Letters in Applied NanoBioScience
Platinum Open Access Journal (ISSN: 2284-6808)

Article
Volume 11, Issue 4, 2022, 4131 - 4138
https://doi.org/10.33263/LIANBS114.41314138

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 H_2SO_4/HNO_3

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Received: 24.07.2021; Revised: 30.08.2021; Accepted: 5.09.2021; Published: 31.10.2021

Abstract: 4-nitro 2-diethylamino 5-methyl pyridine (P-Nitro$C_{10}N_2H_{16}$) 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 H_2SO_4/HNO_3 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 $C_{10}N_2H_{16}$ 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.

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^{o}C [2]. 2,4,6-trimethylpyridine and 1,2,4,6-tetramethyl-pyridinium cation were nitrated with an acid nitrifying mixture (conc. HNO_3 in H_2SO_4) to give the corresponding 5-nitro derivatives of pyridine the same profile of rates was observed, passing through a maximum at 90% H_2SO_4. 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 KNO_3 and H_2SO_4 at a high temperature of 160^{o}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_2SO_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 intrestes[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 ($C_{10}N_2H_{16}$) with H_2SO_4/HNO_3 mixtures to synthesize the 4-nitro 2-diethylamino 5-methyl pyridine (P-Nitro$C_{10}N_2H_{16}$) organic crystal are studied. A novel organic synthesis process of P-Nitro$C_{10}N_2H_{16}$ 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 $C_{10}N_2H_{16}$ with HNO_3/H_2SO_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 ($C_{10}N_2H_{16}$) 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_2SO_4 mixture with stirring. The 2-diethylamino 5-methyl pyridine/H_2SO_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_2SO_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-Nitro$C_{10}N_2H_{16}$) and 2-diethylamino 5-methyl pyridine (O-Nitro$C_{10}N_2H_{16}$) are identified by NMR (Figure 1) and by HPLC analysis in the product of the nitration of 2-diethylamino 5-methyl pyridine with H_2SO_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 $C_{10}N_2H_{16}$ is summarized in Fig 2.

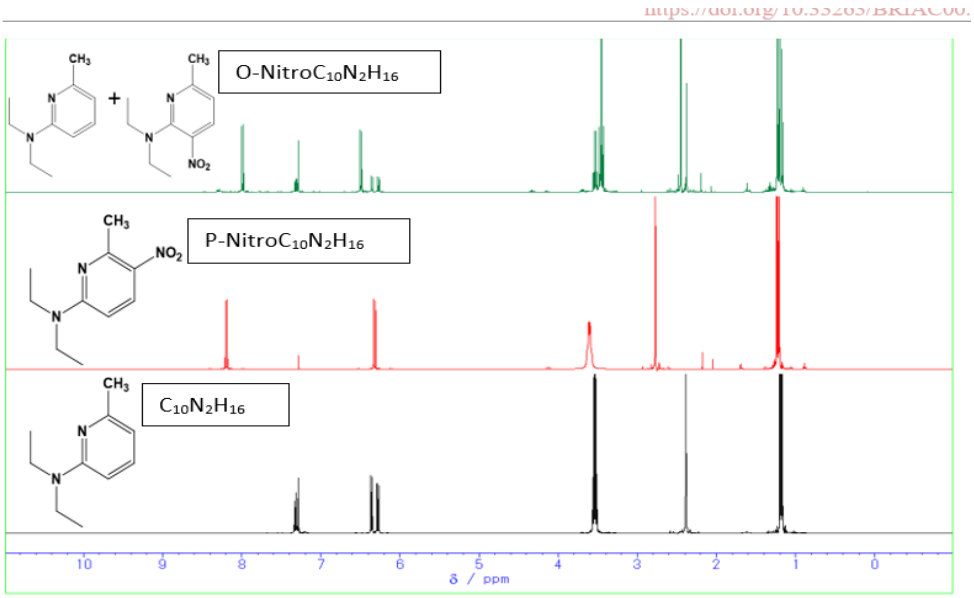

Figure 1. NMR spectra of synthesized products of 5-nitro 2-diethylamino 6-methyl pyridine organic crystal and its isomer of 3-nitro 2-diethylamino 6-methyl pyridine (liquid at room temperature) and the reactant of 2-diethylamino 5-methyl pyridine.

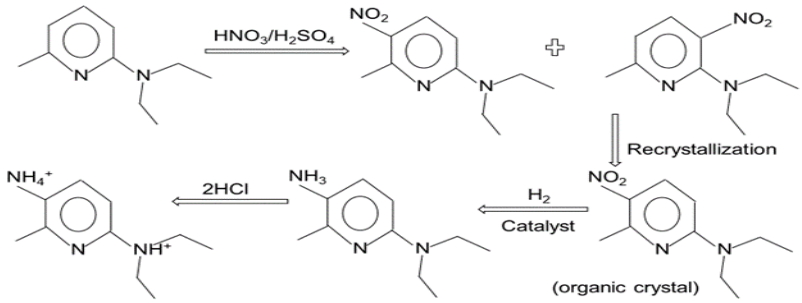

Figure 2. Scheme for the synthesis of 4-nitro 2-diethylamino 5-methyl pyridine crystal from the nitration of $C_{10}N_2H_{16}$.

