A Novel 3E Method for Synthesis of 5-nitro 2-diethylamino 6-methyl pyridine Organic Crystal by Nitration of 2-diethylamino 6-methyl pyridine with H₂SO₄/HNO₃

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Abstract: 4-nitro 2-diethylamino 5-methyl pyridine (P-NitroC₁₀N₂H₁₆) as an organic crystal which is the useful intermediate for pharmaceutical synthesis and for production of organic materials, which was usually synthesized by nitration of 2-diethylamino 5-methyl pyridine with H₂SO₄/HNO₃ mixtures, followed by extraction, chromatography column separation and recrystallization three-step procedures. Here an innovation process for synthesizing 4-nitro 2-diethylamino 5-methyl pyridine crystal from the nitration of C₁₀N₂H₁₆ without needing chromatography column separation step is presented. The novel organic synthesis process is more ecologic, economical, and environmentally-friendly (3E) than the traditional organic synthesis process since the chromatography column separation process is a material-consuming and energy-consuming step, which needs to dispose of a large amount of wasted silica beads.

Keywords: 3E synthesis method; 5-nitro 2-diethylamino 6-methyl pyridine organic crystal; nitration of 2-diethylamino 6-methyl pyridine.

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1. Introduction

Pyridine derivatives display a broad spectrum of pharmacological activities such as antitumor, antihypertensive, anticonvulsant, cytotoxic, and significant analgesic activities. The methods have been studied for the synthesis of Pyridine derivatives such as nitropyridines from pyridines. The electrophilic aromatic substitution reactions of pyridine usually take place with great difficulty [1]. It has been reported that the nitration reaction of pyridine gives only 12 yields of 3-nitropyridine at 350°C [2]. 2,4,6-trimethylpyridine and 1,2,4,6-tetramethylpyridinium cation were nitrated with an acid nitrifying mixture (conc. HNO₃ in H₂SO₄) to give the corresponding 5-nitro derivatives of pyridine the same profile of rates was observed, passing through a maximum at 90% H₂SO₄. It was therefore concluded that 2,4,6-trimethylpyridine reacted as the conjugated acid [3]. It was reported that the nitration reaction of 2-picoline with KNO₃ and H₂SO₄ at a high temperature of 160°C gave a mixture 3- and 5-mononitro derivatives in low yield, and Increasing the number of methyl groups in the pyridine molecule sharply increased the yield of mononitro derivatives and the reaction temperature was decreased [4, 5]. Nitric acid did not give high yields on nitration of picolines [6]. The reactions
of 4-methyl-2-nitramino-, 6-methyl-2-nitramino- and 2- methyl-4-nitraminopyridine in 92% H$_2$SO$_4$ give the isomeric 3- and 5-nitro derivatives of the aminopicolines [7-10]. Pyridinium salts constitute a privileged class of compounds of both natural and synthetic importance [11, 12]. The pyridine-based indanone oximes have been studied as potent and selective B-Raf inhibitors [13]. The synthesis methods [14-19] and their reactions [20-25] of pyridine-based products have been reported. The synthesis of bioactive natural products, key intermediates, and drug candidates from pyridine and its derivatives has attracted increasing interests [26-28]. Synthesis of azaindoles and azaindole derivatives, which yielded several therapeutic agents for various diseases [29-32] from pyridine derivatives, has been recently extensively studied [33-36]. The synthesis route of substituted azaindoles from nitropyridines has been reported [37-41].

In the present study, the nitration of 2-diethylamino 5-methyl pyridine (C$_{10}$N$_2$H$_{16}$) with H$_2$SO$_4$/HNO$_3$ mixtures to synthesize the 4-nitro 2-diethylamino 5-methyl pyridine (P-NitroC$_{10}$N$_2$H$_{16}$) organic crystal are studied. A novel organic synthesis process of P-NitroC$_{10}$N$_2$H$_{16}$ which is more ecologic, economical, and environmentally friendly than the traditional organic synthesis process, has been developed.

2. Materials and Methods

The nitration reaction of C$_{10}$N$_2$H$_{16}$ with HNO$_3$/H$_2$SO$_4$ mixture was conducted under cooling conditions with an ice water bath. 95% sulfuric acid was first added into a 500 ml three mouth glass flask, and then the flask was placed in NaCl ice water bath, and after the internal temperature of the flask was cooling down to below 278K. 33.7 g of 2-diethylamino 5-methyl pyridine (C$_{10}$N$_2$H$_{16}$) raw materials was dropped into it under the internal temperature of below 293K. After homogenously solving 2-diethylamino 5-methyl pyridine in the concentrated sulfuric acid under the internal temperature below 273K by stirring, 19.9g of 65% nitric acid was dropped into the 2-diethylamino 5-methyl pyridine/H$_2$SO$_4$ mixture with stirring. The 2-diethylamino 5-methyl pyridine/H$_2$SO$_4$/HNO$_3$ mixture was stirred under an internal temperature below 283K for about 30 min. After the mixture was reacted for 30 min, it was added into the ice water under an internal temperature below 303K, followed by neutralization with 25wt% NaOH solution. The pH value of the neutralized product mixture solution was adjusted to 6-6.5. The organic phase products were extracted by toluene, followed by washing respectively with water and 25wt% NaCl solution and water removing with adsorbent of Na$_2$SO$_4$. Finally, the product was concentrated by minus pressure evaporation.

3. Results and Discussion

Two nitration product isomers of 5-nitro 2-diethylamino 5-methyl pyridine (P-NitroC$_{10}$N$_2$H$_{16}$) and 2-diethylamino 5-methyl pyridine (O-NitroC$_{10}$N$_2$H$_{16}$) are identified by NMR (Figure 1) and by HPLC analysis in the product of the nitration of 2-diethylamino 5-methyl pyridine with H$_2$SO$_4$/HNO$_3$ mixtures.

