Physical Chemistry

Effect of Natural Zeolite Catalysts, Ultrasound and Microwave Irradiation on the Isonicotinic Acid Ethylation Reaction

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The paper presents the results of the catalytic esterification reaction of isonicotinic acid (INA) with ethanol into target ethyl isonicotinate (INAEE) in the presence of hydrogen forms of natural zeolites as catalysts and under microwave (MW) and ultrasound (US) irradiation. The ethylation was carried out under an inert argon atmosphere at 80°C at different molar ratios of INA and ethanol. Catalysts (H-CL (SiO$_2$/Al$_2$O$_3$ = 23.3), H-HEU-M (SiO$_2$/Al$_2$O$_3$ = 8.2) and H-MOR(SiO$_2$/Al$_2$O$_3$ = 20.1) in a form of crystallites of micrometric (4.8–7.0 µm) and ultradisperse (300–480 nm) size were used; the catalysts were prepared from the initial hydrogen forms of zeolites by their treatment with microwaves (MW, 2450 MHz, 300 W, 2 h) and ultrasound (US, 37 kHz, 330 W, 2 h). Compared to thermocatalytic ethylation, on ultrafine crystallites of H-CL, H-HEU-M and H-MOR zeolites, conversion and selectivity for ethyl isonicotinate increase (up to 35 and 98%, respectively) synergistically under the action of a catalyst with microwaves or ultrasound. In the study, methods of GC/MS, FTIR and NMR were applied. © 2023 Bull. Georg. Natl. Acad. Sci.

ethyl pyridine-4-carboxylate, natural zeolites, microwave- and ultrasound-assisted reactions

Esters are one of the main products of chemical synthesis, and their production is very promising applying both catalytic technologies, which can be used to control the selectivity and productivity of processes and non-catalytic methods, in particular, various types of irradiation [1-7].

The present study concerns the use of both of the aforementioned "green" (environmentally friendly) approaches to the preparation of isonicotinic acid ethyl ester, INAEE (IUPAC name: ethyl pyridine-4-carboxylate, C$_8$H$_9$NO$_2$), Scheme.

INAEE is a precursor for the production of various pharmaceutical and biologically active compounds; in particular, of isoniazid–pyridine-4-carbohydrazide, isonicotinic acid hydrazide (C$_6$N$_3$H$_7$O), a first-line antibacterial drug widely used in medicine for the treatment of tuberculosis [4], for the production of antidepressants. INAEE is also an effective thrips attractant [8].

INAEE is prepared by the esterification reaction of isonicotinic acid (pyridine-4-carboxylic acid), with ethyl alcohol and an acylating agent, for
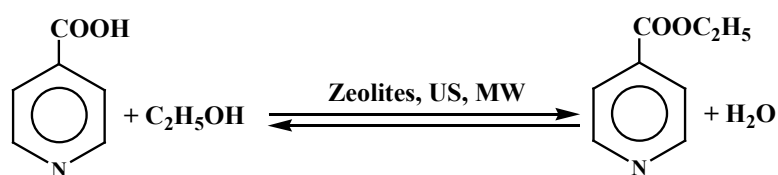
Scheme. Isonicotinic acid esterification reaction with ethanol for synthesis of isonicotinic acid ethyl ester.

example, by heating with concentrated sulfuric acid, by the Fischer-Speier method [9, 10]. The reaction is carried out without a solvent, in alcohol. The ester yield is 80–95% [10-12]. INAEE is also synthesized by the action of thionyl chloride ($SOCl_2$) on isonicotinic acid. The corresponding chloro anhydride C_6H_4NCOCl is obtained, which is reacted with ethyl alcohol to form INAEE [12, 13]; this method is characterized by the difficulty of isolating ester and the need for its distillation. Of the two above methods for obtaining INAEE, the simpler first method, performed in the laboratory according to Vogel [10], is preferable.

