

A Simple and Efficient Process for the Preparation of 1,6-Dimethoxynaphthalene

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Abstract:

1,6-Dimethoxynaphthalene (1,6-DMN) was prepared by the *O*-dimethylation of 1,6-dihydroxynaphthalene (1,6-DHN) with dimethyl sulfate (DMS) in the presence of sodium hydroxide and additives in different solvents. The main reaction determining factors were divided into three categories with respect to yield and purity of 1,6-DMN: (1) Type of solvents and adding methods of NaOH had the highest effect on the results. (2) Amount of DMS and concentration of NaOH were less important. (3) Reaction time and temperature were the least important factors. The best reductant was Na₂S₂O₄, and it was only under N₂ atmosphere that yield and purity were also good. The improved process provides more than 99% yield, which considerably reduces the cost of 1,6-DMN, and more than 98% purity eliminates the purification process in the follow-up industrial production.

1. Introduction

1,6-Dimethoxynaphthalene (1,6-DMN, also as 2,5-dimethoxynaphthalene) is an important fine chemical intermediate,^{1–4} which is a raw material for the synthesis of drugs, dyestuffs, photographic materials, etc.^{5–7} For example, 1,6-DMN was used to prepare 5-methoxy-2-tetralone, which is a pharmacophore in the treatment of depression, schizophrenia, and Parkinson's disease.^{8,9} 1,6-DMN is usually prepared with the Williamson synthesis method, in which methylation reagents are methanol, halomethane, or DMS (dimethyl sulfate). Methanol is a poor methylation reagent and very low yields were achieved in the methylation. Further study has been done to improve the yield and purity of products with special catalysts such as solid acid catalysts.^{10,11} For its high cost, iodomethane, the best active

methylation reagent, was seldom used in the large-scale methylation but was used in the laboratory.^{12–14} In fact, these methylation reagents have not been widely used in the large-scale production of naphthalene ether derivatives including 1,6-DMN. Although DMS is toxic to humans and the environment (mainly due to formation of methanol and sulfuric acid from its hydrolysis), its high activity, the mild reaction conditions, simple postprocessing, and especially the low cost cause its wider application in the industrial production of naphthalene ether derivatives.^{15–19}

There are many large-scale productions of naphthalene ether derivatives using DMS as the methylation reagent in China. According to the location of the methoxy groups on the two naphthalene rings, dimethoxynaphthalenes exist as six isomers. The dimethoxy difference in symmetry influences many parameters in their preparation such as purification, reaction time, temperature, ratio of raw materials, etc. The industrial yield of 1,6-DMN (about 65%) was less than that of 1,7-DMN and 1,4-DMN by the same industrial method used in China. The mechanism of methylation of 1,6-DHN (1,6-dihydroxynaphthalene) with DMS is a typical S_N2 reaction, in which a naphthyloxy anion attacks at the carbon atoms of DMS.^{20,21} The main reaction paths are given in Figure 1. The number of the intermediates 2–8 depends on the alkali concentration, temperature, solvents, and other factors. For economic reasons, commercial aqueous NaOH solutions having concentrations between 20–40% (w/w) are more preferably used, but the yield of 1,6-DMN was only 80–85% (mol/mol) as shown in the previous literature starting from cheap DMS and NaOH.²² Furthermore, a lot of wastewater was also made by using dilute aqueous NaOH.²³ Sometimes, instead of NaOH, alkali-metal carbonate was used, producing much CO₂. Solvents containing much water overflowed and caused ineffective use of equip-

