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Synthesis of 2-amino-4,6-dimethoxypyrimidine with dimethyl carbonate as methylating agent

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Abstract 2-amino-4,6-dimethoxypyrimidine (ADM) was prepared from 2-amino-4,6-dihydroxypyrimidine (ADH) in the presence of potassium carbonate and phase transfer catalyst (PTC), with dimethyl carbonate (DMC) instead of conventional toxic reagents (such as haloalkane and dimethyl sulfate, etc.). The best conversion (87.7 %) of ADH and selectivity (40.5 %) toward ADM were achieved under optimized conditions: tetrabutyl ammonium bromide (TBAB) as PTC, n(ADH):n(DMC):n(TBAB):n(K_2CO_3) = 1:5:0.1:3, reaction time = 10 h and reaction temper ature = 150 °C.

Keywords DMC · PTC · 2-amino-4,6-dihydroxypyrimidine · 2-amino-4,6-dimethoxypyrimidine

Introduction

2-amino-4,6-dimethoxypyrimidine(ADM) is one of the most important pesticide intermediates, which has been widely used for the synthesis of some effective and environmentally friendly pesticides, such as sulfonylurea herbicides [1]. Traditionally, ADM has ben obtained through three steps, first using guanidine nitrate, diethyl malonate to get 2-amino-4,6-dihydroxypyrimidine(ADH), then reacting with phosphorus oxychloride to get 2-amino-4,6-dichloropyrimidine(ADC), finally getting ADM by methylation [2, 3]. Obviously, in this method, the raw materials are toxic and of strong corrosivity, which can cause harm to both the human body and the reactor in the reaction process. Beyond that, the reaction processes are fairly complicated, and the final products are difficult to deal with because of the presence

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of wastes. So, it is necessary to search out a less-polluting and more environmentally friendly synthetic route for ADM.

Dimethyl carbonate(DMC), widely used in the fields of pesticides, medicine, polymer synthesis, and some other fields, is a new type of organic synthesis intermediates, which is non-toxic as well as pollution free [4–6]. It has been reported that DMC has a good biological activity for the presence of methyl, methoxyl, carbonyl, etc.[7–10], and, therefore, it can react with phenol, alcohol, amine, hydrazine, and ester compounds [11, 12], producing many important chemical products. The reaction of catechol with DMC on alumina was studied, and the conversion of catechol was 68 % at a time on-stream of 1 h at 553 K [13]. A series of meso- and microporous materials, previously described and characterised, were tested in the catechol O-alkylation process using methanol and DMC as alkylating reagents, and it was confirmed that DMC is a better methylating agent than methanol with respect to the conversion ratio of catechol and guaiacol [14]. It has also been reported that veratrole was obtained in a high yield by the vapor phase methylation of catechol with DMC when alumina was loaded with various alkali metal compounds [15].

In this work, ADM was prepared from ADH in the presence of K_2CO_3 and PTC [16], using DMC as methylating agent instead of conventional toxic reagents (such as haloalkane and dimethyl sulfate, etc.). The optimum reaction conditions were obtained considering these influencing factors such as kinds of PTC, reaction time, reaction temperature, reactant ratio, and so on. The results show that the synthesis conditions are mild and easy to control. Moreover, both the reactant and the final products are non-toxic and less corrosive, overcoming the deficiencies of the traditional synthetic methods. The synthetic route we reported was more effective, economical and ecofriendly, in accordance with the development direction of green chemistry.

Experimental

Materials and instrumentation

All the chemicals used were from commercial sources without further purification. All reagents were of analytical grade apart from those used as mobile phase for high performance liquid chromatography (HPLC) use, such as methanol and acetonitrile, which were chromatographically pure. HPLC experiments were performed on a liquid chromatograph (Shimadzu, Japan), consisting of a reversed C18 column, ø4.6 × 250 mm and ultraviolet–visible light detector (UVD) system.

Preparation of ADM

ADH (3.5 g, 27.6 mmol), K_2CO_3 (11.4 g, 82.7 mmol), and TBAB (0.9 g, 2.8 mmol) were dissolved in 40 ml DMF in a 100-ml four-necked flask equipped with stirring bar, a reflux condenser, a thermometer, and a 50-ml dropping funnel. Then, DMC was slowly added to the reaction flask under 150 °C over a period of 30 min, and the reaction mixer was stirred for another 10 h under 150 °C. The obtained product was

analyzed by HPLC (see "Analytical method"). The chemical equation is shown as Scheme 1, and a probable reaction process was proposed (Process 1).