The invention [14] describes the preparation of lower alkyl esters of INA by hydrogenolysis of the corresponding alkyl esters of 2,6-dihalopyridine-4-carboxylic acid (with varying the number of carbon atoms in the alkyl radical from 1 to 6) in the presence of a palladium catalyst, organic solvents, and bases. The method is effective due to high yields of esters up to 90%, but it requires high costs for halogenation and then methylation of the starting citrazinic acid (2,6-dihydroxyisonicotinic acid), hydrogenolysis is carried out at pressures above atmospheric, and a large number of solvents and procedures are required. In addition, the used bases, such as morpholine, are not environmentally friendly. INAEE was also obtained by treating pyridine with zinc and ethyl chloroformate and subsequent thermal decomposition of the resulting compound [15]; the process is multi-stage and proceeds with a low yield (up to 20%) of INAEE.

The esterification reaction in an aqueous medium is very important since it allows the process to be carried out without the use of environmentally harmful organic solvents. The development of a method for carrying out esterification in aqueous solutions [2] made it possible to carry out the reaction also with isonicotinic acid, which is slightly soluble in ethanol and water at 25-85°C [16, 17]. It has been established that in the reaction of esterification of INA with ethanol in a homogeneous phase process on a micellar catalyst (N-alkanoyl-N-methyl-1-glycamine polyol, a nonionic surfactant) at 45°C in water, the yield of IEAEE is high and it makes up 90% [1].

The MW and US activation method allows conduct processes faster and even catalyst- and solvent-free. Today are known several thousand chemical reactions, accelerated by this irradiation [5, 18-21].

In this work, we studied the effect of acidic forms of natural zeolites, microwave and ultrasound irradiation on the esterification of INA with ethanol. In comparison with thermocatalytic ethylation on ultrafine crystallites of zeolites H-CL, H-HEU-M and H-MOR, conversion and selectivity for the target product – ethylisonicotinate increase (up to 35 and 98%, respectively) synergistically under the action of a catalyst with microwaves or ultrasound.

Experimental Chemicals

Pyridine-4-carboxylic acid (Rotisolv, 99.9% HPLC), ethyl pyridine-4-carboxylate (98%, Sigma-Aldrich, USA), ethanol (99.9%, HPLC, CarlRoth, Germany) were used without purification. Argon (99.999%) was used as an inert medium during reactions. As heterogeneous catalysts were used solid acids – hydrogen forms of nanoporous natural zeolites clinoptilolite (CL, 95%, $v(Si)/v(Al) = 4.4$),

mordenite (MOR, 50-60%, $v(Si)/v(Al)$ = 6.5), and heulandite (as monomineral, HEU-M, $v(Si)/v(Al)$ = 3.4), from Georgian deposits of Dzegvi, Bolnisi-Ratevani and Akhaltsikhe, respectively. Catalysts were prepared from the corresponding natural zeolites according to the method described below.

Preparation of Catalysts

Some of the catalysts based on natural zeolites studied in this work were previously tested by us in the reaction of esterification of 4-nitrobenzoic acid. These are natural zeolites with *micrometric* and *ultrafine* crystallites [20].

Catalysts with micrometric crystallites. The catalysts have been prepared from the museum samples of natural zeolites of Georgia. Light pink crystals of monomineral heulandite sample (HEU-M, SiO_2/Al_2O_3 = 6.8, 0.5 cm in size) were selected from natural heulandite manually under a binocular microscope. Starting forms of natural zeolites – CL, HEU-M, and MOR were ground down to a powder finer than 6 μm, washed with distilled water and dried. The hydrogen forms of catalysts obtained from them and denoted respectively, H-CL, H-HEU-M, H-MOR were prepared by the following methods.

Catalysts H-CL and **H-MOR**. Natural CL and MOR were leached once with 1M HCl solution (10 ml solution/g zeolite) for 3 h at reflux temperature; the suspension was filtered and the precipitate was washed with hot distilled water until a negative reaction for chlorine ions and dried in air at 40°C [22].

