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# Cleaner and convenient preparation of 3-(4,6-dimethoxy-pyrimidin-2-yloxy)-2-methyl-phenol*

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**Abstract:** Environmental concerns have highlighted the need of cleaner technologies. A cleaner, convenient and selective technology has been developed for the preparation of 3-(4,6-dimethoxy-pyrimidin-2-yloxy)-2-methyl-phenol (DPMP) from 2-methyl-benzene-1,3-diol in water as solvent. The isolated yield of DPMP is up to 86% in good selectivity. The product structure was characterized by conventional methods, $^1$H-NMR and MS. This technology belongs to the modern concept of environmentally friendly low wastes or non-wastes technology (LWNWT).

**Key words:** Cleaner preparation, Greener technology, Selective synthesis, 2-methyl-benzene-1,3-diol, 3-(4,6-dimethoxy-pyrimidin-2-yloxy)-2-methyl-phenol

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## INTRODUCTION

Environmental concerns have been growing for the past two decades. High industrial density, human population density and the use of old and polluting technologies all cause increasing levels of pollutant emissions. This situation has highlighted the need for cleaner technologies (Rao *et al.*, 2003; Muthusubramanian *et al.*, 2003). Cleaner technology has the following advantages: (a) Waste minimization; (b) Pollution prevention; and (c) Green productivity. Implementing cleaner production may not solve all environmental problems at a facility, but it will decrease the need for end-of-pipe equipment and result in less toxic waste to treat and dispose of.

3-(4,6-dimethoxy-pyrimidin-2-yloxy)-2-methyl-phenol (DPMP) is an important synthetic intermediate for preparation of pyrimidyloxy salicylic derivatives as pesticides. Its synthesis involves the selective alkylation reaction of phenol with 2-methane-sulfonyl-4, 6-dimethoxypyrimidine. In the past, it was prepared in organic solvents such as THF. However, the problems are the low selectivity of reaction and production of most waste (II) (Fig.1).

Thus, cleaner and more convenient preparation of DPMP must be explored further.

Here, we report a cleaner, more convenient and selective technology for the preparation of 3-(4,6-dimetoxy-pyrimidin-2-yloxy)-2-methyl-phenol (DPMP) from 2-methyl-benzene-1,3-diol in water as solvent.

## MATERIAL AND METHODES

The reaction equation used to represent the

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reaction involved in the process is expressed in Fig.2.

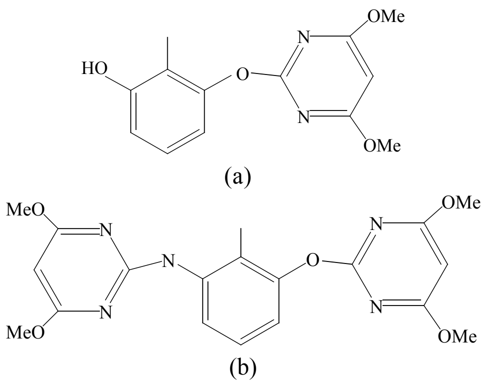

**Fig.1 The structure of product DPMP (a) and waste II (b)**

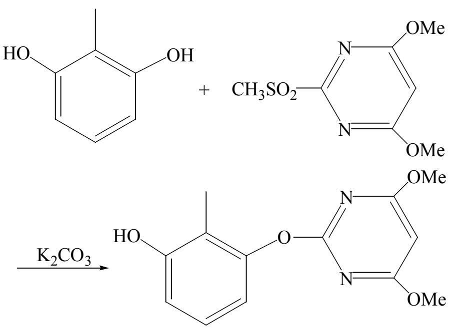

**Fig.2 The reaction equation involved in the process**

### Method A

Thirty ml of acetone, 1.5 g (0.0072 mol) of 2-methane-sulfonyl-4,6-dimethoxypyrimidine and 0.5 g (0.0036 mol) of anhydrous potassium carbonate were added to 0.994 g (0.0072 mol) of 2-methyl-benzene-1,3-diol, and the mixture was refluxed under heat for 12 hours. The completion of the reaction was checked by thin layer chromatography. A formed salt was removed by filtration, and the acetone was distilled off under reduced pressure. Then, ethyl acetate was added to the residue, and the mixture was washed successively with 1 mol/L HCl, saturated sodium chloride aqueous solution. The mixture was dried over anhydrous sodium sulfate, and then the ethyl acetate was distilled off.

