

Synthesis of Diethyl 5-Ethyl-2,3-Pyridinedicarboxylate

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Diethyl 5-ethyl-2,3-pyridinedicarboxylate was synthesized using ammonium acetate as the nitrogen source. The optimum process conditions were obtained by exploring the reaction mechanism and researching the effects of reactant ratio, reaction temperature and solvent amount on the yield from all sides. Diethyl 5-ethyl-2,3-pyridinedicarboxylate yield was 98 % analysis by HPLC and the overall yield 96.8 % calculated by 2-chloro-3-oxo-succinic acid diethyl ester. The optimum process has the advantages of available initial material, simple waste-water treatment and environmental friendliness which are more applicable for industrial production.

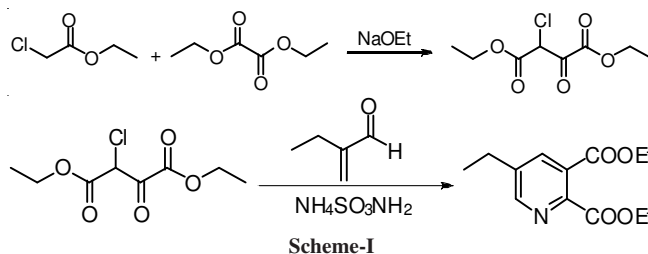
Keywords: Diethyl 5-ethyl-2,3-pyridinedicarboxylate, Ammonium acetate, Synthetic methods, Reaction mechanisms, Solvent effects.

INTRODUCTION

Diethyl 5-ethyl-2,3-pyridinedicarboxylate is an important organic intermediate and used in the field of dye, medicine and pesticide widely. Meanwhile, it also shows some biological activity. With the application of the efficient imidazolinone herbicides¹⁻⁹ which developed by American Cyanamid Company in the 1980's, the market demand risen dramatically¹⁰. However, because of the backward domestic technology and equipment conditions, current process for diethyl 5-ethyl-2,3-pyridinedicarboxylate comes with many disadvantages, such as high cost, low yield, serious pollution, *etc.*, which significantly decrease the economic and social benefits. Therefore, a new efficient method for the preparation of diethyl 5-ethyl-2,3-pyridinedicarboxylate is desired¹¹⁻¹⁵.

The general process of diethyl 5-ethyl-2,3-pyridinedicarboxylate is shown in **Scheme-I**. It takes diethyl oxalate and ethyl chloroacetate as raw materials, sodium ethoxide as catalyst to synthesize 2-chloro-3-oxo-succinic acid diethyl ester (**M1**) via Claisen condensation. Then in the presence of ammonium sulfamate, diethyl 5-ethyl-2,3-pyridinedicarboxylate is obtained by cyclizing **M1** and 2-ethyl acrolein. However, there are a lot of problems about this process. Firstly, the current molar ratio of **M1** and ammonium sulfamate is 1: 2.2. But the theoretical ratio is only 1:1, the excess nitrogen atom in the reaction flows into the waste water, which increases the difficulty of waste-water treatment. Secondly, the general method to deal with waste-water is evaporating concentration and burning organic substance in the waste water. Besides, burning the organic substances containing S atoms may give off sulfur dioxide

which will causes secondary pollution. Finally, ammonium sulfamate is not suitable for the large-scale production because of its high cost.



EXPERIMENTAL

All solvents and reagents were obtained from commercial sources and used without further purification. ¹H NMR spectra was recorded in CDCl₃ solution on a Mercury 300 MHz spectrometer.

Typical experimental procedure for the synthesis of 2-chloro-3-oxo-succinic acid diethyl ester (M1): According to the reference^{16,17}, a four-necked flask equipped with a mechanical stirrer and a thermometer was charged with sodium ethoxide (11.7 g, 0.170 mol) and toluene (65.0 mL). The mixture was stirred at room temperature for 45 min. Then diethyl oxalate (17.7 g, 0.121 mol) was added in 1 h at 25-40 °C. After another 0.5 h, the mixture was cooled to 25 °C and ethyl chloroacetate (12.4 g, 0.101 mol) was added in 2 h. Keeping the temperature at 32-35 °C for 3 h, ice-water (20 mL) and hydrochloric acid (30 %, 22.1 g, 0.181 mol) were added. The

organic phase was dried, filtered and concentrated to a red liquid (15.7 g) which was the compound **M1**.