Catalysts H-HEU-M. It is prepared also as a catalyst H-CL and H-MOR from zeolites starting form HEU-M; in order to prevent destruction of the HEU-M crystal structure the 0.25 M solution of hydrochloric acid (10 mL solution/g zeolite) was taken.

Zeolite catalysts with ultrafine crystallites. For dispersing of micrometric particles of hydrogen forms of the studied zeolites of their suspensions (10%) in water were subjected to ultrasonic or microwave processing using for this purpose ultrasonic cleaner (Elma P 120H, Germany, frequency – 37 kHz, power – 330 W) and the Ultrasonic-Microwave (hybrid) reactor UMR-300B, Japan; microwave frequency – 2450 MHz, power – 300 W), respectively. Ultrasonic irradiation of samples was carried out for 7.5 h; before and after irradiation, after 1, 2, 3 and 7.5 hours, the particle size distribution of zeolites was measured.

By ultrasound irradiation water temperature in the ultrasonic cleaner rose up to 55°C and it was supported throughout the entire period. Irradiation by microwaves was carried out at 40°C for 2 h.

Characterization of Catalysts

The partial chemical composition of the catalysts was determined by X-ray fluorescence analysis carried out on energy-dispersive X-ray fluorescence spectrometer EDX3600B (Skyray Instrument Ltd., China) [22].

Particle size determination. After ultrasonic and microwave treatment of zeolites, the size distribution for catalysts H-CL, H-HEU-M, H-MOR was determined on a laser light scattering particle size analyzer (Analysette 12-DynaSizer, Fritsch).

Isonicotinic Acid Ethylation Reaction Procedure

Thermocatalytic reactions were carried out in argon atmosphere under static conditions in a three-necked flask with a reflux condenser and a thermometer on a magnetic stirrer with thermoregulation (MSKh-300). Reactions under microwave and ultrasonic irradiation were carried out in a hybrid reactor (UMR-300B) under the same conditions. The catalyst preliminarily regenerated in air at 300°C was added in a flask to isonicotinic acid in absolute ethanol, the mixture was heated at the

boiling temperature of the alcohol mixture during few hours; in particular, in the case of zeolite catalysts for 1-6 hours, the time of microwave and ultrasonic exposure to the reaction mixture was 0,5-2 hours. INA and ethyl alcohol were taken into the reaction in molar ratios, respectively: 1/15–1/11,5–1/9,40. Upon completion of the reaction, the resulting solution was filtered on a Buchner funnel to remove the catalyst, and INAEE was isolated from the obtained filtrate according to known procedures [10]. Specifically, after removing the catalyst, the resulting reaction solution was transferred to a separating funnel, and the resulting INAEE was extracted three times with 15-15 ml of a solution of diethyl ether, dichloroethane or ethyl acetate. The organic phase was washed with water, further with common salt solution; the reaction product was dried over Na_2SO_4 and filtered off. Diethyl ether (or dichloroethane or ethyl acetate) was removed by distillation of the organic phase with isonicotinic acid ethyl ester on a rotary evaporator and continued heating until a dry product, INAEE was obtained. These were white needles and were identified by GC/MS. The main product of the isonicotinic acid esterification reaction is isonicotinic acid ethyl ester. The catalytic activity was characterized by conversion of INA, selectivity of INAEE formation and its yield.

Analysis of the Reaction Products

GC-MS analysis (Agilent Technologies, 5890B/5977A, USA) of the esterification reaction products was performed in the EI mode, 70 eV, capillary column HP-5ms, Ultra Inert, 30 m×0.32 mm×0.25 μm,

helium (1.0 mL/min) as a carrier gas, methanol as solvent; analyzes were carried out in program mode: hold at 80°C for 5 min, ramp to 230°C at 30°/min, hold at 230°C for 10 min. The identification of the compounds was made by comparing the spectra with NIST 2014 library.

