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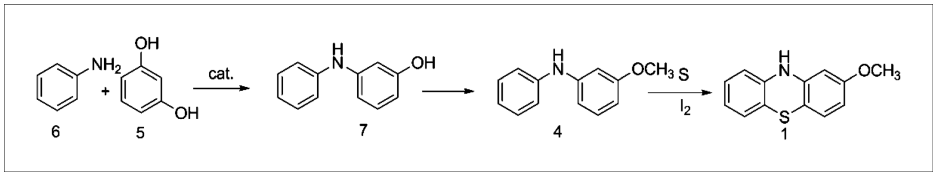

A procedure for synthesis of 2-methoxyphenothiazine (**1**) has been developed, starting from resorcinol and aniline by condensation, following methylation and cyclization. *p*-Toluenesulfonic acid and polysubstituted aromatics were employed as the catalyst of condensation and the solvent of cyclization, respectively, to improve the yield. The use of parallel experiments, statistical experimental design, and multivariate modeling made the total yield of the procedure as high as 74.2%.

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INTRODUCTION

2-Methoxyphenothiazine (**1**) (Chart 1) is an important phenothiazine (**2**) derivative, which was widely used in the preparation of antioxidants [1], pharmaceuticals [2], and polymerization inhibitors [3]. Further, it shows remarkable electronic properties in organic light-emitting diode (OLED) [4] and light-sensitive materials [5] in recent research.

According to concerned references, two substantial processes have been reported for the synthesis of phenothiazine and its derivatives. One was from the cyclization of diphenylamine **3** and sulfur, catalyzed by iodine [6–10] or aluminum chloride [11] with heating (Scheme 1). For example, the reaction reported by Silva *et al*. [6] was a 89% yield one at 180–200°C for 30 min. The reaction could give 95.6% yield by carbondioxide-pumping-in to remove the hydrogen sulfide [7]. However, synthesis of **1** is hard to achieve because of the existence of electron-donating methoxyl and thus the asymmetry structure could give rise to by-products forming and significant selectivity decrease. Compound **1** was got in 83% yield from 3-methoxy-*N*-phenyl-benzenamine (**4**) and sulfur with sulfolane as solvent [8]. The other method [12] for the synthesis of **1** started from diphenyl sulfide derivatives and followed by Ullmann condensation or Smeils rearrangement. However, the route suffers from poor selectivity and rare raw material.

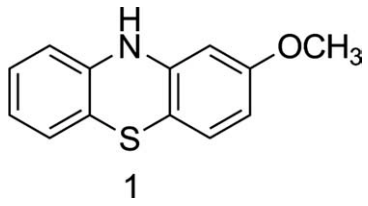
A new route was developed in this article for the synthesis of **1** from resorcinol (**5**) and aniline (**6**) (Scheme 2) with **4** as the key intermediate. We successfully developed an efficient synthetic route of **4** and following cyclization with sulfur to yield the title compound **1**.

RESULTS AND DISCUSSION

Synthesis of 3-hydroxydiphenylamine (7). $ZnCl_2$ and phosphoric acid were previously reported as catalysts in the synthesis of **7** [13,14], but our attempts to reproduce the reported procedure led to poor yields. Results with several acids as catalysts were shown in Table 1. It was found that *p*-toluenesulfonic acid gave better yield (92.4%) with 3.0 wt % amount. With the reaction mechanism shown in Scheme 3, we presumed that the quantity of protons was important to dehydration–condensation reaction. $ZnCl_2$ and phosphoric acid were low activity acids, so the less quantity of protons led to poor yield with the same reaction condition. On the other hand, sulfuric acid was so strong to cause many side reactions. Moreover, the amount of sulfuric acid or phosphoric acid was larger than others. Therefore, *p*-toluenesulfonic was adopted as the catalyst.

Synthesis of 3-methoxy-*N*-phenyl-benzenamine (4). Dimethyl sulfate was chosen as the reagent. The O-methylation was finished in 90.5% yield according to literature [15].

