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Experimental Comparison of 2-methylimidazole Nitration by Nitric Acid and Nitrate Salts of Alkali Metals

LYAPUNOVA Maria V.[a], MALKOV Victor S.[b]

Tomsk State University, 36, Lenina avenue, Tomsk, 634050, Russia

[a]lyapunova.mari@mail.ru, [b]malkov.vics@gmail.com

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Abstract. The processes of nitration of 2-methylimidazole to produce 2-methyl-4(5)-nitroimidazole are considered in this paper. The processes of nitration by mixture of nitric and sulfuric acids and nitrate salts of alkali metals were compared. It was found the nitration of nitrate salts of alkali metal proceeds smoother. The yield of the desired product 2-methyl-4(5)-nitroimidazole was 85 % and 95% in case of nitric acid and nitrate salt.

Introduction

Heterocyclic compounds are widespread in nature and play an important role in the chemistry of natural compounds along with proteins, fats and carbohydrates. This explains their wide use in medicine. Literature review shows that, currently, vascular, cancroid and infectious diseases are the major diseases influencing on heavy mortality. The main components of the drugs to treat diseases of these groups are heterocyclic compounds. Besides, heterocyclic compounds can be used as dyes, structure-forming polymers, and also used in the production of plastics and in vulcanization of rubber.

One of the representatives of this class of compounds is imidazole. The imidazole ring is a part of such important substances as nitrogen bases, vitamins, enzymes as well as amino acids. The nature of the substitute in imidazole ring effects significantly on the application area.

Theoretical

Nitro derivatives of imidazole are very valuable in medical applications. These compounds possess antibiotic properties, influence on various bacterial and fungal diseases, and are useful as anthelmintic agents. Such drugs demonstrate selective bactericidal effect towards nitrate-reducing microorganisms. The active reduced forms of drugs disturb DNA replication and protein synthesis in the bacterial cell and inhibit tissue respiration [1, 2].

Currently, nitroimidazole-based drugs, such as metronidazole, tinidazole, ornidazole, secnidazole, satranidazol, etc., are widely used in clinical practice [1]. 2-Methyl-4(5)-nitroimidazole is one of the valuable imidazole-based compounds. Demand for this compound is quite high, and many scientists deal with preparation, isolation and purification of the nitration product. Nitration of azoles representing introduction of NO_2-group into imidazole ring, is a reaction proceeding via electrophilic substitution mechanism [3]. There are many methods to prepare 2-methyl-4(5)-nitroimidazole, which differ from each other by the initial reagents, synthesis temperature, and reaction time. Almost all nitration processes proceed under hard conditions, but the yield of the desired product is relatively low.

The classical approach to introduce nitro-group into the imidazole ring is nitration of 2-methylimidazole by a mixture of concentrated nitric and sulfuric acids [4]. In this case nitric acid (99% mas.) is added to the mixture of water, 93% mas. sulfuric acid, dry sodium sulfate and 2-methylimidazole with stirring and heating to up to 130 °C. The mixture is heated at 130-132 °C for 4 hours. The yield of the obtained products is 63-66 %. This synthesis method is difficult to use in industrial production, since highly concentrated acids and high temperatures increase corrosiveness of the reaction media. The low yield as well as low product quality is also observed.

To simplify the technology, low temperatures were recommended for 2-methylimidazole nitration [5]. 2-Methylimidazole is added into the nitrating mixture comprising 86-92% mas. sulfuric acid, 64-72% mas. nitric acid, and water at a temperature of no more than 30 °C. The mixture is stirred for 3 hours, then the temperature is raised to up to 40 °C, the process is exposed under these conditions for 1 hour. After stirring the reaction mass is left off for 5-6 hours. The yield of 2-methyl-4(5)-nitroimidazole is 55-91 %. In this case additional energy consumption is necessary because the reaction mass must be cooled constantly. Another disadvantage of these methods is application of highly concentrated acids.

2-Methylimidazole can be nitrated in a special reactor designs by sulfuric acid (95% mas.), nitric acid (65% mas.) in an amount of 2-5 moles per 1 mole of imidazole at 245 °C in the presence of urea. The yield is 71 % [6]. The disadvantages of this method are low yield of the desired product, insufficient product quality, high synthesis temperature, high corrosion activity of the reaction mixture and application of specific equipment.