The reaction product INAEE was identified by FTIR and NMR spectroscopy. FTIR studies were conducted on a Nicolet[TM] iS50 spectrometer (Thermo Fisher Scientific, $4000 – 400\,cm^{-1}$, resolution $4\,cm^{-1}$); NMR spectra were recorded on Bruker NMR-400 operating at 400 MHz for ^1H, chemical shifts are given relative to solvent DMSO: 2.50 ppm (^1H-NMR) and 39.50 ppm (^{13}C-NMR).

Results and Discussion

Composition and size distribution of catalyst particles tested in ethylation reaction of pyridine-4-carboxylic acid

From Table 1, it is apparent that after the catalysts are irradiated with microwaves and ultrasound, their particle sizes decrease – ultrafine samples with particle sizes of 300-480 nm are obtained from the initial catalysts with micrometric-sized crystallites.

The dependence of the conversion degree of INA on the mass (0,1–1,0 g) of catalyst, on the power of ultrasound and microwaves (200–300–450 W), and on temperature (40–80°C) was studied. Optimal conditions for carrying out the INA esterification reaction were experimentally selected, in particular, the mass of the catalyst was 0.5 g (Fig. 1), the temperature was 80°C, the molar ratio of INA and ethyl alcohol was 1/11,5; power of ultrasound and microwaves, equal to 450 watts.

Table 1. Composition of the catalysts and the average particle size of the hydrogen forms of natural zeolites after their ultrasonic (300 W, 7.5 h, 55°C) and microwave (300 W, 1 h, 40°C) treatment [22]

Zeolite catalysts	$v(SiO_2)/v(Al_2O_3)$	Particles size, nm		
		Before irradiation	After irradiation	
			ultrasound	microwave
H-CL	23.3	5600-5800	300-325	470-480
H-HEU-M	8.2	6000-6200	350-360	390-400
H-MOR	20.1	6500-7000	350-370	400-410

With an increase in temperature from 40 to 80°C, the initial rate of conversion of INA increases, but at a higher temperature, apparently the microwave absorption efficiency decreases and the INA conversion reduces.
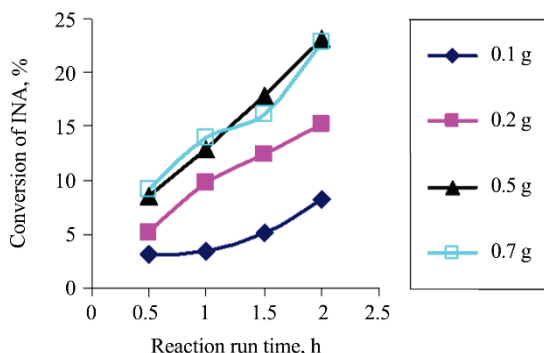
Fig. 1. INA conversion dependence on the mass of catalyst H-HEU-M (350-360 nm). Reaction conditions: argon atmosphere, temperature – 80°C, molar ratio of INA and ethyl alcohol – 1/11, 5, mass of INA – 1.6 g, catalyst mass – 0.1-0.7 g, duration of run – 2 h.

## Isonicotinic acid ethylation under influence of natural zeolites, microwave and ultrasound irradiation

Under the influence of ultrasound or microwave radiation, INA is slightly converted in ethylation reaction, its conversion is only 7-9%, which is also less than the degree of INA conversion on the initial hydrogen forms of zeolites with micrometric crystallite size (Table 2, Entries 1–5). With decrease in the size of crystallites of zeolites H-CL, H-HEU-M and H-MOR from 5.6-7.0 µm to 300-480 nm, their catalytic activity increases, in particular, the conversion of INA up to 25% and the selectivity of the formation of the target product – INAEE up to 90% (Table 2, Entries 6–11).

