International Pharmacy Acta. 2022;5(1):e1
Original Research Article
OPEN ACCESS
ISSN: 2645-3266

Green Synthesis of Nalidixic Acid by Ionic Liquid

Hamid Reza Ahfad-Hosseini[a], Hasan Bagheri[a], Salimeh Amidi[b,*]

a. Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.
b. Department of Medicinal Chemistry, School of Pharmacy and Pharmaceutical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Article Info:
Received: November 2021
Accepted: May 2022
Published online: June 2022

* **Corresponding Author:**
Salimeh Amidi
Email: s.amidi@sbmu.ac.ir

Abstract:

In this study, a green process was applied for the preparation of nalidixic acid by the assistance of an ionic liquid. Nalidixic acid was prepared by reaction of 6-methylpyridin-2-amine, ethyl formate and diethyl malonate in tris-(2-hydroxyethyl) ammonium acetate solution as ionic liquid (IL) which was provided by reaction of triethanolamine and acetic acid. The ^{1}HNMR, ^{13}CNMR, FTIR, mass spectroscopy and melting point were used to characterize the structure of the synthesized compounds. The ionic liquid was recovered and reused for four runs**.** This method introduces a novel idea for synthesis of nalidixic acid with high yield (86%) and the least damage to the environment. This IL can be used as a green solvent in synthesis of compounds instead of using harmful solvents.

Keywords: Nalidixic acid; Ionic liquid; Synthesis.

Please Cite this article as: Ahfad-Hosseini H.R., Bagheri H., Amidi S. Green Synthesis of Nalidixic Acid by Ionic Liqui. Int. Pharm. Acta. 2022;5(1):e1
DOI: https://doi.org/10.22037/ipa.v5i1.36873

1. Introduction

Naphthyridine nucleus is an important core in many natural products, drugs and synthetic compounds. 1,8-naphthyridine derivatives have demonstrated a wide range of biological effects such as antibacterial, antimalarial, antiplatelet and anticancer [1, 2].
Nalidixic acid (1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid) was discovered in 1962 and was the first synthetic quinolone antibiotics with 1,8-naphthyridine core. Nalidixic acid is known to be effective against gram-negative infections of the urinary tract and in some gastrointestinal infections such as shigellosis [1, 3].
Several methods were reported for synthesis of naphthyridine and quinolone derivatives. Singh reported the synthesis of nalidixic acid and related quinolones by the modification of Gould-Jacob method [4]. A series of 4-oxo-1,4-dihydroquinoline-3-carboxylic acids were also prepared by the Gould–Jacobs reaction [5]. 2-Methyl-5-hydroxy-6-carbethoxy-1,8-naphthyridine was synthesized from ethyl ethoxymethylenemalonate and 6-methyl-2-aminopyridine [6].
Organic solvents such as diphenyl ether often are used in the synthesis of nalidixic acid [4]. These organic solvents are responsible for organic impurities of the final products (residual solvents or organic volatile impurities) and environmental contaminations. Due to environmental and health concerns about the toxic effect of solvents, developing new and efficient synthetic methods with green medium or solvent free conditions is increasing [7]. In the last decade, ionic liquids (ILs) have come up as alternative to conventional organic solvents because of their attractive chemical and physical properties such as enhancement in reaction rates and selectivity, very low vapor pressure, nonflammability, high thermal stability, high ionic conductivity, wide range of polarity and easily recycled. These compounds can be used as catalysts or/and solvents in organic reactions. [8-10]. ILs are defined as salts with melting points below 100 °C [11, 12]. Alizadeh, et al used 2-hydroxyethylammonium formate (2-HEAF), as IL in synthesis of β-nitrostyrene derivatives [13]. Preparation of 4-aryl-3-methyl-1-phenyl-7,8-dihydro-1*H*-pyrazolo[3,4-b] [1,6]naphthyridin-5(4*H*)-one analogs in ionic liquids was reported by Feng et al. [14]. In our previous work, we have reported the synthesis of celecoxib using tris-(2-hydroxyethyl) ammonium acetate as IL [15].

In continuation of our work in synthesizing of drugs with ionic liquids, the green method for the synthesis of nalidixic acid in tris-(2-hydroxyethyl) ammonium acetate as IL was developed. In this method, the tris-(2-hydroxyethyl) ammonium acetate was synthesized and used in synthesis of nalidixic acid. The structure of synthesized nalidixic acid was characterized by ^{1}HNMR, ^{13}CNMR, FTIR, Mass spectroscopy and melting point. The effects of solvents, IL concentrations and reaction temperature on the nalidixic acid yield were studied. Also the ionic liquid was recovered and used several times to check out the catalytic activity of the ionic liquid.