Typical experimental procedure for the synthesis of diethyl 5-ethyl-2,3-pyridinedicarboxylate: A four-necked flask equipped with a mechanical stirrer and a thermometer was charged with ammonium acetate^{18,19} (19.3 g, 0.248 mol) and absolute ethanol (70 mL) and heated to 80 °C. Then a mixture of **M1** (26.9 g, 0.099 mol) and 2-ethyl acrolein (10.1 g, 0.119 mol) was added. After 5 h, the solvent was removed under reduce pressure and the residue solved in toluene (60 mL) was washed to be neutral with water (10 mL × 2). The organic phase was dried, filtered and concentrated into a dark brown liquid (26.4 g) which was the target product diethyl 5-ethyl-2,3-pyridinedicarboxylate with the yield 96.5 %. ¹H NMR (CDCl₃, 300 MHz) δ : 1.30 (t, J = 7.5 Hz, 3H), 1.36-1.44 (m, 6H), 2.76 (q, J = 7.5 Hz, 2H), 4.33-4.52 (m, 4H), 7.96 (s, 1H), 8.60 (s, 1H).

RESULTS AND DISCUSSION

In order to explore a route with high yield and environmental friendliness, we first discussed the mechanism²⁰ of the reaction. We inferred that the mechanism belonged to Knoevenagel-Fries modification based on reaction substrates and reaction conditions.

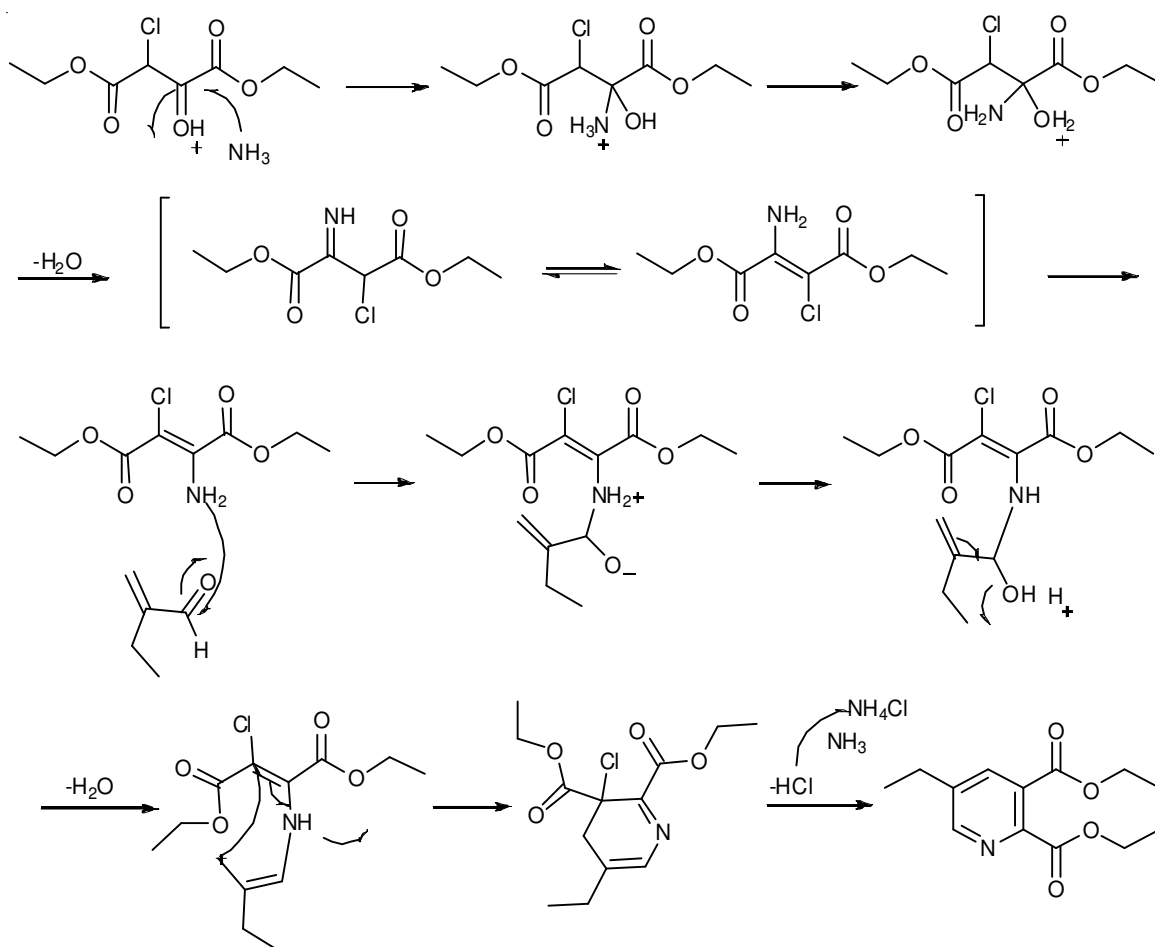
As shown in **Scheme-II**, the nitrogen source not only offers N atom to participate the reaction, but also absorbs hydrochloric acid. Thus, 1 mol reagent consumes 2 mol N atoms