The data of Fig. 2 and Table 2, Entries 12–17, indicate the synergy of the action of ultrasound or microwaves and the investigated ultrafine zeolite catalysts; indeed, for example, by simultaneously influence of catalyst and microwave irradiation

Table 2. Effect of ultrasound (450 W, 37 kHz) and microwave (450 W, 2450 MHz) irradiation on the esterification reaction of pyridine-4-carboxylic acid (INA), and effect of these irradiation together with catalysts–hydrogen forms of natural zeolites with micrometric and ultrafine crystallites; m (INA) = 1.6 g, catalyst weight– 0.5 g, molar ratio $v(INA)/v(C_2H_5OH)$ = 1/11,5, reaction atmosphere – argon, reaction temperature – 80°C, reaction run time – 2 h

Entry	Irradiation type (frequency and power) and catalysts (particle size, nm)/Irradiation	Conversion of INA, %	Yield of INAEE, %	Selectivity of INAEE,%
1	US (37 kHz. 450 W)	7.1	5.2	73.2
2	MW (2450 MHz. 450 W)	8.6	5.7	66.3
3	H-CL(5600-6800)	9.2	7.3	79.5
4	H-HEU-M(6000-6200)	15.7	13.5	85.9
5	H-MOR(6500-7000)	12.3	10.3	83.7
6	H-CL (300-325)*US	15.6	13.1	84.0
7	H-CL (470-480)*MW	17.2	15.4	89.5
8	H-HEU-M (350-360)*US	23.1	20.8	90.0
9	H-HEU-M(390-400)*MW	24.8	22.9	92.3
10	H-MOR (350-370) *US	19.8	17.0	85.8
11	H-MOR (400-410) *MW	21.9	19.5	89.0
12	H-CL (300-325) /US	21.3	19.6	92.1
13	H-CL (470-480)/MW	29.6	28.3	95.7
14	H-HEU-M (350-360)/US	29.5	28.6	97.1
15	H-HEU-M (390-400)/MW	34.7	34.1	98.4
16	H-MOR (350-370)/US	24.3	23.6	97.5
17	H-MOR (400-410)/MW	32.5	31.5	97.0