2. Materials & Methods

2.1. Chemistry

All the compounds were purchased from Merck Chemical Company (Darmstadt, Germany) as synthesized grade. Perkin Elmer FT-IR spectrum Gx was used to obtain IR spectra. The NMR spectra were obtained using a Jeol FT-NMR-400 MHz in DMSO solvent. Tetramethylsilane (TMS) was used as an internal standard. Melting points of compounds were determined on an Electrothermal apparatus.

2.2. Synthesis of tris-(2-hydroxyethyl) ammonium acetate

The ionic liquid was synthesized according to the previously reported method [15]. In brief, acetic acid (5 mmol) and triethanolamine (5 mmol) were added to 10 mL dichloromethane and stirred at room temperature. After 2 hours, the reaction was filtered. The isolated compound was washed twice with diethyl ether and dried in vacuum oven.
Yield 98%, FTIR: υ 3200-3500, 3150, 1690, 1410, 1320 cm^{-1} [16, 17], ^{1}H NMR (400 MHz, DMSO-d$_6$): δ-ppm 2.1 (s, 3H, CH_3), 3.4 (t, 6H, CH_2N), 3.8 (t, 6H, CH_2O), 4.7 (s, 3H, OH), 6.8 (s, 1H, N-H), ^{13}C NMR (100 MHz, DMSO-d6): δ-ppm 151, 55.2, 54.9, 21.4.

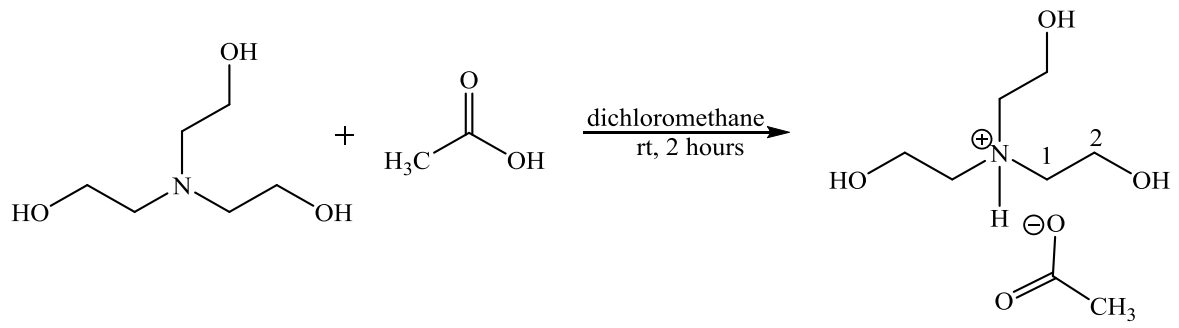
2.3. Synthesis of the nalidixic acid (*1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid*)

6-methylpyridin-2-amine (1 mmol), ethyl formate and IL (0.1 mol) were added to water (8 mL) and EtOH (2 mL) and stirred at room temperature for 10 minutes. Then diethyl malonate (1 mmol) was added to the mixture. After 30 minutes the mixture was filtered and washed with water and ethanol (50/50 v/v %). The mixture of obtained powder, water (5 mL), iodoethane (1 mmol) and IL (0.1 mol) was stirred at room temperature and filtered after 30 minutes. The obtained product was stirred at 60 ˚C for 20 minutes in presence of water (5 mL) and NaOH (1 mmol). Finally the cream-color powder was isolated via filtration. The isolated precipitate was washed with water and ethanol (50/50 v/v %) and dried in vacuum oven.
Cream color powder, yield 86%, mp: 228–229 °C; FTIR (KBr): υ 3400, 3000, 2800, 1690, 1595, 1500, 1400 cm^{-1}, ^{1}H NMR (400 MHz, DMSO-d$_6$): δ-ppm 1.4 (m, 3H, CH_3), 2.4 (s, 3H, Ar-CH_3), 4.2 (m, 2H, CH_2), 7.0 (d ,1H, H-6), 7.8 (d, 1H, H-5), 9.2 (s, 1H, H-2), 13.9 (s, 1H, O-H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ-ppm 173, 165, 164, 148, 146, 134, 122, 118, 108, 46, 25, 14. MS: $[M+H]^+$ *m/z* 233.

3. Results and Discussion

3.1. IL synthesis

Tris-(2-hydroxyethyl) ammonium acetate as the ionic liquid (IL) was obtained through the reaction of acetic acid and triethanolamine in dichloromethane as shown in scheme 1. The structure of the IL has been confirmed by ^{1}HNMR, ^{13}CNMR and FTIR spectra.