2-methylimidazole can be nitrated at sufficiently low temperatures [7]. In this case sulfuric acid (96 %) and acetic anhydride are added to the suspension of 2-methylimidazole in acetic acid. This suspension must be cooled down to 10 °C. The reaction mixture is kept for 30 min at 60-65 °C and then cooled down. Then nitric acid (98 % mas.) is added. The received media is exposed to 3-3.5 h at 18-20 °C, cooled down, neutralized by 25% ammonia solution to pH = 6,5-7, filtered, washed with water and dried. The yield of 2-methyl-4(5)-nitroimidazole is 90 %. However, as in the previous cases, this method utilizes highly concentrated acids as well as acetic anhydride, and constant cooling is required.

Another method of nitration of 2-methylimidazole is known. The reaction proceeds in a solution of ammonium nitrate in 98 % nitric acid at 65-97 °C for 1.5-6 h. The weight ratio between 2-methylimidazole, ammonium nitrate, nitric acid and water is 1: 1.5-5,.4: 5.9-16.0: 0.10-0.35. The yield of 2-methyl-4(5)-nitroimidazole is 76 % [8]. The disadvantages of this method are low yield, high synthesis temperature and high mass flow of highly concentrated nitric acid.

The nitration of imidazole by mixtures of acids [9] and sodium nitrate [10] were t currently taken into account. In the first case imidazole is slowly added to sulfuric acid (95 %mass.). After its total dissolving the solution is heated to 70 ºC and nitric acid (69 %) is slowly introduced. Then currently the temperature is raised to up to 100 ºC and the reaction mixture is exposed for 5 hours. Then the mixture is cooled down, diluted with water and neutralized by 25 % aqueous ammonia solution. The yield of 2-methyl-4(5)-nitroimidazole is 78 %.

The second method is based on the nitration of 2-methylimidazole by sodium or potassium nitrate in the presence of 94-96 % sulfuric acid at a temperature of 125-140 °C for 4.5-5 hour. The next step is a neutralization by soda solution to pH=3. The final product has constant quality and low yield of 50-52 %. Thus, these processes require application of highly concentrated acids, high temperatures, additional energy costs due to the exothermicity of the nitration reaction. However, these conditions do not supply sufficient yield and purity of the desired product.

Experimental

Synthesis of 2-methyl-4(5)-nitroimidazole. 2-Methyl-4(5)-nitroimidazole was synthesized by two method. In the first case the nitration was carried out with nitric acid, while in the second case the nitrating agent represented sodium nitrate. Syntheses were carried out in the 10 L Büchi AG glas uster reactor with external jacket, fluoroplastic propeller mixer with vertical shaft. Ethylene glykol was used as heat-transfer material. The mixture temperature was kept at 100 °C, when nitric acid was used. In case sodium nitrate the temperature of the mixture increased to 130 °C. The resulting product was isolated by 25 % ammonia solution. The yellow precipitation of 2-methyl-4(5)-nitroimidazole was formed in both cases. The resulting product was recrystallized from water, and white powder with melting point 253 ÷ 256 °C was isolated.

Qualitative analysis. The resulting products of 2-methylimidazole nitration were identified using NMR and melting point.

NMR^{1}H spectra were measured in DMSO solution using «Avance-300» NMR spectrometer (Bruker). The operating frequency of hydrogen nuclei was 300 MHz at 25 °C.

Melting point of the final product was measured using Melting Point M-560 (Buchi) in an opened capillary.

IR spectra were taken using IR spectrometer Thermo Electron Company Nicolet 6700 with the add-on Smart Orbit adapter.

Elemental analysis was carried out using CHNS-O elemental analyzer EuroEA-3000 with software Callidus 5.1.

Quantitative analysis. Imidazole was analyzed using gas chromatography and gas chromato-mass spectrometry. Chromato-mass spectra of the compound were measured in DMSO solution using GC-MS Trace DSQ (Thermoelectron corp.). Analysis conditions were as follows: evaporator temperature was 280 °C, thermostat temperature was 70° C (1 minute), thermostat final temperature was 280 °C, heating rate was 100 °C /min, (3 minute). Carrier gas rate was 1 ml/min; scanning range was 33 - 300 a.e.m.