### Method B

Thirty ml of benzene, 1.5 g (0.0072 mol) of 2-methane-sulfonyl-4,6-dimethoxypyrimidine, 0.1 g tetrabutylammonium iodide and 0.5 g (0.0036 mol) of anhydrous potassium carbonate were added to 0.994 g (0.0072 mol) of 2-methyl-benzene-1, 3-diol in 20 ml water, and the mixture was stirred and heated at 80 °C for 12 hours. The mixture was washed successively with 1 mol/L HCl, saturated sodium chloride aqueous solution. The mixture was dried over anhydrous sodium sulfate, and then the benzene was distilled off.

### Method C

Thirty ml of acetone, 9.4 g (0.0432 mol) of 2-methane-sulfonyl-4,6-dimethoxypyrimidine and 0.5 g (0.0036 mol) of anhydrous potassium carbonate were added to 0.994 g (0.0072 mol) of 2-methyl-benzene-1,3-diol, and the mixture was refluxed under heat for 12 hours. A formed salt was removed by filtration, and the acetone was distilled off under reduced pressure. Then, ethyl acetate was added to the residue, and the mixture was washed successively with 1 mol/L HCl, saturated sodium chloride aqueous solution. The mixture was dried over anhydrous sodium sulfate, and then the ethyl acetate was distilled off.

### Method D

Thirty ml of ethanol, 1.5 g (0.0072 mol) of 2-methane-sulfonyl-4,6-dimethoxypyrimidine and 0.5 g (0.0036 mol) of anhydrous potassium carbonate were added to 0.994 g (0.0072 mol) of 2-methyl-benzene-1,3-diol in 20 ml water, and the mixture was heated at 80 °C for 12 hours. The ethanol was distilled off under reduced pressure. Then, ethyl acetate was added to the residue, and the mixture was washed successively with 1 mol/L HCl, saturated sodium chloride aqueous solution. The mixture was dried over anhydrous sodium sulfate, and then the ethyl acetate was distilled off.

### Method E

Eighty ml of water, 16.9 g (0.077 mol) of 2-methane-sulfonyl-4,6-dimethoxypyrimidine and 6.2 g (0.045 mol) of anhydrous potassium carbonate were added to 8.4 g (0.068 mol) of 2.2-methyl-benzene-1,3-diol, and the mixture was stirred and heated at 80 °C for 24 hours. After the completion of the reaction, water was removed by filtration, and the residue was washed successively with 1 mol/L HCl, water, and air dried. Yield was 86% at purity of 93%.

## RESULTS AND DISCUSSIONS

The result of method A showed that when 2-methane-sulfonyl-4,6-dimethoxypyrimidine reacted with 2-methyl-benzene-1,3-diol in acetone in molar ratio of 1:1, a little DPMP was produced. In contrast, waste II became the main product. Because the reaction environment of two hydroxyl in 2-methyl-benzene-1,3-diol is the same, 2-methane-sulfonyl-4,6-dimethoxypyrimidine can attack one hydroxyl or two at the same time. Thus, there are two products (DPMP and waste II).

Bredereck studied the selective methylation reaction of phenols and found three main factors: (a) pH 8–9, (b) limited dimethylsulfate, and (c) a suitable solvent (Zhao *et al.*, 1984). Also, the optimum methylation condition of benzene-1,3-diol were (a), (b), and (c) a two-phase system containing water and organic solvents such as nitrobenzene. Also, Mckillop *et al.*(1974) reported the use of phase-transfer catalysis for the synthesis of phenol ethers. We investigated the use of phase-transfer catalysis for preparation of DPMP in method B. Both tetrabutylammonium iodide and PEG 600 were used as PTC catalyst. However, the procedure was found to be ineffective for preparation of DPMP. In practice, the phenol is converted into the corresponding quaternary ammonium phenoxide in the aqueous phase. The latter salt has limited solubility in the organic phase and consequently, transportation of the phenoxide ion into the benzene solution. Thus two hydroxyls in 2-methyl-benzene-1,3-diol can be attacked by more 2-methane-sulfonyl-4,6-dimethoxypyrimidine molecules. Also, benzene is not an environmentally friendly solvent.

Xiao *et al.*(1999) reported diethlyeneglycol monobutylether synthesis by diethlyeneglycol etheration. The reaction molar ratio was 6–8, the yield was over 80% and no phase-transfer catalyst were needed in this method. So, we turned our attention to this method as shown in method C. With a 1:6 molar ratio of 2-methyl-benzene-1,3-diol: 2-methane-sulfonyl-4, 6-dimethoxypyrimidine, the product ratio of DPMP:II achieved was 6:4. However, because of the dissolvability of 2-methyl-benzene-1,3-diol in water and similar characteristic of DPMP and II, we had difficulty in reuse of 2-methyl-benzene-1,3-diol and separation of products DPMP and byproduct II. For cleaner production, this method is not an environmentally friendly low wastes or non-wastes technology.