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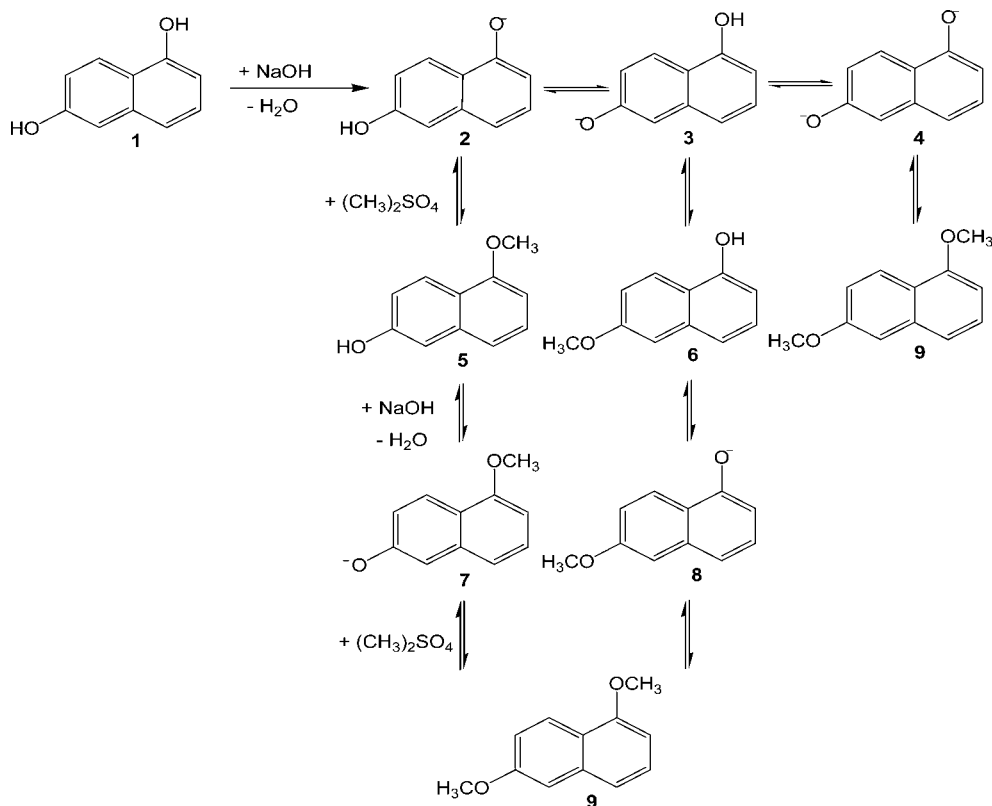


Figure 1. Reaction paths from 1,6-DHN (1) to 1,6-DMN (9).

ment. On the other hand, all previous preparations needed extraction with great quantities of organic solvent and recrystallization to purify 1,6-DMN.^{22,24} Thus far, to our knowledge, neither the solvent effect nor the feeding mode on the synthesis of 1,6-DMN has been reported. Our paper focuses on both the feeding mode of reactants and the solvent effect on the synthesis of 1,6-DMN. Other factors such as reaction time, temperature, ratio of raw materials, and addition of reducing agent are also described. This new process assures high yield and high purity of 1,6-DMN and eliminates the purification process in the follow-up industrial production.

2. Experimental Section

1,6-DHN (purity >99%) and 1,6-DMN (purity = 99.6%) were obtained as a gift from Nantong Baisheng Chemical Co., Ltd. (China). Methanol, ethanol, acetone, petroleum ether, NaOH, and *n*-hexane of AR grade were obtained from Tianjin Benchmark Chemical Reagents Co., Ltd. (China). HPLC scans were acquired on a Shimadzu LC-10AT (Japan) with Shim-Pack VP-ODS, 4.6 mm × 150 mm column; methanol/water, 7:23 v/v; flow rate 1.0 mL/min; wavelength 254 nm.

The reaction was carried out in a mechanically agitated round-bottomed, 500-mL glass flask which was equipped with a thermometer and a reflux condenser. A two-blade stirrer with a dimension of 1.8 cm in diameter was made of polytetrafluoroethylene, centrally located at a distance of 1.2 cm from the flask bottom and stirred at 300 rpm. The entire flask assembly was immersed in a thermostatic water bath, which was maintained at the desired temperature with an accuracy of ±0.5 °C. A

typical procedure was as follows: To a solution of 1,6-DHN (16.02 g, 100 mmol) in ethanol (50 mL) and DMS (27.75 g, 220 mmol) was added a little sodium dithionite (Na₂S₂O₄) as additive. An aqueous NaOH solution (264 mmol) was dripped into the solution during 90 min, while maintaining the reaction temperature at 45 ± 0.5 °C by water bath. After 60 min at 65 ± 0.5 °C, water (60 mL) was added to the reaction mixture. After cooling to room temperature, the precipitate was filtered off. The filtered cake was washed with water (2 × 75 mL) and dried in a vacuum oven at 45 °C /0.01 MPa for 10 h to afford 1,6-DMN as yellowish powder with mp 58.3–59.1 °C (lit.²³ mp 58–59 °C).