Analytical method

The product was analyzed by HPLC under the following operating conditions:

ODS C_{18} column, 250 mm × 4.6 mm (inner diameter) particle size 5 μm;
Mobile phase: CH_3OH-H_2O = 9:1 (v/v); Flow rate: 0.4 mL/min;
Detection wavelength: 254 nm; Injection volume: 20 μl.

The yield and selectivity of ADM were calculated through the standard curve method. The HPLC analysis result is shown in Fig. 1. The compound at retention time 5.285 min was ADM.

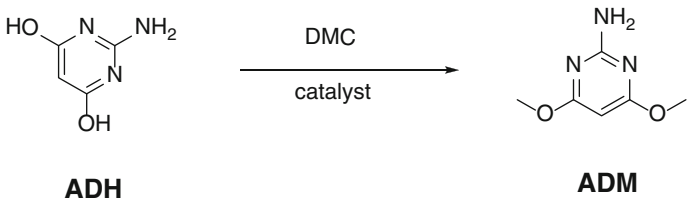
Results and discussion

Effect of DMC/ADH ratio on the reaction results

Figure 2 shows the effect of DMC/ADH ratio on the conversion of ADH and selectivity of the product at 150 °C for 10 h with a TBAB/ADH ratio of 0.1 and a K_2CO_3/ADH ratio of 3. The selectivity of ADM increased gradually when increasing the ratio of DMC to ADH. At a ratio of 5, the highest conversion and selectivity were 87.5 and 41.7 %, respectively. However, the yield and selectivity of ADM decreased when continuing to increase the ratio of DMC to ADH. Therefore, a DMC/ADH ratio of 5 was appropriate.

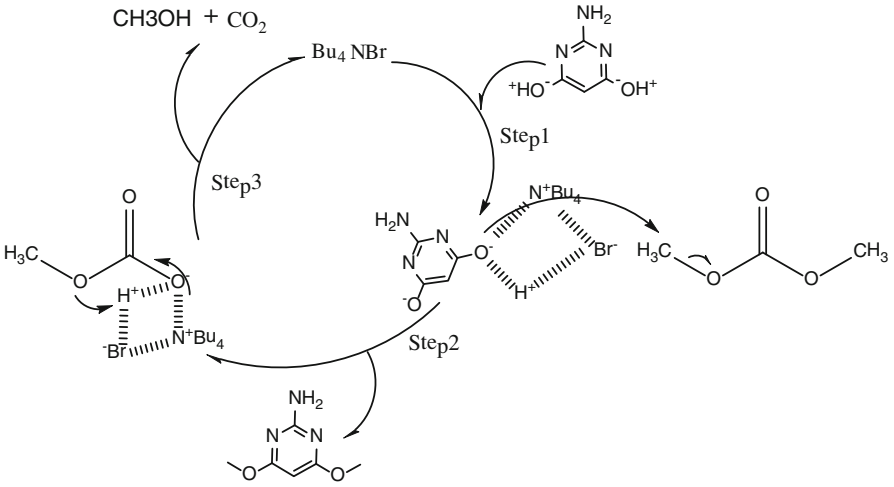
Effect of reaction temperature on the reaction results

The effect of reaction temperature on the conversion of ADH and selectivity of ADM was examined at a DMC/ADH ratio of 5; the results are shown in Fig. 3. In the temperature range studied, the best conversion was 87.5 %. The selectivity of ADM increased with the enhancement of reaction temperature from 130 to 150 °C. However, due to some side reactions, the selectivity of ADM did not show a continuous increase when the reaction temperature was enhanced. For, on the one hand, DMC broke down easily under alkaline conditions at higher temperature, while on the other hand, quaternary ammonium PTC have a poor thermal stability.