Gas chromatography measurements were carried out in DMSO solution over gas Chromatograph Crystal 5000.2 equipped with gas chromatography capillary column CP-Sil 24CB 30 m*0.25 mm*0.5mkm. Analysis conditions: carrier gas rate was 30 ml/min, hydrogen rate was 50 ml/min, air rate was 500 ml/min, thermostat column temperature was 250 °C, evaporator temperature was 200 °C, and detector temperature was 230 °C. Analysis was carried out under isothermal conditions.

Results and discussion

In each case the temperature of the reaction mixture and the reagent ratio was varied during the reaction. It was found that the 2-methylimidazole nitration using a mixture of highly concentrated acids at temperatures lower than 50 ^{o}C resulted in significant reduction in the product yield. It was shown that the reaction can be carried out in a temperature range from +50 °C to +150 °C. However, subsequent increase in the reaction mixture temperature leads to reduction of the product yield due to side oxidative ring opening reactions. Nitration at lower temperatures resulted in lower yields, which can be connected with insufficient activation of imidazole ring. It was found that the highest product yield is observed in the temperature range of 100-110°C if, when highly concentrated nitric currently and sulfuric acids are used, and of 120-140°C if sodium salt is used. The results of these experiments are shown in the figures (refer with: Fig. 1). The influence of the molar ratio of the starting reagents was studied in the next series of experiments. The yield of 2-methyl-4(5)-nitroimidazole dependence on the amount of water and sodium nitrate added was observed. The maximal yield was observed when 71.19 g (1.13 mol) of nitric acid. When sodium nitrate was used, 55.82 g (0.66 mol) of the agent was added, which corresponded to 2-methyl-4(5)-nitroimidazole yield higher than the one in the first case (refer with: Fig. 2).

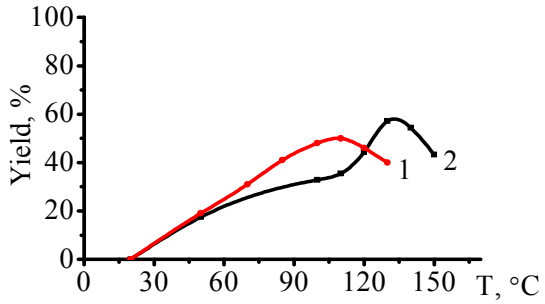

Fig.1. Temperature dependence of 2-methyl-4(5)-nitroimidazole yield
1 − in case of nitration by acid mixture,
2 − in case of nitration by sodium nitrate.

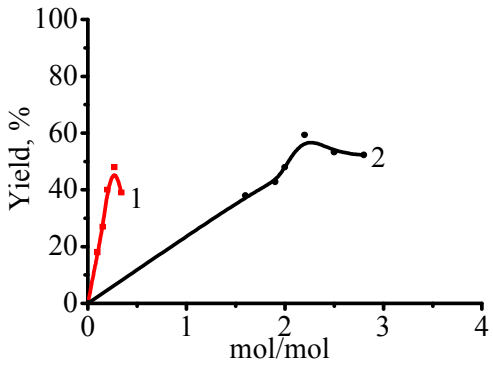

Fig. 2. Effect of 2-methylimidazole / nitrating agent molar ratio on the product yield
1 − 2-methylimidazole / HNO_3 molar ratio,
2 − 2-methylimidazole / $NaNO_3$ molar ratio.

It was stated that the amount of water added also influenced on the yield of the desired product. The optimal 2-metilimidazol/H_2O ratio was found to be 0.3:1.34 (refer with: Fig. 3).

One can see from the figures that the 2-methyl-4(5)-nitroimidazole product yield has maximal values in all cases, which correspond to optimal conditions. Thus, the comparison of the results obtained allowed us to find the process conditions corresponding to 85% 2-methyl-4(5)-nitroimidazole yield. The optimal conditions were as follows: process temperature was 100 °C, 2-methylimidazole/HNO molar ratio was 0.3:1.13. In case of sodium nitrate the optimal conditions, namely, process temperature of 130 ºC, 2-methylimidazole/H_2O/$NaNO_3$ molar ratio of 1.0:6.4:2.2, resulted in 95% yield of the desired product. If the optimal conditions are not fulfilled, the yield of the final product reduces drastically, which is connected with proceeding of side-processes. Thus, we can conclude that the yield of the desired product depends on the temperature of the reaction mixture and the molar ratio between 2-methylimidazole and water, salt, sodium nitrate and nitric acid.