3. Results and Discussion

3.1. Solvent Effect. Solvent effect comes from the various intermolecular solute/solvent interaction forces such as non-specific van der Waals and electrostatic Coulombic interactions as well as specific hydrogen-bond interactions.²⁵ It is related to the properties of the solvent such as molecule size, solvent polarity, solvent discreteness.^{26,27} Solvent polarity can be represented by the relative permittivity (ϵ_r) or dipole moment (μ).²⁸ It is well-known that the activation barrier for the S_N2 reaction is strongly affected by solvent polarity in homogeneous phase. A transition state is less polar than the separated reactants in the typical S_N2 reaction, and the original polar nucleophile is solvated by the strong polar solvent. So the strong solvent polarity cannot be propitious to a typical S_N2 reaction, whereas

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Table 1. Influence of solvents on the yield and purity of 1,6-DMN^a

entry	solvent	ϵ_r	μ/D	solvent/		
				mL	yield/%	purity/%
1	water	78.5	1.85	50	76	76.4
2	methanol	32.7	1.70	50	82	89.3
3	ethanol	24.6	1.69	50	89	89.7
4	acetone	21.0	2.72	50	65	90.3
5	<i>n</i> -hexane	2.0	0	50	69	94.2
6	petroleum ether	1.8	0	50	52	96.4

^a Conditions: solvent 50 mL; 1,6-DHN 100 mmol; DMS 220 mmol; aqueous NaOH 2.0 M, 128 mL (one-time feeding, 6 min); 2.5 h; 45 °C.

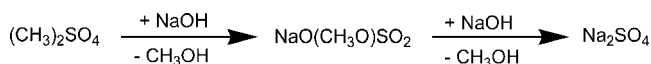
it is propitious to the S_N1 reaction. Water, methanol, and ethanol are polar protonic solvents. In this study, naphtholate ion was solvated in the aqueous solution mainly caused by hydrogen-bond formation, and the hydrate reactants highly increased the reaction barrier height.^{29–31} This effect did not succeed in forming the transition state, which formed ---ONA (NA = naphthalene) partly and weakened the C–O bond (H₃C–OSO₃CH₃) synchronously. As the solvent polarity decreased from water, methanol, ethanol, the yield and purity of 1,6-DMN increased gradually (Table 1), which definitely proved that the dominant mechanism was S_N2. Furthermore, with adding all of the aqueous NaOH solution, the reactant phase was not an entirely homogeneous system. There was a diffusion resistance between the naphtholate ion in the water phase and the DMS phase although the reaction solution was agitated at 300 rpm. Obviously, the use of solvents with suitable polarity and solubility is important for this reaction.

The reaction was nonhomogeneous in the presence of low-polarity *n*-hexane or petroleum ether as reaction media with dissolved DMS in the organic phase and sodium naphtholate in the aqueous phase. Although these two solvents could increase the purity of 1,6-DMN, only low reaction rates were observed because of insufficient contact in the heterogeneous environment.

Acetone has been applied as a good solvent in many S_N2 reactions. Although it was conducive to the S_N2 reaction according to its ϵ_r or μ , it is the strong NaOH base that produced an acetone enolate anion attacking the carbon atom of DMS, which resulted in the formation of methyl ethyl ketone. This side effect consumed some DMS, and the intermediates of sodium monomethoxy-naphtholate (water-soluble material was removed by dissolving and washing) could not be remethylated. It caused the lower yield of 1,6-DMN.

3.2. Effect of NaOH Feeding Modes. As we know, in the methylation of 1,6-DMN monomethoxy-naphtholate ions as the most important intermediates can only be produced under certain basic conditions, but DMS is easily hydrolyzed in alkaline solution (see Figure 2). The method of adding NaOH to control the pH value is a key factor which influences the reaction outcome.