ADH **ADM**

Scheme 1 Methylation of ADH to ADM



Process 1 Probable progress of reaction with DMC as methylation in the system

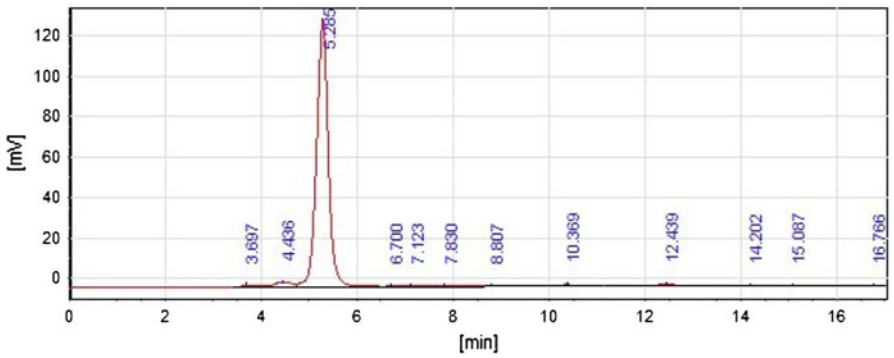


Fig. 1 HPLC result of ADM

Therefore, both of these may cause the decrease in activity at higher temperatures. Thus, a reaction temperature range of 150 °C was the most appropriate.

Effect of reaction time on the reaction results

The effect of reaction time on the conversion of ADH and selectivity of ADM was examined at 150 °C with a TBAB/ADH ratio of 0.1 and a K_2CO_3/ADH ratio of 3; the results are shown in Fig. 4. The conversion of ADH steadily increased and attained 88.1 % when the reaction time was 10 h. The selectivity of ADM went through maxima and decreased. The maximum yield and selectivity of ADM were

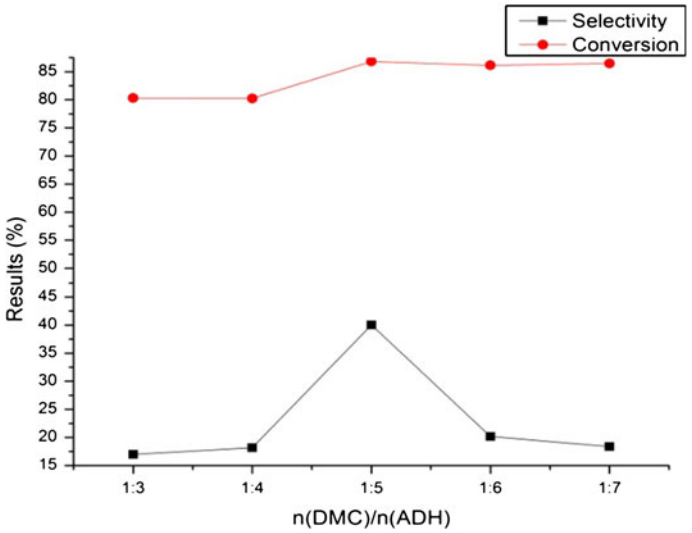


Fig. 2 Effect of DMC/ADH ratio on the results

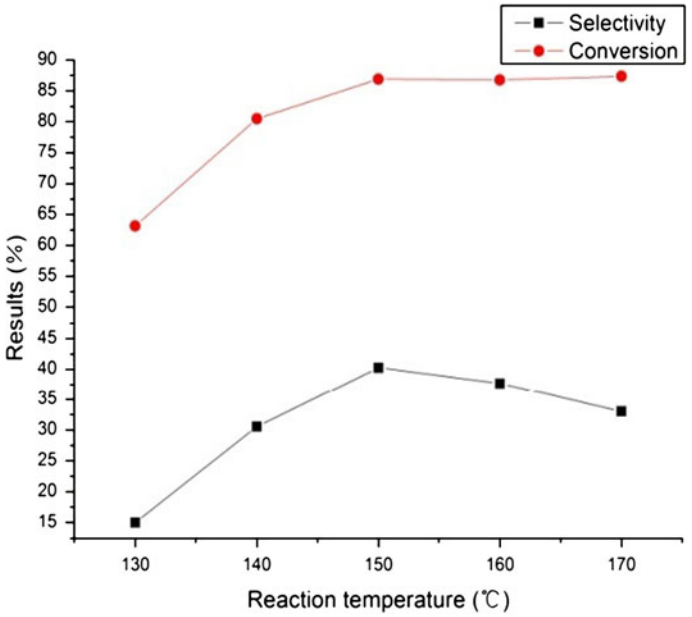


Fig. 3 Effect of reaction temperature on the results

35.0 and 40.3 %, respectively. Then, they decreased gradually at longer reaction times, as a result of the fact that ADM may react with methanol over catalysts at much longer reaction times. Thus, a reaction time of 10 h was the most appropriate.