Scheme 1: Preparation of tri-(2-hydroxyethyl) ammonium acetate

3.2. Nalidixic acid synthesis

Nalidixic acid was synthesized by reaction of 6-methylpyridin-2-amine with ethyl formate and diethyl malonate in the presence of the IL, EtOH and aqueous NaOH at 60 ˚C. The structure of nalidixic acid has been described by ^{1}HNMR, ^{13}CNMR, FTIR and Mass spectroscopy. The synthesis route of nalidixic acid is shown in Scheme 2.

The ^{1}HNMR spectrum of obtained nalidixic acid is shown the sharp singlet peak at 13.9 ppm belongs to the acidic proton and the singlet peak which is observed at 9.2 ppm related to H-2. The aromatic protons H-5 and H-6 appear as a doublet peak at 7.8 and 7.0 ppm, respectively. A multiplet is observed at 4.2 ppm for -CH_2 protons. The protons of the methyl group attached to the aromatic ring and the -CH_3 protons of the ethyl group appear as singlet and multiplet peaks at 2.4 and 1.4 ppm, respectively.

In the ^{13}CNMR spectrum of nalidixic acid peaks appear at 173 and 165 ppm related to C-4 and C-8a, respectively. The peak of carbonyl carbon of the carboxylic acid group is observed at 164 ppm. Other peaks at 148 and 146 ppm related to C-2 and C-7, respectively while the peak of C-4a appeared at 118 ppm and the peak of C-3 observed at 108 ppm.

3.3. Effect of solvents on the yield of nalidixic acid

To choose the best solvent for this reaction, various solvents were used and the yield of reaction was determined (Table 1). As shown in Table 1, when the mixture of water and ethanol was used the yield of reaction is increased. It was reported previously this effect may be due to the formation of hydrogen bond with three OH groups of cationic part of the ionic liquid which increase solubility of the ionic liquid, stability of cation and acceptable performance of the ionic liquid. Addition of ethanol can help to increase the solubility of reactants [15].

Table 1. Effect of different solvents on synthesis yield of nalidixic acid

Entry	Solvent	Reaction time (min)	Yield (%)
1	H_2O	60	80
2	Solvent-free	60	82
3	**H_2O / C_2H_5OH**	**60**	**86**
4	C_2H_5OH	60	82
5	CH_3CN	60	55
6	CH_3CO_2Et	60	50
7	CH_2Cl_2	60	20
8	Toluene	60	10

3.4. Effect of ionic liquid concentration on the yield of nalidixic acid

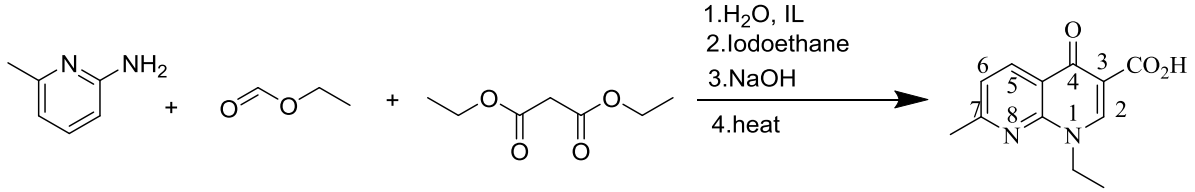
The reaction was carried out using different concentrations of IL (Table 2). It was demonstrated that by increasing the amount of IL to 10 mol%, the yield of the reaction is increased at constant temperature. Using IL with concentration greater than 10 mol% did not improve the yield. So, 10 mole% is the least amount of the IL which caused maximum yield at a reaction temperature of 70 ˚C.

3.5. Effect of reaction temperature on the yield of nalidixic acid

When the reaction was performed at 60 ºC and 100 ºC for 60 min, without IL the obtained yield of product was 10% and 25%, respectively. At the optimum concentration of IL, the temperature changes did not affect the reaction yield.

Table 2. Effect of the ionic liquid concentration and reaction temperature on nalidixic acid yield

Entry	Catalyst loading (mol%)	Reaction temperature (ºC)	Reaction time (min)	Yield (%)
1	—	60	60	10
2	—	100	60	25
3	1	70	60	45
4	2	80	60	60
5	5	80	60	70
6	5	70	60	80
7	**10**	**70**	**60**	**86**
8	10	100	60	86
9	15	70	60	86
10	15	100	60	86



Scheme 2. Synthesis route of nalidixic acid.

3.6. Reusability of IL

The reusability of the IL was studied for the preparation of nalidixic acid. The nalidixic acid has poor solubility in water and could be easily filtered and separated. The results of this section were presented in figure 1. According to obtained results the filtered reaction medium could be reused in four reactions without lowering the yield and decreasing the performance of IL. So, it was usable for several times.

3.7. The mechanism of reaction

The suggested mechanism for the synthesis of nalidixic acid was demonstrated in scheme 3. The intermediate (I) results from the reaction of diethyl malonate and ethyl formate. The reaction between 6-methylpyridine-2-amine and intermediate (I) starts with Michael addition and finally intermediate (II) was generated. The intermediate (II) undergoes cyclization to give compound (III).