In Table 2 (with the exception of entry 11), the aqueous NaOH solution was added into the mixture of ethanol, 1,6-

**Figure 2. Hydrolysis path of DMS.**

DHN, and DMS in four different ways such as one time, two times, dripping, etc. For entry 11, DMS was slowly dripped into the solution after a one-time addition of NaOH. The total reaction time was 2.5 h including the feeding time. Clearly, the purity and yield of entry 11 decreased more significantly than that of the other four entries. It was the main reason that aqueous NaOH solution added all at once at the beginning maintained strong basicity to hydrolyze DMS that was added by dripping for a longer time. Insufficient DMS could not remethylate the intermediates of sodium monomethoxy-naphtholate removed by dissolving and washing. Another obvious fact was that the color of the reaction solution for entry 11 was darker than the others. At higher pH values, methoxy-naphtholate ions were susceptible to the oxygen in the air and likely changed into some byproduct of quinone compounds which would be further oxidized to carboxylic acid.^{32,33} These two factors led to lower yield and purity of 1,6-DMN, so this direct way of adding DMS to aqueous NaOH solution is undesirable.

The results of the entries 7–10 in Table 2 show that the yield and purity of 1,6-DMN changed very little by different feeding modes for aqueous NaOH after DMS addition. The yield changed from 88% to 93%, and the purity, from 89.7% to 95.8%, with the feeding-time increase in entries 7–10. It indicates that it was more conducive to reduce the side reaction of hydrolysis and oxidation by slowly adding aqueous NaOH. Furthermore, we found that the results among entries 8, 9, and 10 were similar in the first 0.5 h, which seemed to demonstrate their fast initial rates and the small hydrolytic amounts of DMS.

3.3. Effect of DMS Amount. At 45 °C, the yield of 1,6-DMN was increasing by adding more DMS (Table 3). However, only one methyl group of DMS was used at 45 °C, and another required either a higher temperature or no aqueous conditions to activate.^{34,35} Meanwhile, some DMS was hydrolyzed to methanol and sulfuric acid in aqueous NaOH solution. The purity and yield of 1,6-DMN changed a little when the amount of DMS was more than 1.2 times the stoichiometric necessary value. Considering the side reaction and cost, we conclude that the proper molar ratio of DMS to 1,6-DHN is 2.4.

3.4. Effect of NaOH Concentration. Although low NaOH concentrations reduced the hydrolysis rate of DMS, it was not conducive to the rate and extent of the methylation reaction and effective use of equipment; meanwhile wastewater increased more in large-scale production.

NaOH has a great solubility in ethanol. High NaOH concentration (see entries 19, 20 in Table 4) speeds up not only the methylation rate but also the rates of hydrolysis and alcoholysis of DMS with C₂H₅ONa.³⁶ With less DMS, sodium monomethoxy-naphtholate increased. Meanwhile, the local

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Table 2. Influence of NaOH feeding modes on the yield and purity of 1,6-DMN^a

entry	feeding mode of NaOH	total feeding time/h	yield/%	purity/%
7	one time	0.1	88	89.7
8	two times (second time after 0.5 h)	1.5	90	92.4
9	a half, then dripping the rest	1.5 (dripping after 0.5)	92	94.3
10	dripping	1.5	93	95.8
11 ^b	one-time addition of NaOH, dripping DMS	1.5	78	75.1

^a Conditions: ethanol 50 mL; 1,6-DHN 100 mmol; DMS 220 mmol; aqueous NaOH solution 2.0 M, 128 mL; 2.5 h (total time including dripping), 45 °C. ^b Adding all of the aqueous NaOH solution one time at the beginning, then dripping DMS.

Table 3. Influence of amount of DMS on the yield and purity of 1,6-DMN^a

entry	DMS/mol	yield/%	purity/%
12	0.20	88	88.0
13	0.22	92	93.8
14	0.24	94	95.8
15	0.26	94	96.0
16	0.27	94	96.1

^a Conditions: ethanol 50 mL; 1,6-DHN 100 mmol; aqueous NaOH solution 2.0 M, 128 mL (dripping in 90 min); 2.5 h (all time including dropping); 45 °C.

Table 4. Influence of NaOH concentration on the yield and purity of 1,6-DMN^a

entry	aqueous NaOH concen./M	yield/%	purity/%
17	2.0	94	95.8
18	4.0	96	96.7
19	6.0	91	95.8
20	8.0	88	96.4

^a Conditions: ethanol 50 mL; 1,6-DHN 100 mmol; DMS 240 mmol; aqueous NaOH solution (264 mmol, dripping in 90 min); 2.5 h (total time, including dripping); 45 °C.