Denotations *US and *MW refer to ultrafine catalyst samples prepared respectively. by ultrasonic and microwave treatment of initial zeolites with micrometric crystallites
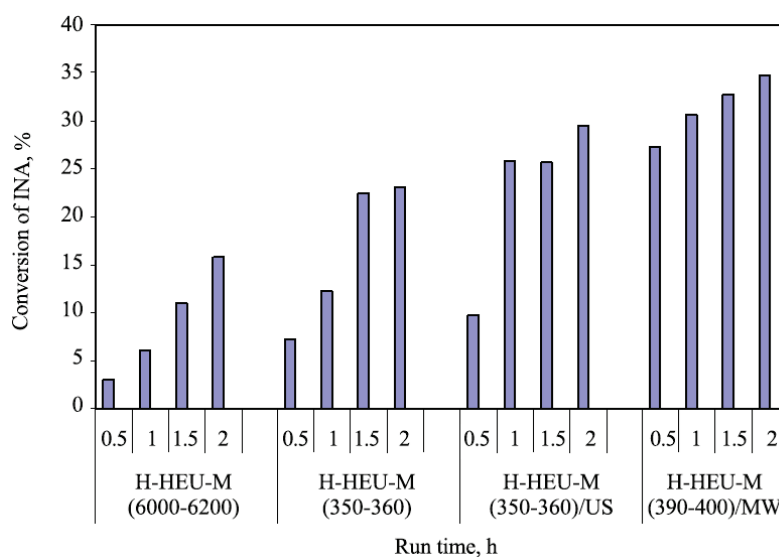
Fig. 2. Comparison of the catalytic activity of H-HEU-M with different particle size (indicated in brackets) in the esterification reaction of INA during its thermocatalytic conversion and with simultaneous action of a catalyst and ultrasound or microwaves. Reaction conditions: molar ratio – $v(INA)/v(C_2H_5OH) = 1/11,5$, m(INA) = 1,6 g, catalyst weight– 0,5 g, duration of run– 0,5-2 h, reaction atmosphere – argon, reaction temperature – 80˚C.
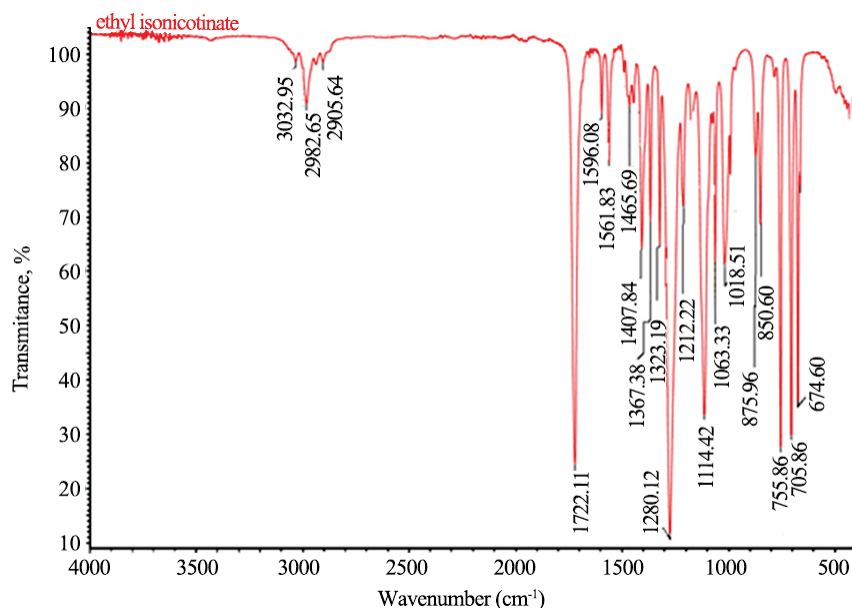
Fig 3. FTIR spectra of ethyl pyridine-4-carboxylate (ethyl isonicotinate), synyhesized by synergic action of H-MOR (400-410 nm) and MW (450 W, 2450 MHz) irradiation in esterification reaction of pyridine-4-carboxylic acid (isonicotinic acid); molar ratio $v(INA)/v(C2H5OH) = 1/11,5$, reaction atmosphere– argon, reaction temperature was 80˚C, duration of run–2 h.

(H-MOR(400-410)/MW and H-HEU-M (390-400)/ MW), INA conversion and INAEE selectivity increase to 32.5-34.7 and 97.0-98, 4%, respectively (Table 2, Entries 15, 17).

Comparison of the activities (conversion, selectivity) of catalysts with ultrafine crystallites and those during irradiation (Table 2, Entries 5-11 and 12-17) shows the predominant role of the nature of

the catalysts and their acidic nature in the ethylation of INA.

Synthesized Ethyl Pyridine-4-Carboxylate Identification

In the IR spectrum of the synthesized ethyl isonicotinate (Fig. 3), there are absorption bands characteristic of aromatic esters (cm^{-1}): 1722.11 (carbonyl $C=O$ stretch), 1280.12 (of the alpha carbon, carbonyl carbon, and carbonyl oxygen C-C-O asymmetric stretch) and 1114.42 (of the ester oxygen and the alkyl two carbons, C-C-C asymmetric stretch) [23, 24]. Other absorption peaks belong to (ν, cm^{-1}): 3032 (C-H aromatic ring stretch), 2982 and 2905 (ethyl C-H stretch), 1599 (aromatic stretch) 1323 (aromatic CN stretch).

The presence of these characteristic frequencies in the FTIR spectrum and their comparison with the spectrum of the starting pyridine-4-carboxylic acid indicates the formation of ethyl pyridine-4-carboxylate, which corresponds to the its standard FTIR spectrum [24].