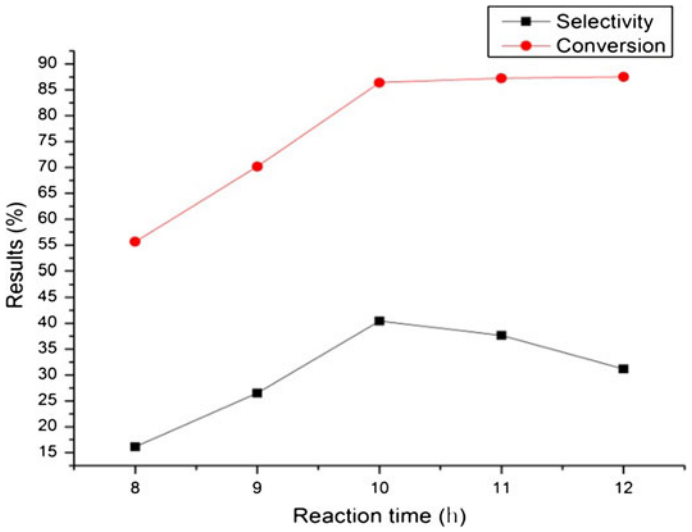


Fig. 4 Effect of reaction time on the results

Effect of different species of PTC on the reaction results

Figure 5 shows the changes in the conversion of ADH and selectivity of ADM over different species of PTC at 150 °C for 10 h with a DMC/ADH ratio of 5 and a K_2CO_3/ADH ratio of 3. Of note, only poor conversion and selectivity were achieved when there were no species of PTC to add in; among the different species of PTC,

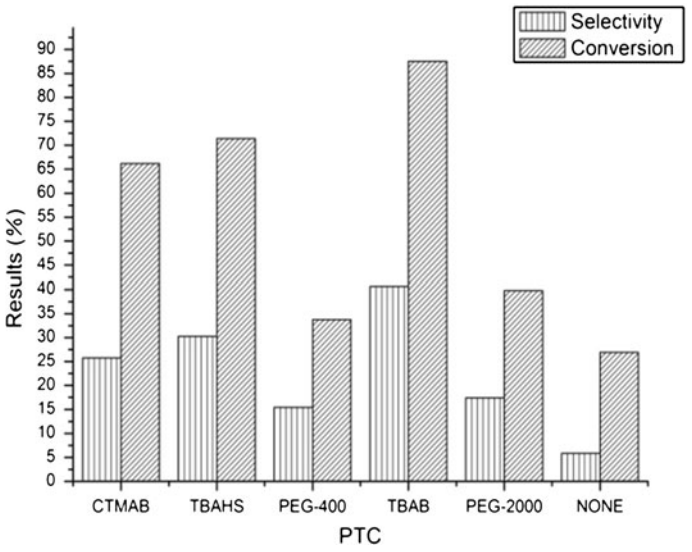


Fig. 5 The effect of different species of PTC on the results

TBAB exhibited higher catalytic activity than others. Therefore, it is appropriate to select TBAB as PTC.

Effect of TBAB/ADH ratio on the reaction results

The effect of TBAB/ADH ratio on the conversion of ADH and selectivity of ADM was speculated at 150 °C for 10 h with a DMC/ADH ratio of 5 and a K_2CO_3/ADH ratio of 3; the results are shown in Fig. 6. The conversion of ADH and selectivity of ADM increased gradually with increasing the ratio of TBAB to ADH. At a TBAB/ADH ratio of 0.1, the highest conversion and selectivity were 87.3 and 41.5 %, respectively. The yield and selectivity of ADM showed no significant gain with continuous increase of the ratio of TBAB to ADH. Thus, the optimum ratio of TBAB/ADH was 0.1.