NaOH concentration in the vessel was high due to inadequate mechanical agitation, and it accelerated oxidation of naphthols to quinones, even to carboxylic acid. The increase of water-soluble byproduct caused relatively high purity and low yield of 1,6-DMN. In our experimental conditions, NaOH, 4 M, was an appropriate concentration for the methylation reaction at 45 °C by the dripping method.

3.5. Effect of Reaction Time and Temperature. The reaction result is closely related to the reaction time and temperature. In addition to the above-mentioned side effects, DMS may react with alcohol at high temperature and low water content to form (CH₃)HSO₄ and C₂H₅OCH₃.³⁶ The effect of temperature and time on the yield and purity of 1,6-DMN was studied in the range of 1 h to 3 h and 45 to 65 °C under otherwise similar conditions (Table 5). By these experiments on reaction temperature and time, the experiment results revealed that the best yield and purity was achieved at 65 °C for 1 h. It also showed that the yield and purity depends less on time and temperature at 45–65 °C and 1–3 h compared with type of solvents and feeding methods of aqueous NaOH solution.

3.6. Effect of Additives. As mentioned in the previous section, methoxy-naphtholate ions as the intermediates were susceptible to oxygen in the air and likely changed into some byproduct of quinones, thus making the color darker. Some common reductants were used to inhibit oxidation reactions in this study, such as Na₂S₂O₄, N₂H₄·H₂O, HCHO, NaHSO₃, and CO(NH₂)₂ (Table 6). The experimental results indicated that

Table 5. Influence of reaction time and temperature on the yield and purity of 1,6-DMN^a

entry	time after dripping /h	temperature after dripping/°C	yield/%	purity/%
21	1.0	45	96	96.3
22	2.0	45	98	97.7
23	3.0	45	98	96.5
24	1.0	55	97	97.9
25	2.0	55	97	97.2
26	3.0	55	98	96.5
27	1.0	65	99	97.7
28	2.0	65	95	98.0
29	3.0	65	93	95.6

^a Conditions: ethanol 50 mL; 1,6-DHN 100 mmol; DMS 240 mmol; aqueous NaOH solution, 4.0 M, 64 mL (dripping in 90 min at 45 °C).

Table 6. Influence of additives on the yield and purity of 1,6-DMN^a

entry	additive	amount/g	yield/%	purity/%
30	Na ₂ S ₂ O ₄	0.5	~100	98.2
31	N ₂ H ₄ ·H ₂ O	0.5	98	97.7
32	HCHO	0.5	black agglomerate	
33	NaHSO ₃	0.5	87	95.7
34	CO(NH ₂) ₂	0.5	79	90.6
35 ^b	N ₂	bubbling	99	98.4

^a Conditions: ethanol 50 mL; 1,6-DHN 100 mmol; DMS 240 mmol; additive, aqueous NaOH solution, 4.0 M, 64 mL (dripping in 90 min at 45 °C); 60 °C, 1 h after dripping. ^b Reaction under N₂ atmosphere.

Na₂S₂O₄, and N₂H₄·H₂O were more effective on the purity of 1,6-DMN than HCHO, NaHSO₃, and CO(NH₂)₂. The best way to antioxidation is under N₂ atmosphere due to its convenience and low cost.

Conclusions

The *O*-dimethylation of 1,6-dihydroxynaphthalene (1,6-DHN) with dimethyl sulfate (DMS) in the presence of sodium hydroxide and additives in different solvents was investigated. Successful completion of the reaction especially depends upon (1) adding method of reactants and the type of solvent, (2) the amount of DMS and the aqueous NaOH concentration, and (3) reaction time and temperature. The best reductant was Na₂S₂O₄, and it was only under N₂ atmosphere that the yield and purity were also good.

The optimized method was as follows with almost quantitative yield and excellent purity: under N₂ atmosphere, 4 M aqueous NaOH solution was dripped to an ethanol solution of 1,6-DHN and DMS in 90 min at 45 °C. The molar rate of 1,6-DHN/DMS/NaOH was 1:2.4:2.64. The purity and yield of 1,6-DMN were found to be 98.4% and 99%, respectively, at 60 °C in 60 min after

dripping aqueous NaOH solution. More than 98% purity eliminates the purification process. The simplified method will help to optimize the *O*-methylation of 1,6-DHN with DMS in industrial-scale production.

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