at least. Besides, the solubility of nitrogen source in ethanol and the cost of nitrogen source were also taken into account. Based on above principles, we have tried following nitrogen sources: ammonium acetate, ammonia chloride²¹, ammonium sulfate and ammonia and ammonium acetate were chosen as the most suitable nitrogen source²². Based on the process information retrieval, this is the first time to use ammonium acetate as nitrogen source for the synthesis of diethyl 5-ethyl-2,3-pyridinedicarboxylate.

Effects of molar ratios of raw materials on the yield:

The effects of molar ratios of **M1**, 2-ethyl acrolein and ammonium acetate were studied in this part. The results are shown in Table-1.

It can be inferred from Table-1, keeping the reaction at 80 °C for 5 h, the molar ratios of the raw materials have pronounced effect on the yield. When the amount of 2-ethyl acrolein was constant, the yield increased due to the amount of ammonium acetate (Entries 1-3). But when the molar ratio of **M1** and ammonium acetate exceeded 2.5 equivalents, the yield decreased slightly (Entries 3-5). Therefore, it is reasonable that the molar ratio of **M1** and ammonium acetate was 1: 2.5. Furthermore, fixing the molar ratio of **M1** and ammonium acetate, the effect of different amount of 2-ethyl acrolein was investigated (entries 6-9). It shows that the yield was higher when the molar ratio of **M1**, 2-ethyl acrolein and ammonium acetate was 1:1.2:2.5. Finally, the optimized molar ratio of **M1**, 2-ethyl acrolein and ammonium acetate was 1:1.2:2.5.



Scheme-II

TABLE-1
EFFECTS OF MOLAR RATIOS OF RAW MATERIALS ON
THE YIELD AMOUNT OF ETHANOL (550 g/mol) AT 80 °C

Entry	Molar ratio ^a	Yield (%)
1	1:1.2:2.0	75.0
2	1:1.2:2.2	85.5
3	1:1.2:2.5	96.5
4	1:1.2:3.0	93.3
5	1:1.2:3.2	92.1
6	1:1.05:2.5	78.8
7	1:1.1:2.5	85.9
8	1:1.4:2.5	90.3
9	1:1.5:2.5	89.9

^a Molar ratio of M1, 2-ethyl acrolein and ammonium acetate

Effects of different temperatures on the yield: Making the molar ratio of M1:2-ethyl acrolein: ammonium acetate at 1:1.2:2.5. We required to emphasize the reaction temperature is different. The results are shown in Fig. 1.