The 5-nitro 2-diethylamino 6-methyl pyridine organic crystal is the target product for the nitration reaction of 2-diethylamino 5-methyl pyridine. The scheme for synthesizing 4-nitro 2-diethylamino 5-methyl pyridine crystal from the nitration of C$_{10}$N$_2$H$_{16}$ is summarized in Fig 2.
Figure 1. NMR spectra of synthesized products of 5-nitro 2-diethylamino 6-methyl pyridine organic crystal and its isomer of 3-nitro 2-diethylamino 6-methyl pyridine (liquid at room temperature) and the reactant of 2-diethylamino 5-methyl pyridine.

Figure 2. Scheme for the synthesis of 4-nitro 2-diethylamino 5-methyl pyridine crystal from the nitration of C10N2H16.

4-nitro 2-diethylamino 5-methyl pyridine (P-NitroC10N2H16) as an organic crystal which is the useful intermediate for pharmaceutical synthesis and for production of organic materials, which was usually synthesized by nitration of 2-diethylamino 5-methyl pyridine with H2SO4/HNO3 mixtures, followed by extraction, chromatography column separation, and recrystallization three-step procedures. Here the high concentration of 4-nitro 2-diethylamino 5-methyl pyridine in the product is obtained by maximizing the conversion and selectivity for nitration of C10N2H16. The organic crystal of 4-nitro 2-diethylamino 5-methyl pyridine is easily separated from the product mixture without needing the chromatography column separation step because of its high concentration in the product mixture. This novel organic synthesis process is more ecologic, economical, and environmentally-friendly (3E) than the traditional organic synthesis process. The chromatography column separation process, which is a material-consuming and energy-consuming step, needs to dispose of a large amount of wasted silica beads is not needed.

To obtain the maximum yield of the target product, the dependence of the conversion and selectivity on the mole ratio of HNO3 to reactant of 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal by nitration with H2SO4/HNO3 is studied at the reaction temperature of 266-270K. The results are summarized in Fig 3. We can see from Fig 3 that the conversion of C10N2H16 and the selectivity of P-
NitroC_{10}N_{2}H_{16} get the maximum value at the HNO_{3} to 2-diethylamino 5-methyl pyridine mole ratio of about 1.2.

![Graph showing conversion and selectivity vs mole ratio](image)

**Figure 3.** Dependence of the conversion and selectivity on the mole ratio of HNO_{3} to 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal by nitration with H_{2}SO_{4}/HNO_{3} and H_{2}SO_{4}/2-diethylamino 5-methyl pyridine ratio of 5 at the reaction temperature of 266-270K.

Dependence of product composition on the mole ratio of HNO_{3} to 2-diethylamino 5-methyl pyridine to synthesize 5-nitro 2-diethylamino 5-methyl pyridine organic is also studied as shown in Fig 4.

![Graph showing product composition vs mole ratio](image)

**Figure 4.** Dependence of product composition on the mole ratio of HNO_{3} to 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal by nitration with H_{2}SO_{4}/HNO_{3} and H_{2}SO_{4}/2-diethylamino 5-methyl pyridine ratio of 5 at the reaction temperature of 266-270K.

We can see from Fig 4 that the unconverted C_{10}N_{2}H_{16} can be minimized at the HNO_{3} to 2-diethylamino 5-methyl pyridine mole ratio of about 1.2.

Dependence of the conversion and selectivity on the mole ratio of H_{2}SO_{4} to 2-diethylamino 5-methyl pyridine is also studied to synthesize 5-nitro 2-diethylamino 5-methyl
pyridine organic crystal by nitration with H$_2$SO$_4$/HNO$_3$, and the results are summarized in Fig 5.

![Conversion and selectivity vs. mole ratio](image)

Figure 5. Dependence of the conversion and selectivity on the mole ratio of H$_2$SO$_4$ to 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal by nitration with H$_2$SO$_4$/HNO$_3$ and HNO$_3$/2-diethylamino 5-methyl pyridine ratio of 1.1 at the reaction temperature of 266-270K.

It is clear in Fig 5 that the maximum conversion and selectivity are obtained at the H$_2$SO$_4$/C$_{10}$N$_2$H$_{16}$ ratio of 5.

![Conversion vs. mole ratio](image)

Figure 6. Conversion of 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal as a function of H$_2$SO$_4$/HNO$_3$ molar ratio.

Fig 6 shows the conversion of 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal as a function of H$_2$SO$_4$/HNO$_3$ molar ratio. We can see from Fig 6 that the conversion of 2-diethylamino 5-methyl pyridine of nearly 100% has been obtained at the H$_2$SO$_4$/HNO$_3$ molar ratio of 5.

4. Conclusions

4-nitro 2-diethylamino 5-methyl pyridine (P-NitroC$_{10}$N$_2$H$_{16}$) organic crystal is successfully synthesized by nitration of 2-diethylamino 5-methyl pyridine with H$_2$SO$_4$/HNO$_3$ mixtures. The pure P-NitroC$_{10}$N$_2$H$_{16}$ organic crystal product is obtained by an innovation
process without needing a chromatography column separation step. The novel organic synthesis process is more ecologic, economical, and environmentally-friendly (3E) than the traditional organic synthesis process since the chromatography column separation process is a material-consuming and energy-consuming step, which needs to dispose of a large amount of wasted silica beads.

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**Conflicts of Interest**

The authors declare no conflict of interest.

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