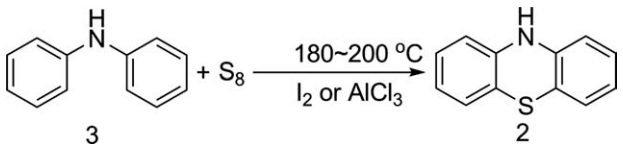
Synthesis of 2-methoxyphenothiazine (1). The cyclization of **4** is the key step in this route. The aromatic ring of **4** was no longer symmetric for the introduction of methoxyl. And thus, the cyclization of **4** led to the



1

Chart 1. 2-Methoxyphenothiazine (**1**).

Scheme 1. Novel approach to synthesis of **2**.



3 2

generation of two different products: **1** and 4-methoxyphenothiazine (**8**) (Chart 2). The influence of different solvents was studied with iodine as the catalyst, and the results were shown in Table 2.

The formation of **8** was the major reaction at low temperature, but other side reactions forming black color by-products with high boiling point would occur at high temperature. From Table 2, sulfolane and polysubstituted aromatics were considered to be the most effective solvents. The by-product **8** was almost insoluble in polysubstituted aromatics at high temperature, but product **1** could finely dissolve at the same condition. Thus, **8** could be removed by filtration at high temperature, and **1** could be precipitated out after cooling. Solvent could be reused after filtration. On the contrary, both the impurity and the product were well dissolved in sulfolane regardless the temperature. Therefore, polysubstituted aromatics were adopted as solvent.

In addition, statistical experimental design and multivariate modeling were used to optimize the reaction. Parallel experimental results showed that the following factors were worthy to consider: temperature (*A*), the molar ratio of catalyst and **4** (*B*), and the molar ratio of raw materials (*C*). The yield was expressed with *Y*. Thus, only the variables *A*, *B*, and *C* were explored in 15 sets of experiments (Tables 3 and 4).

The response *Y* (%)–yield, and the variables x_1–x_3 with their interactions were multivariate-correlated using the polynomial regression method to obtain a regression model as given in eq. 1 with R^2 of 0.96685.

Table 1

Screening of catalysts for synthesis of **7**.

Catalysts	Catalyst: resorcinol **5** (wt %)	Time (h)	Yield (**7**) (%)
$ZnCl_2$	3	6	65.0
Phosphoric acid	15	10	70.9
Sulfuric acid	10	5	61.3
p-Toluenesulfonic acid	3	5	92.4

$$\text{Yield} = 84.43 + 2.69 \times A + 1.64 \times B - 1.05 \times C - 0.68 \times A \times B + 0.5 \times A \times C - 0.15 \times B \times C - 5.08 \times A^2 - 2.73 \times B^2 - 4.35 \times C^2 \quad (1)$$

By using design expert software, the three-dimensional response surface and contour map were obtained by combination of two independent variables, as shown in Figure 1. Optimized results were: the reaction temperature 162.5°C, mass ratio of catalyst and **4** 1.1%, molar ratio of sulfur and **4** 2.22:1. Yield expected was 86.3%. Experimental yield was 88.2%.

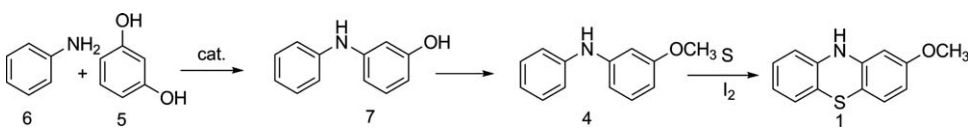
CONCLUSION

1. A method of industrial interest for the synthesis of 2-methoxyphenothiazine was designed and optimized. In the first step, p-toluenesulfonic acid was employed as the catalyst, giving a high yield of 92.4%. Dimethyl sulfate was chosen for O-methylation in 90.5% yield. The product **1** was obtained in high yield of 88.2% using polysubstituted aromatics as the solvent.
2. Statistical experimental design and multivariate modeling have allowed the development of new high yield for the reaction. A quadratic equation for the reaction was set up by response surface methodology, which can accurately predict the yield of the final reaction.