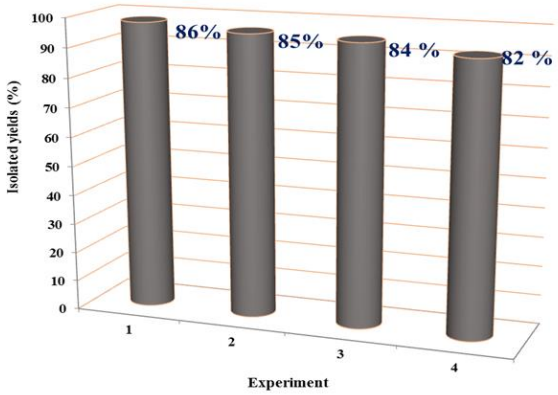
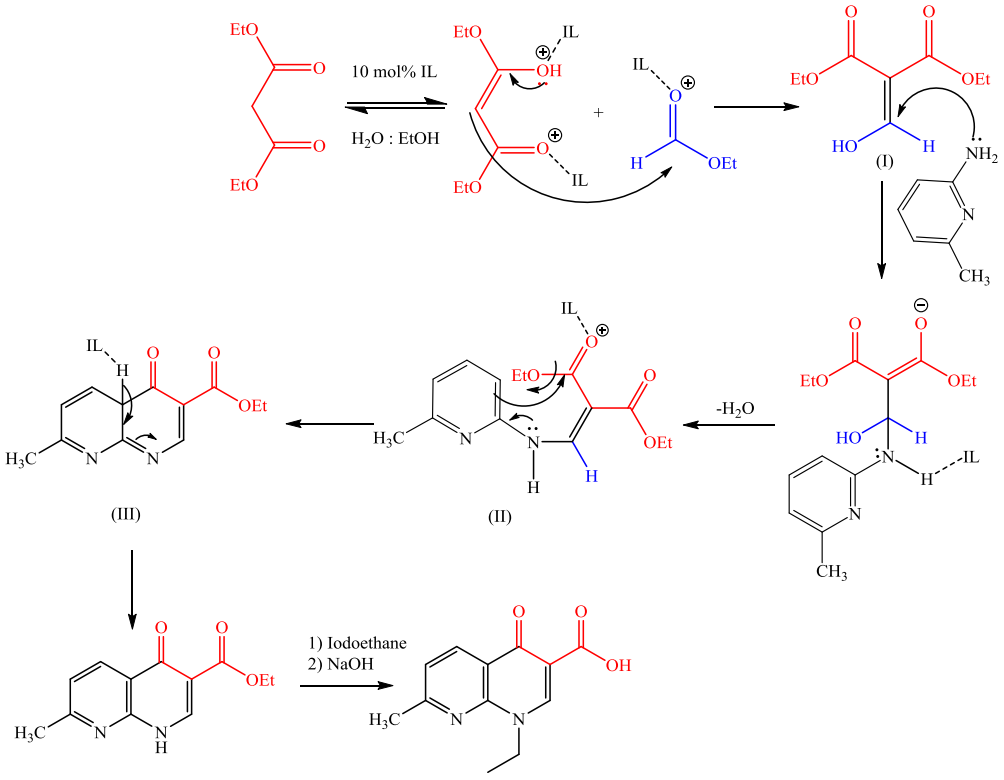


Figure 1. Study of the ionic liquid reusability.



Scheme 3. The suggested mechanism for the synthesis of nalidixic acid in the presence of ionic liquid.

4. Conclusion

In summary, an efficient IL namely tris-(2-hydroxyethyl) ammonium acetate was synthesized and characterized by FTIR, ^{1}HNMR, ^{13}CNMR. The application of this IL in different solvents and temperature was considered in the synthesis of nalidixic acid. The obtained results showed that IL plays a key role in nalidixic acid synthesis reaction. The advantages of this study are shorter reaction time, higher yield, lower cost, application of green solvents, reusability of the IL and ease of product isolation.

Acknowledgements

This work was supported by the Pharmaceutical Sciences Research Center of Shahid Beheshti University of Medical Sciences.

Conflict of interest

The authors have no conflicts of interest to declare.

Sources of support and fundings declaration
This work was supported by a grant from the Pharmaceutical Sciences Research Center of Shahid Beheshti University of Medical Sciences.

Ethics

IR.SBMU.RETECH.REC.1395.743

Funding/ Support

None.

Authors' ORCIDs

Hasan Bagheri: https://orcid.org/0000-0003-2895-6189
Salimeh Amidi: https://orcid.org/0000-0002-6032-3237

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