chlorpromazine **11a**, triflupromazine **11b**, and acepromazine **11c** in 75–81% yields (Scheme 1). These three compounds are clinically used psychotropic drugs, whilst chlorpromazine **11a** has shown potential for the treatment of tuberculosis.



Scheme 1. Synthesis of three psychotropic promazine drugs.

In conclusion, we have developed a new approach to construct functionalized phenothiazines, starting from substituted 2-iodoanilines and 2-bromobenzenethiols, based on a sequentially controlled CuI/L-proline-catalyzed cascade process. The efficiency and substituent tolerance of this procedure have been fully demonstrated by synthesizing a number of functionalized phenothiazines. Some of these products are known psychotropic drugs or intermediates for preparing bioactive compounds. Considering the inexpensive catalytic system, and the convenient availability of the starting materials, this method can find numerous applications in organic synthesis.

Experimental Section

Typical procedure: An oven-dried Schlenk tube was charged with 2-iodoaniline **6a** (0.5 mmol), CuI (19 mg, 0.1 mmol), L-proline (11.5 mg, 0.2 mmol), and K_2CO_3 (2.5 mmol). The tube was evacuated and backfilled with argon, and then 2-bromobenzenethiol **7a** (0.55 mmol) and 2-methoxyethanol (2.0 mL) were added. The reaction mixture was stirred at 90 °C for 24–48 h and then heated to 110 °C for 48–72 h. After removal of the solvent in vacuo, the residue was partitioned between ethyl acetate and water. Extraction work-up followed by silica gel chromatography gave the desired phenothiazine.

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[18] Under CuI/L-proline catalysis, S-arylation of aryl iodides and aryl thiols occurred at 70 °C, whilst N-arylation of aryl iodides and anilines took place at 90 °C; see references [16a] and [17a].