^{1}H NMR (400 MHz, CDCl$_3$) spectra of the prepared ethyl pyridine-4-carboxylate shows following signals (δ ppm): 8.32 (d, $J = 6.1$ Hz, 2H, Ar), 7.35 (d, $J = 6.0$ Hz, 2H, Ar), 3.93 (q, $J = 7.2$ Hz, 2H, CH$_2$), 0.93 (t, $J = 7.2$ Hz, 3H, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$, δ ppm): 164.35 (1C, C=O); 150.35 (2C, Ar); 137.05 (1C, Ar); 122.26 (2C, Ar); 61.18 (1C, CH$_2$); 13.65 (1C, CH$_3$). The NMR spectral data of ethyl pyridine-4-carboxylate synthesized on the zeolite catalysts and under influence of US or MW irradiation are in full agreement with the literature data [24].

Conclusion

In the reaction of isonicotinic acid ethylation at 80°C in an argon atmosphere on ultrafine hydrogen forms of natural zeolites H-CL, H-HEU-M and H-MOR, or by simultaneous exposure to these catalysts and ultrasound or microwaves, ethyl isonicotinate is synthesized with a high selectivity of 90-98%, but with a small yield (20-34%); higher activity is found under microwave irradiation and with H-HEU-M and H-MOR catalysts.

ფიზიკური ქიმია

ბუნებრივი ცეოლითური კატალიზატორების, ულტრაბგერითი და მიკროტალღური გამოსხივების გავლენა იზონიკოტინის მჟავას ეთილირების რეაქციაზე

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**აკადემიის წევრი, ივანე ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, პეტრე მელიქიშვილის ფიზიკური და ორგანული ქიმიის ინსტიტუტი, თბილისი, საქართველო
§სან დიეგოს სახელმწიფო უნივერსიტეტი საქართველოში, თბილისი, საქართველო

კვლევაში წარმოდგენილია ბუნებრივი ცეოლითების წყალბადური ფორმების თანდასწრებით მიკროტალღებით და ულტრაბგერით დასხივებისას იზონიკოტინმჟავას ეთანოლით კატა-ლიზური ესტერიფიკაციის რეაქციის შედეგები სამიზნე ეთილიზონიკოტინატში. ეთილირება ტარდებოდა არგონის ატმოსფეროში 40–80°C ტემპერატურებზე იზონიკოტინმჟავას და ეთა-ნოლის სხვადასხვა მოლური თანაფარდობებისას. გამოყენებული იყო კატალიზატორები (H-CL (SiO₂/Al₂O₃ = 23,3), H-HEU-M (SiO₂/Al₂O₃ = 8,2) და H-MOR(SiO₂/Al₂O₃=20,1) მიკრომეტ-რული (4,8–7,0μm) და ულტრადისპერსული (300–480ნმ) ზომების კრისტალიტებით; ეს უკა-ნასკნელი მიღებული იყო ცეოლითების საწყისი წყალბადური ფორმების დამუშავებით მიკ-როტალღებით (MW, 2450 MHz, 300 W, 2სთ) და ულტრაბგერით (US, 37 kHz, 330 W, 2სთ). H-CL, H-HEU-M და H-MOR ცეოლითების ულტრადისპერსულ კრისტალიტებზე თერმოკატა-ლიზურ ეთილირებასთან შედარებით, იზონიკოტინმჟავას გარდაქმნის ხარისხი და ეთილ-იზონიკოტინატის მიმართ სელექტიურობა სინერგიულად იზრდება (შესაბამისად, 35 და 98%-მდე) ერთდროულად კატალიზატორის და მიკროტალღების ან ულტრაბგერის მოქმედებისას. კვლევაში გამოყენებული იყო GC/MS, FTIR და NMR სპექტროსკოპიის მეთოდები.

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