Lin and Huang (1992) studied the mono-alkylation of 4,4'-biphenyldiol in ethanol-water as-solvent. With a 2:1 volume ratio of ethanol: water, the yield was 55%. So we adopted ethanol-water as solvent for selective preparation of DPMP (method D). In a ratio range of 2–4, GC-MS (as shown in Fig.3) revealed that DPMP was a main product, and a little waste II was observed at retention time of 11 minutes; many raw material 2-methyl-benzene-1, 3-diol observed may be attributed to: (1) phase-transfer catalysis of 2-methyl-benzene-1,3-diol itself; it can transport 2-methane-sulfonyl-4, 6-dimethoxypyrimidine into water; (2) mainly dissolvability of ethanol, which slowly dissolve 2-me-

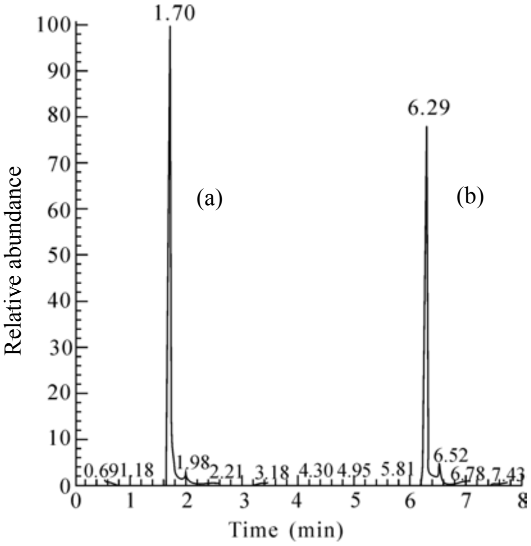

**Fig.3 The gas chromatograms of (a) 2-methyl-benzene-1,3-diol and (b) DPMP**

thane-sulfonyl-4,6-dimethoxypyrimidine into water. Thus, a 2-methane-sulfonyl-4,6-dimethoxypyrimidine molecule meets many 2-methyl-benzene-1,3-diol molecules in water. This environment (shown in Fig.4) is favorable for selective preparation of DPMP. Due to the presence of 2-methyl-benzene-1,3-diol in the reaction mixture, this method is also not a cleaner technology. But, this method gives us some enlightenment, if reaction is carried out in water, not in ethanol-water, thus, the reaction environment may be more favorable for selective preparation. We therefore investigated method E. Fortunately, the isolated yield of DPMP was up to 86% in good selectivity as shown in Fig.5. The product structure characterized by $^1$H-NMR and MS may be mainly attributed to phase-transfer catalysis of 2-methyl-benzene-1,3-diol itself.

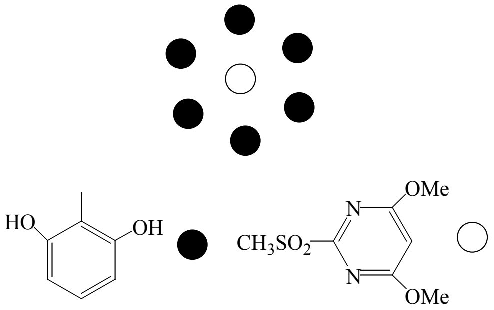

**Fig.4 The schematic diagram of selective reaction path way of 2-methyl-benzene-1,3-diol**

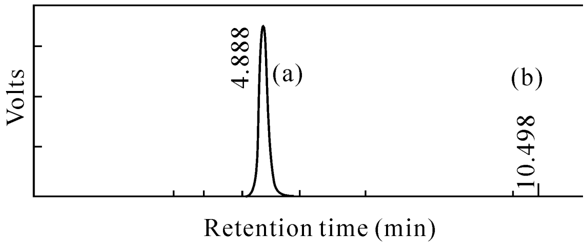

**Fig.5 The HPLC chromatograms of DPMP (a) and byproduct II (b)**

## CONCLUSION

In conclusion, a cleaner, more convenient and selective technology has been developed for the preparation of 3-(4,6-dimethoxypyrimidin-2-yloxy)-2-methyl-phenol (DPMP) from 2-methyl-benzene-1,3-diol in the presence of $K_2CO_3$ in water as solvent. The alkylation yielded a high yield and purity product not available through other synthetic methods. In addition, the simplicity and convenience of this procedure make this new method a highly useful technique in cleaner production. This technology belongs to the modern concept of environmentally friendly low wastes or non-wastes technology.

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