4-nitro 2-diethylamino 5-methyl pyridine (P-Nitro$C_{10}N_2H_{16}$) 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 H_2SO_4/HNO_3 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 $C_{10}N_2H_{16}$. 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 HNO_3 to reactant of 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal by nitration with H_2SO_4/HNO_3 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 $C_{10}N_2H_{16}$) and the selectivity of P-

Nitro$C_{10}N_2H_{16}$ get the maximum value at the HNO_3 to 2-diethylamino 5-methyl pyridine mole ratio of about 1.2.

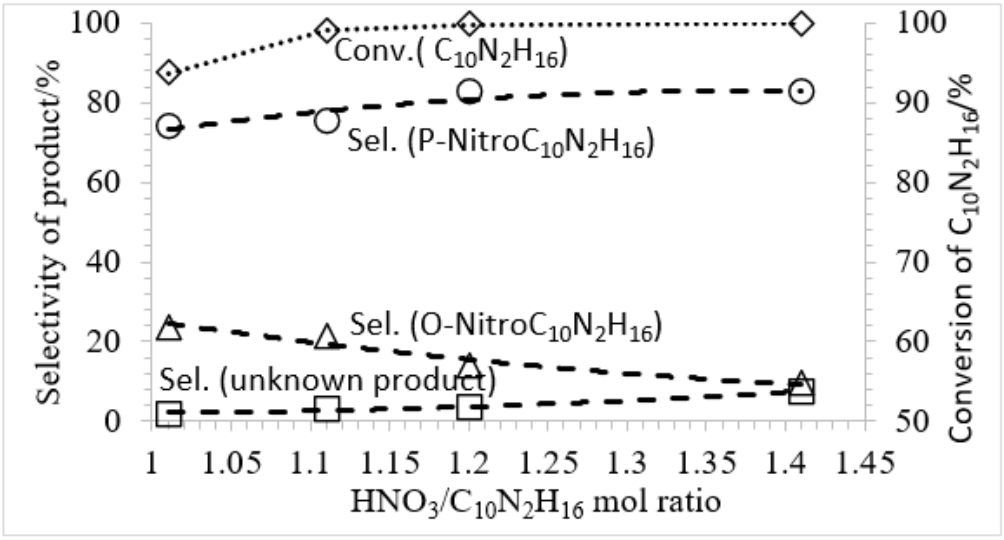

Figure 3. Dependence of the conversion and selectivity on the mole ratio of HNO_3 to 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal by nitration with H_2SO_4/HNO_3 and H_2SO_4/2-diethylamino 5-methyl pyridine ratio of 5 at the reaction temperature 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.

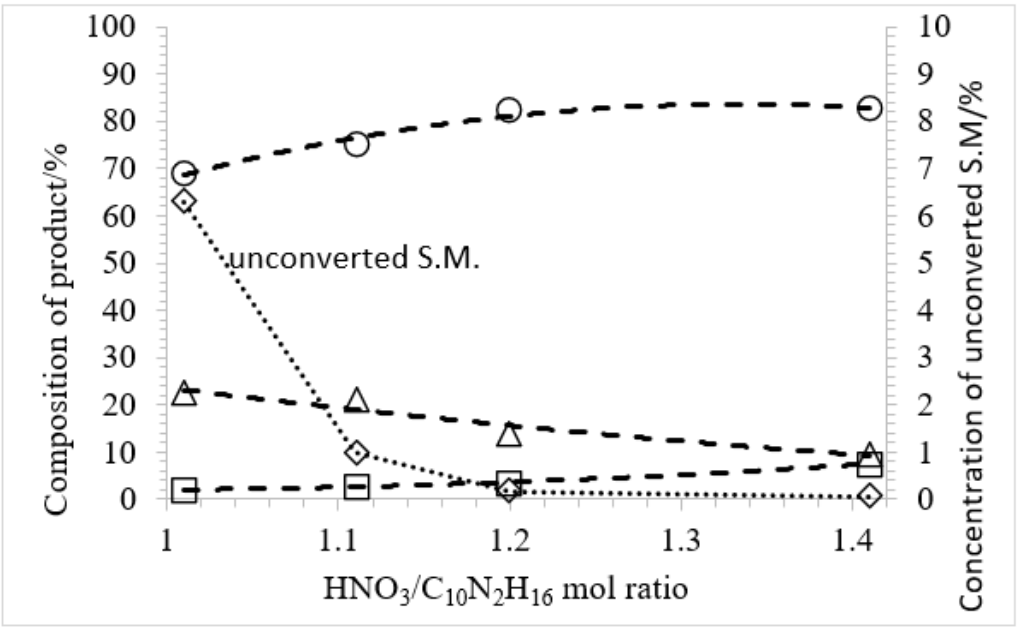

Figure 4. Dependence of product composition on the mole ratio of HNO_3 to 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal by nitration with H_2SO_4/HNO_3 and H_2SO_4/2-diethylamino 5-methyl pyridine ratio of 5 at the reaction temperature of 266-270K.