EXPERIMENTAL

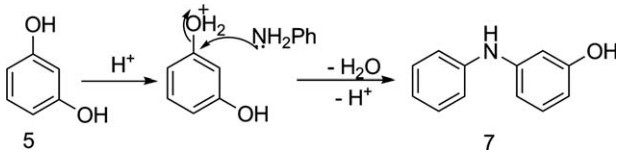
General methods. Melting points were determined by using the capillary method on WRR melting point apparatus. Gas chromatography (GC) analyses were performed on GC Agilent 1790F series. HPLC analyses were executed on high performance liquid chromatography (HPLC) Agilent 1100 series charged with C18 column. Thin layer chromatography (TLC)

Scheme 2. Improved process for synthesis of **1.**



6 5 7 4 1

Scheme 3. Mechanism of condensation.



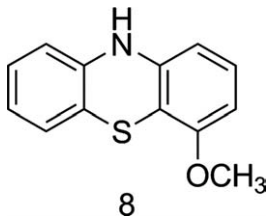


Chart 2. 4-Methoxyphenothiazine (**8**).

analyses were performed on glass plate (30 × 100 mm^2). ^1H NMR spectrums were recorded in dimethyl sulfoxide (DMSO) or $CDCl_3$ using 400 MHz on a NMR spectrometer (Bruker, AV 400).

Starting materials and reagents were commercially purchased and used without further purification.

Preparation of 3-hydroxydiphenylamine (7). A 250-mL four-necked flask equipped with a mechanic stirrer, a thermometer, a distilling apparatus and a water separator, charged with resorcinol (**5**) (16.5 g, 0.15 mol) and aniline (6) (16.7 g, 0.18 mol) was heated until the solid completely dissolved. p-Toluenesulfonic acid (0.5 g) was added into the mixture under stirring. The reaction was run under vigorous stirring at 190°C, and the water produced was separated. The reaction was complete until no water produced. The excess aniline (**5**) was distilled under vacuum to give solid. The solid was washed by water, then dried to give 3-hydroxydiphenylamine (**7**) (25.6 g, 92.4% yield and 99.1% GC purity) as dull-red solid. Melting point: 77.5–77.9°C (lit. 16; mp: 76–79°C); ^1H NMR (400 MHz, DMSO): δ 6.24(d, 1H), 6.48(d, 1H), 6.51–6.52(t, 1H), 6.77–6.81(t, 1H), 6.96–7.00(t, 1H), 7.03–7.05(d, 2H), 7.19–7.22(t, 2H), 8.01(s, 1H, N—H), 9.16(s, 1H, O—H).

Preparation of 3-methoxy-*N*-phenyl-benzenamine (4). To a 250-mL three-necked flask with a mechanic stirrer, a thermometer and a water separator, 3-hydroxydiphenylamine (**7**) (28.0 g, 0.15 mol), toluene (100 mL), sodium hydroxide (7.2 g, 0.18 mol), and water (5 mL) were added. Yellow crystal was precipitated when no water was separated. To this yellow crystal, dimethyl sulfate (24.0 g, 0.19 mol) was added slowly in 5 h, keeping the temperature below 50°C. The reaction was complete when dimethyl sulfate was completely dropped. The reaction mixture was filtered while hot to remove solid impurity. The filtrate was performed by rotary evaporator to give crude product. 3-Methoxy-*N*-phenyl-benzenamine (**4**) (27.2 g, 90.5% yield and 99.5 GC purity) was obtained by recrystallization in a mixture solution (ethanol:water = 2:1, volume ratio). Melting point: 69.6–70.7°C (lit. 1 mp:70–71°C); ^1H NMR (400 MHz, $CDCl_3$) δ: 3.83(s, 3H), 5.77(s, 1H), 6.54–6.56(d, 1H), 6.70–6.72(d, 2H), 6.98–7.02(t, 1H), 7.13–7.15(d, 2H), 7.20–7.25(t, 1H), 7.31–7.35(t, 2H).

