

## A simple method for preparing 2,3,4-trimethoxybenzonitrile

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### ABSTRACT

A simple method was developed for preparing 2,3,4-trimethoxybenzonitrile from one-step reaction of 1,2,3-trimethoxybenzene using  $K_3[Fe(CN)_6]$  as the cyanation reagent,  $AgNO_3/CuCl_2 \cdot 2H_2O$  as the catalyst system and iodine as the oxidant.

**Keywords:** 2,3,4-trimethoxybenzonitrile, 1,2,3-trimethoxybenzene, iodine, catalyst

### 1. Introduction

2,3,4-trimethoxybenzonitrile is a key intermediate used in the manufacture of trimetazidines and some kinase inhibitor drugs<sup>[1]</sup>. To our knowledge, there are several methods for preparing trimethoxybenzonitrile: (1)<sup>[2]</sup> trimethoxybenzoic acid is reacted with thionyl chloride to give trimethoxybenzoyl chloride, then the ammonification of trimethoxybenzoyl chloride product is followed by the dehydration of the resulting product (trimethoxybenzamide) to provide the desired trimethoxybenzonitrile product; (2)<sup>[3]</sup> another useful alternative is direct conversion of trimethoxybenzaldehyde in the presence of glacial acetic acid, nitropropane and phosphoric acid to the desired trimethoxybenzonitrile product; (3)<sup>[4]</sup> Xingquan Chen and co-workers recently report a method with 1,2,3-trimethoxybenzene as the raw material where the bromination of 1,2,3-trimethoxybenzene is followed by the cyanation of the resulting product to give 2,3,4-trimethoxybenzonitrile. On the other hand, although many methods have been developed to synthesize aryl nitriles,<sup>[5-8]</sup> the method for preparing 2,3,4-trimethoxybenzonitrile through C-H bond activation is unknown. We herein report a simple method for preparing 2,3,4-trimethoxybenzonitrile from one-step reaction of 1,2,3-trimethoxybenzene using  $AgNO_3/CuCl_2 \cdot 2H_2O$  as the catalyst system,

$K_3[Fe(CN)_6]$  as the cyanation reagent and iodine as the oxidant.

### 2. Experimental

#### 2.1 Materials and instruments

1,2,3-trimethoxybenzene was purchased from Aladdin Reagent Company. Other chemicals were commercially available and were used without further purification.

<sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded on a Bruker 400 MHz instrument with chemical shifts reported in ppm relative to the internal standard tetramethylsilane. Purification by flash chromatography was performed using 60 Å 230-400 mesh  $SiO_2$  with compressed air as a source of positive pressure.

#### 2.2 Procedure for preparing 2,3,4-trimethoxybenzonitrile

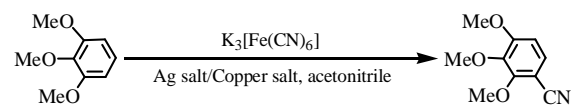
0.3 mmol  $CuCl_2 \cdot 2H_2O$ , 0.3 mmol  $AgNO_3$  and 1 mL acetonitrile were added into a dried 40 mL tube. After the mixture was stirred at room temperature for about 5 min to give a homogeneous solution, 0.3 mmol 1,2,3-trimethoxybenzene, 0.2 mmol  $K_3[Fe(CN)_6]$ , 0.2 mmol  $I_2$ , and 1 mL acetonitrile were added. The reaction tube was sealed with a septum and placed in a constant-temperature oil bath set at 180 °C to perform the reaction for 28 h.

Once the reaction time was reached, the mixture was cooled to room temperature. The cyanation product was purified by column chromatography, and identified by  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$ .

### 3. Results and discussion

In our initial study,  $\text{AgI/CuCN}$  was chosen as the catalytic system to perform the cyanation of 1,2,3-trimethoxybenzene, and the cyanation product was obtained in only 6% yield. Luckily, the cyanation with  $\text{AgNO}_3/\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  as the catalyst system gave 2,3,4-trimethoxybenzointrile in high yield (Table 1, entry 9). Subsequently, a series of copper salts were screened to ascertain the optimal catalyst system. As seen from Table 1,

**Table 1:** Cyanation of 1,2,3-trimethoxybenzene catalyzed by silver salt/copper salts<sup>[a]</sup>



Entry	Silver salt	Copper salt	Isolated yield [%]
1	AgI	CuCN	6
2	AgNO <sub>3</sub>	CuCN	8
3	AgNO <sub>3</sub>	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	32
4	AgNO <sub>3</sub>	CuSO <sub>4</sub> ·5H <sub>2</sub> O	25
5	AgNO <sub>3</sub>	CuO	12
6	AgNO <sub>3</sub>	Cu <sub>2</sub> O	5
7	AgNO <sub>3</sub>	CuBr <sub>2</sub>	51
8	AgNO <sub>3</sub>	CuCl	6
9	AgNO <sub>3</sub>	CuCl <sub>2</sub> ·2H <sub>2</sub> O	67

[a] Reaction conditions: 1,2,3-trimethoxybenzene (0.3 mmol),  $\text{K}_3[\text{Fe}(\text{CN})_6]$  (0.2 mmol), copper salts (0.3 mmol), silver salts (0.3 mmol),  $\text{I}_2$  (0.2 mmol), acetonitrile (2 mL), 180 °C, 28 h.

$\text{AgNO}_3/\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  was optimal as the catalyst system. Generally, monovalent copper was more effective than divalent copper. For example, the cyanation with CuCl or  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  afforded 2,3,4-

trimethoxybenzointrile in 6% and 67% yields respectively (Table 1, entries 8, 9).

After identifying a suitable catalyst, we optimized other critical parameters such as catalyst loading, solvent, temperature and so on. The cyanation of 1,2,3-trimethoxybenzene proceeded efficiently with as low as 60 mol%  $\text{AgNO}_3$  and 60 mol%  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ . We tried to reduce the catalyst loading to 10 mol%, but found that this was not possible without sacrificing product yield even if the reaction time was prolonged to 60 h. The same was true when we tried to decrease reaction temperature. Among the screened solvents including toluene, acetonitrile, dimethylformamide, dichloromethane, *N*-methyl-2-pyrrolidone, ethylacetate and dimethyl sulfoxide, acetonitrile was the most effective one.

### 4. Conclusion

In conclusion, a simple method was developed for preparing 2,3,4-trimethoxybenzointrile from one-step reaction of 1,2,3-trimethoxybenzene using  $\text{AgNO}_3/\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  as the catalyst system and iodine as the oxidant. 2,3,4-trimethoxybenzointrile product was obtained in up to 63% yield. Among the screened solvents, acetonitrile was the most effective one. A further investigation of mechanism is underway in our laboratory.

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