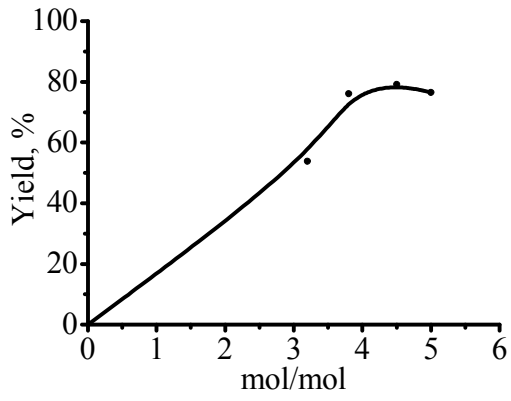

Fig. 3. Influence of molar ratio 2-methylimidazole / H_2O on the product yield.

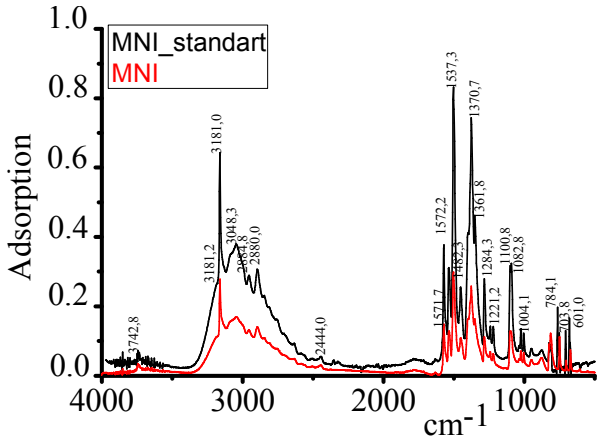

Fig. 4. IR spectrum 2-methyl-4(5)-nitroimidazole.

The structure of the obtained compound is confirmed by IR and NMR spectrums (refer with: Fig. 4, Fig. 5, Fig. 6). Comparison of the IR spectrum of the synthesized 2-methyl-4(5)-nitroimidazole and the material accepted as a standard shows that they are identical. In the capacity of standard was applyed 2-methyl-4(5)-nitroimidazole from Sigma Aldrich company. It is confirmed the structure of the obtained compound and the absence of impurities.