We can see from Fig 4 that the unconverted $C_{10}N_2H_{16}$) 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_2SO_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_2SO_4/HNO_3, and the results are summarized in Fig 5.

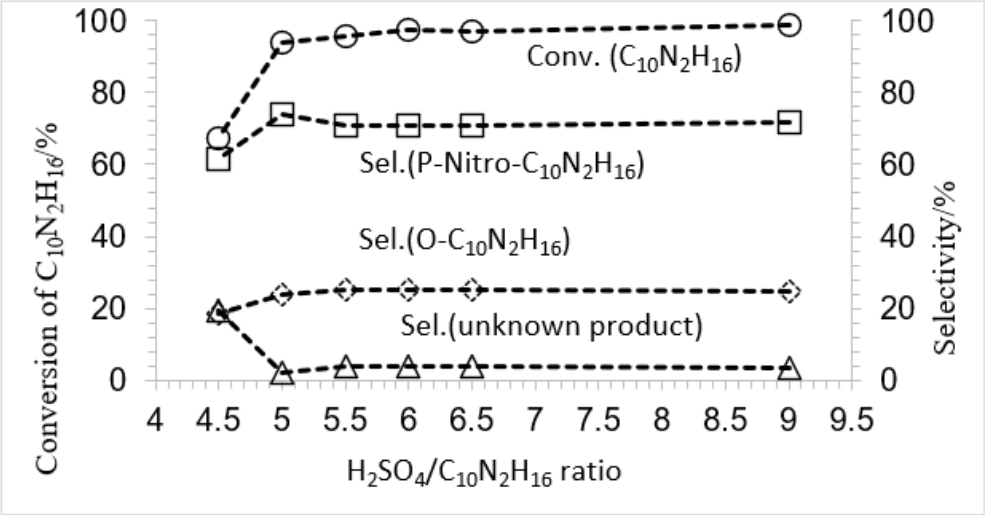

Figure 5. Dependence of the conversion and selectivity on the mole ratio of H_2SO_4 to 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal by nitration with H_2SO_4/HNO_3 and HNO_3/2-diethylamino 5-methyl pyridine ratio of 1.1 at the reaction temperature of 266-270K.

It is clear in Fig 5 that the maximum conversion and selectivity are obtained at the $H_2SO_4/C_{10}N_2H_{16}$ ratio of 5.

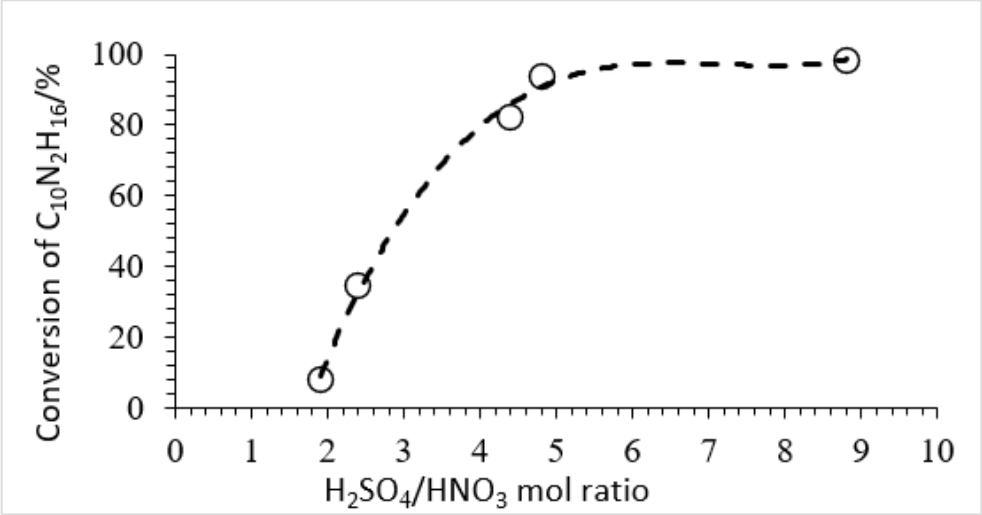

Figure 6. Conversion of 2-diethylamino 5-methyl pyridine for the synthesis of 5-nitro 2-diethylamino 5-methyl pyridine organic crystal as a function of H_2SO_4/HNO_3 molar ratio.

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_2SO_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_2SO_4/HNO_3 molar ratio of 5.

4. Conclusions

4-nitro 2-diethylamino 5-methyl pyridine (P-Nitro$C_{10}N_2H_{16}$) organic crystal is successfully synthesized by nitration of 2-diethylamino 5-methyl pyridine with H_2SO_4/HNO_3 mixtures. The pure P-Nitro$C_{10}N_2H_{16}$ 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.

Funding

This research received no external funding.

Acknowledgments

This research has no acknowledgment.

Conflicts of Interest

The authors declare no conflict of interest.

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