Effect of K_2CO_3/ADH ratio on the reaction results

The effect of K_2CO_3/ADH ratio on the conversion of ADH and selectivity of ADM was estimated at 150 °C for 10 h with a DMC/ADH ratio of 5 and a TBAB/ADH ratio of 0.1; the results are shown in Fig. 7. The conversion of ADH and selectivity of ADM increased gradually with enhancement of the ratio of K_2CO_3 to ADH. At a K_2CO_3/ADH ratio of 3, the highest conversion and selectivity were achieved. The selectivity of ADM decreased gradually with continuous increase of the ratio of K_2CO_3 to ADH. These results show that DMC may be broken down easily when continuing to enhance the alkalinity of the reaction system. Therefore, it seems that the production of ADM in the reaction of ADH with DMC needs weakly basic sites. Thus, a K_2CO_3/ADH ratio of 3 could show the best yield and selectivity.

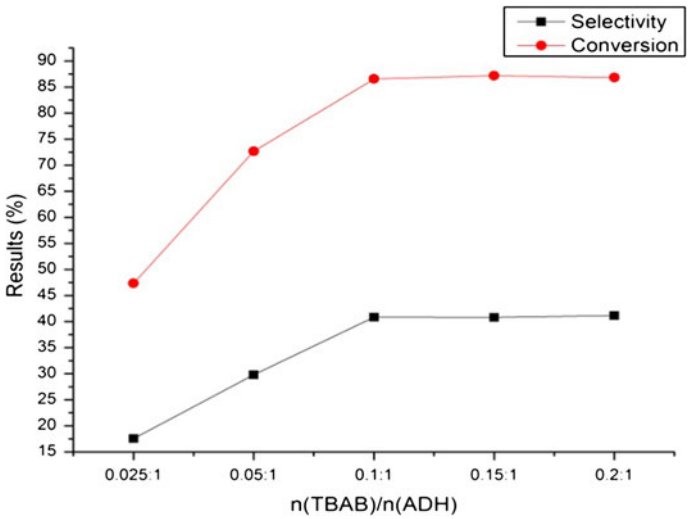


Fig. 6 The effect of TBAB/ADH ratio on the results

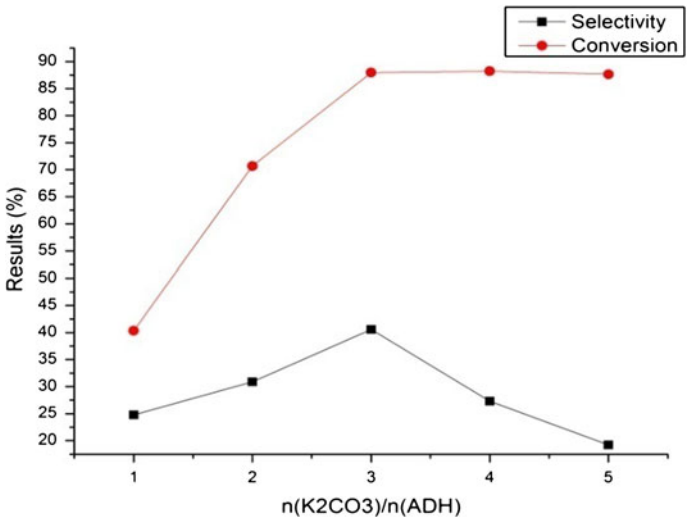


Fig. 7 Effect of K_2CO_3/ADH ratio on the results

The repeated experiments

The effect of repeated experiments on the conversion of ADH and selectivity of ADM was examined over K_2CO_3/TBAB at 150 °C for 10 h with a DMC/ADH ratio of 5, the results are listed in Table 1. The average conversion and selectivity were about 87.7 and 40.5 %, respectively. Thus, the reproducibility of the experimental results are good.

Conclusion

K_2CO_3/TBAB showed high catalytic activity and selectivity for the O-methylation of ADH with DMC to yield ADM. Thus, the highest conversion (87.7 %) of ADH and selectivity (40.5 %) of ADM were achieved at 150 °C for 10 h with a ADH/DMC/TBAB/K_2CO_3 ratio of 1/5/0.1/3. Compared with the traditional synthesis methods which are bad for the environment, the synthetic route reported (which has not previously been reported) was more ecofriendly, in accordance with the development direction of green chemistry.

Table 1 Results of repeated experiments

Repetition	1	2	3	4	5	Average
Conversion %	88.1	86.0	86.4	90.1	87.9	87.7
Selectivity %	40.1	40.2	41.4	40.8	40.2	40.5

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