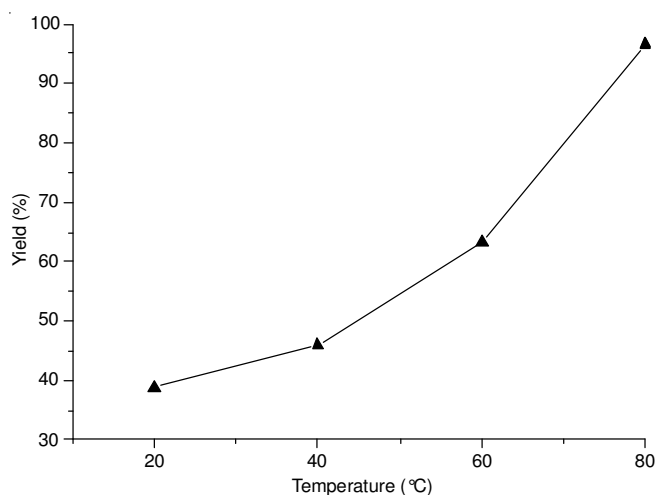


Fig.1. Effects of different reaction temperatures on the yield

It can be seen from Fig. 1, the yield increased as the temperature raise, which can reach highest at 80 °C. It is possible that the reaction rate is very slow when the temperature is low. With the increase of temperature, the reaction rate accelerates. Finally, the reaction temperature 80 °C was chosen as the optimum temperature.

Effects of solvent amount on the yield: Making the molar ratio of M1:2-ethyl acrolein:ammonium acetate at 1:1.2:2.5. We required to emphasize the amount of ethanol is different. The results are shown in Fig. 2.

It can be found from Fig. 2, with the increase of the amount of ethanol, the yield shows a trend that the yield increased at first and then decreased. Because when the amount of ethanol is less, ammonium acetate can't be dissolved throughly in ethanol, which will block the reaction. Then, if there is more ethanol, it will make the concentration very low, the reaction rate decreases and side reactions increase. Finally, the optimum amount of ethanol was 550 g/mol.

Conclusion

In conclusion, we have successfully developed an easy, efficient and versatile method for the synthesis of diethyl 5-ethyl-2,3-pyridinedicarboxylate starting from M1 and 2-ethyl

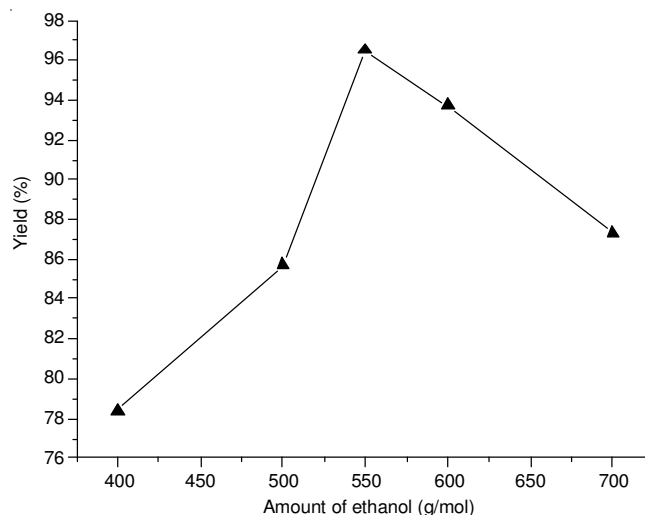


Fig. 2. Effects of different solvent amount on the yield

acrolein. In addition, we have taken ammonium acetate for the first time as the source of nitrogen to synthesize diethyl 5-ethyl-2,3-pyridinedicarboxylate. The optimum process is obtained: ethanol as the solvent, M1:2-ethyl acrolein: ammonium acetate = 1:1.2:2.5 (molar ratio), keeping reaction temperature at 80 °C for 5 h. Under this condition, the yield can reach 96.8 %. Besides the new process can decrease the salinity of the wastewater and reduce the pressure to environment, which is expected to apply to the large-scale industrial production.

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