Preparation of 2-methoxyphenothiazine (1). A 500-mL four-necked flask with a mechanic stirrer, a reflux condenser, a thermometer and a tail gas absorber, was charged with polysubstituted aromatics (180 mL). To the flask, 3-methoxy-*N*-phenylbenzenamine (**4**) (50.0 g, 0.25 mol) and sulfur (17.8 g, 0.56 mol) were added under stirring. After the addition was complete, the mixture was heated to 163°C. Iodine (0.55 g) was added after the temperature was stable. The reaction was monitored by TLC. The reaction was complete when the 3-methoxy-*N*-phenyl-benzenamine (**4**) disappeared. Thereafter, the reaction mixture was cooled to 120°C to give a black layer and a yellow layer. The yellow layer was obtained and cooled to 20°C to give yellow solid. 2-Methoxyphenothiazine (**1**) (50.0 g, 88.2% yield and 99.8% HPLC purity) was obtained by recrystallization in a mixture solution (ethanol:-water = 2:1, volume ratio). Melting point: 183.9–185.4°C

Table 2

Results from solvent screening for the synthesis of **1**.

Solvent	Time (h)	*T* (°C)	Yield (%)
Free	1.5	140	64.0
n-Butyl alcohol	1.5	118	72.2
N,*N*-Dimethylformamide	1.5	140	74.3
Sulfolane	1.5	160	86.1
n-Octane	1.5	125	71.2
Polysubstituted aromatics	1.5	160	85.3

Table 3

Response surface experiment encoding table.

		Levels		
Factors	Code	-1	0	1
T (°C)	A	150	160	170
n(iodine)/*n*(**4**)	B	0.005	0.01	0.015
n(sulfur)/*n*(**4**)	C	2	2.25	2.5

Table 4

Experimental conditions with corresponding measured and calculated responses of the reaction for synthesis of **1**.

	Experimental variables			Experimental yield	Responses
No.	*A*	*B*	*C*	*y* (%)	*Y* (%)
1	150	0.005	2.25	71.5	71.6
2	170	0.005	2.25	78.7	78.2
3	150	0.015	2.25	75.9	76.2
4	170	0.015	2.25	80.4	80.2
5	150	0.01	2	74.5	73.8
6	170	0.01	2	78.4	78.1
7	150	0.01	2.5	70.6	70.7
8	170	0.01	2.5	76.5	77.0
9	160	0.005	2	76.1	76.5
10	160	0.015	2	79.9	80.1
11	160	0.005	2.5	75.1	74.7
12	160	0.015	2.5	78.3	77.7
13	160	0.01	2.25	85.2	84.3
14	160	0.01	2.25	84.5	84.3
15	160	0.01	2.25	83.6	84.3