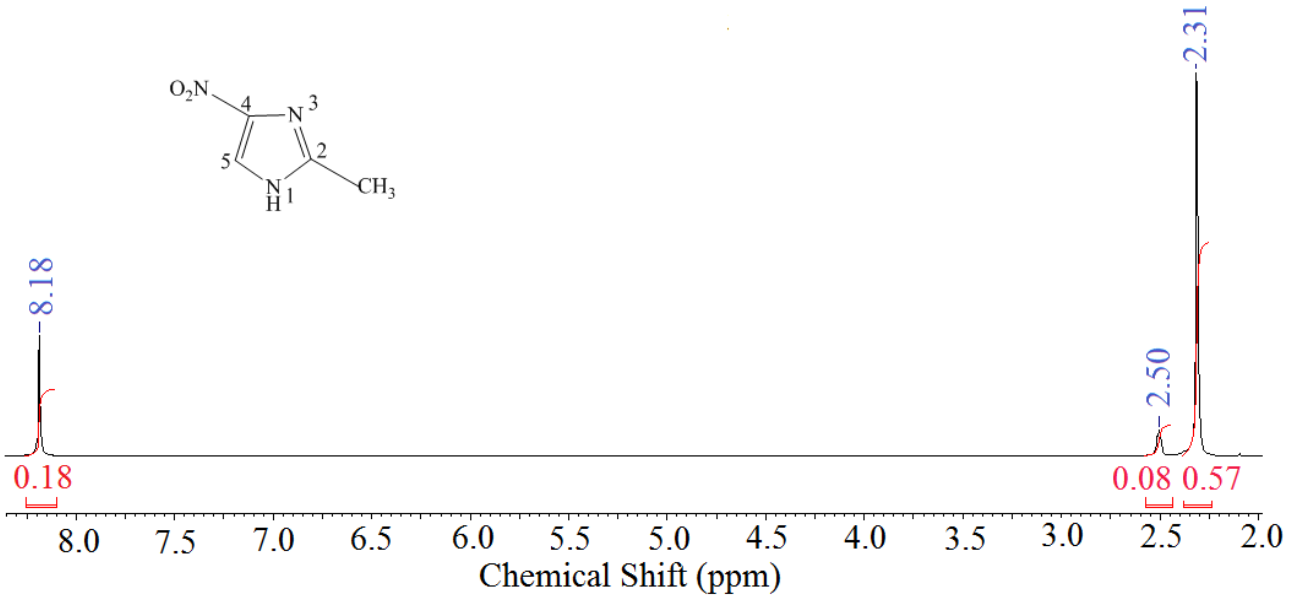

Fig. 5 ^{1}H NMR spectrum 2-methyl-4(5)-nitroimidazole (δ 13,76, δ 110,09, δ 144,78, δ 146.82).

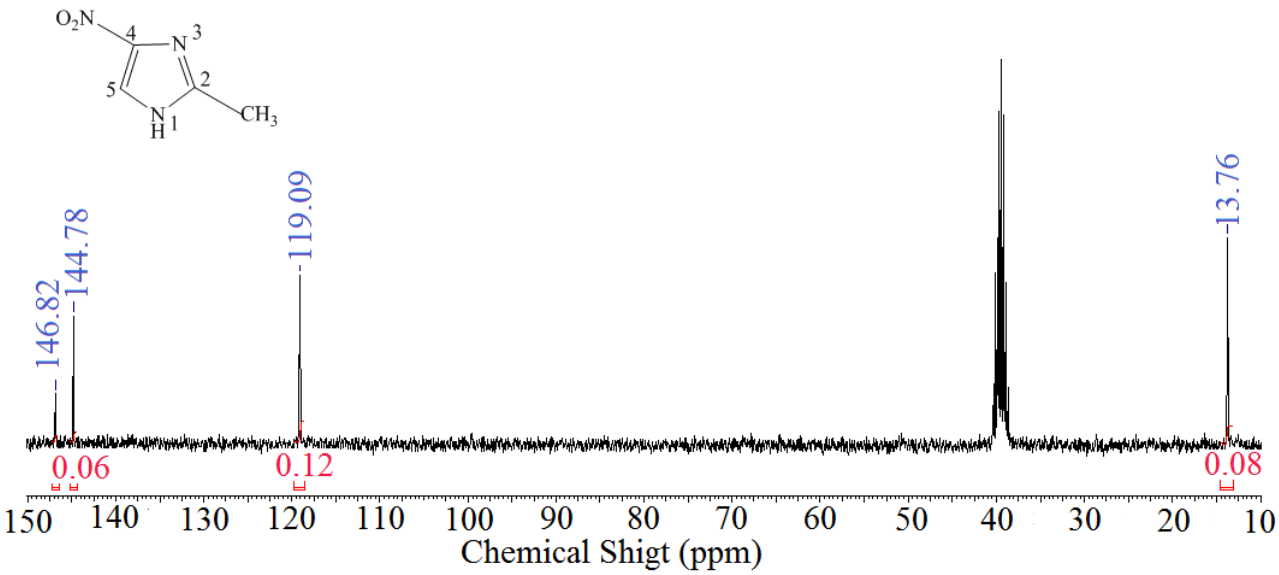

Fig. 6 ^{13}C NMR spectrum 2-methyl-4(5)-nitroimidazole (δ 2,31 (s, 3H), δ 8,18 (s, 1H).

Conclusions

The main regularities of the synthesis of 2-methyl-4(5)-ntroimidazole is presented. The processes of nitration of 2-methylimidazole with nitric acid and nitrate salts of alkali metals were compared. It was established that the nitration reaction proceeded at a lower rate despite elevated temperature when the salts of alkali metals were used. In this case the desired product with good yield and purity is formed. The synthesized compounds have been characterized by spectral analysis data.

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