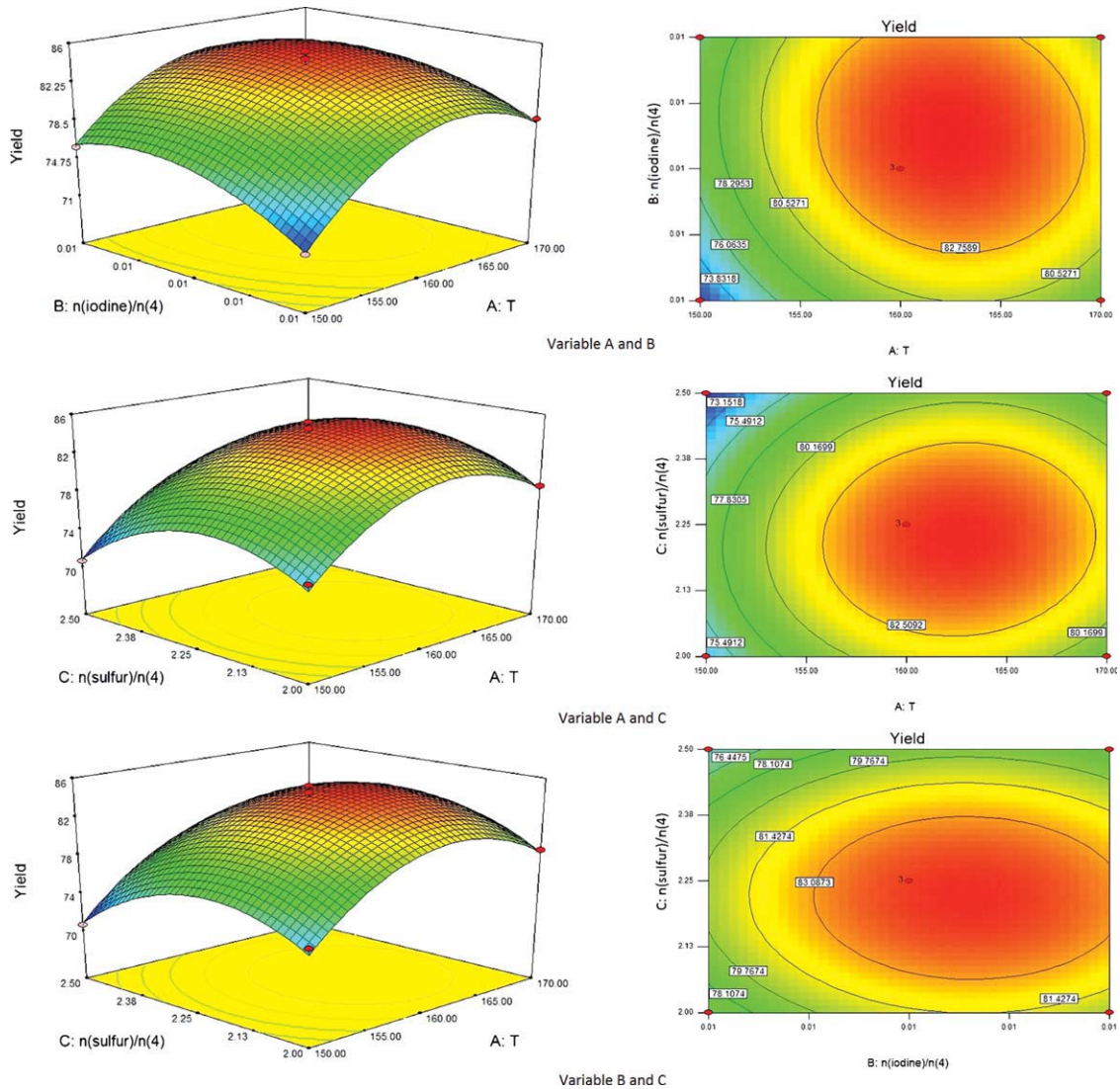


Figure 1. The three-dimensional response surface and contour map. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(lit. 17 mp: 184–184.5°C); ^{1}H NMR (400 MHz, DMSO) δ: 8.57(s, 1H, N—H), 6.95–6.99(t, 1H), 6.89–6.91(d,1H), 6.79–6.82 (d,1H), 6.72–6.76(t,1H), 6.65–6.67(d,1H), 6.35–6.38(m, 1H), 6.30–6.31(d,1H), 3.67(s, 3H).

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REFERENCES AND NOTES

[1] Yao, J. W. J Yantai Univ (Natural Science and Engineering Edition) 2007, 20, 231.

[2] Rubin, H. PNAS 2005, 98, 9836.

[3] Yu, M. J.; Mccowan, J. R. J Med Chem 1992, 35, 716.

[4] Miller, M. T.; Gantzel, P. K.; Karpishin, T. A. J Am Chem Soc 1999, 121, 4292.

[5] Pope, M.; Kallmann, H. P.; Magnante, P. J Chem Phys 1963, 38, 2042.

[6] Silva, G. A.; Costa, L. M. M.; Brito, F. C. F., Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. Bioorg Med Chem 2004, 12, 3149.

[7] Mitchell, J. US Pat. 2,415,363, 1947.

[8] Duchesne, J. P. France Pat. 2635523, 1990.

[9] Jiang, W.; Wang, Q. L. Chin Chem Lett 1997, 8, 381.

[10] Kayano, T.; Inoe, T. Jpn. Pat. 07138243, 1995.

[11] Britton, E. C. US Pat. 2,353,292, 1941.

[12] Taurand, G. Ullmann's Encyclopedia of Industrial Chemistry; Wiley: New York, 2005.

[13] Zhou, Y.; Zhang, H. R.; Zhang, S. Q.; Song, G. Q. J Jiangsu Polytech Univ 2004, 16, 30.

[14] Semen, V. Z.; Anna, N. G. Brit. Pat. 1218965, 1971.

[15] Bjorsvik, H. R. Org Process Res Dev 2000, 4, 534.

[16] Hoch, H.; Scheuermann, H. US Pat. 4,067,903, 1978.

[17] Criag, J. C.; Green, D. E.; Roy, S. K. J Med Chem 1965, 8, 392.