

АЦЕТАТ РТУТИ(II) НА ПОДЛОЖКЕ ИЗ ХИТОЗАНА В КАЧЕСТВЕ КАТАЛИЗАТОРА РЕАКЦИЙ ТРАНСВИНИЛИРОВАНИЯ АЗОЛОВ

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Нанесение гомогенных катализаторов - соединений переходных металлов – на органические полимеры имеет большой интерес среди исследователей. Наиболее исчерпывающий анализ в этой области был опубликован в 1983 г, где подробно рассматривались результаты 1217 работ, и это число постоянно растет. Гетерогенные катализаторы часто служат очень долго, их легко отделить от реагентов и продуктов реакции и можно многократно использовать. Гомогенный катализатор на гетерогенном носителе действует так, как если бы он находился в растворе, однако одновременно он представляет собой отдельную неподвижную фазу. Исходя из вышесказанного, в этой работе мы попытались использовать хитозан в качестве носителей для ионов двухвалентных металлов, в частности ртути, заранее зная, что хитозан является хорошим лигандом для переходных металлов. Интерес к хитозанам связан с их уникальными физиологическими и экологическими свойствами, такими как биосовместимость, биодеструкция и хелатирующая способность. Описан эффективный и простой способ винилирования азолов в присутствии нанесенной на хитозан гетерогенной каталитической системы ацетата ртути(II). В результате было синтезировано несколько продуктов с высокими выходами. Разработанная методика проста в исполнении, требует меньшего количества катализатора, сокращает время реакции, исключает образование побочных продуктов и обеспечивает более высокие селективные выходы винилированных продуктов. Кроме того, можно извлекать катализатор из реакционной смеси и повторно использовать эту каталитическую систему более четырех раз. Это позволяет уменьшить загрязнение сточных вод ионами ртути.

Ключевые слова: винилирование, азолы, катализатор на полимерном носителе, хитозан, винилацетат

CHITOSAN-SUPPORTED MERCURY(II) ACETATE AS A CATALYST FOR TRANSVINYLATION REACTIONS OF AZOLES

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The application of homogeneous catalysts - transition metal complexes - on organic polymers is of a great interest among researchers. Heterogeneous catalysts often have a long life span and are easy to separate from the reactants and reaction products, and they can also be reused. A homogeneous catalyst on a heterogeneous support acts as if it were in solution, but simultaneously it is a separate stationary phase. In this study we tried to use chitosan as a carrier for metal ions (particularly mercury(II), knowing in advance that chitosan is a good ligand for transition metals). Interest in chitosan is associated with their unique physiological and environmental properties, such as biocompatibility, biodegradation, and chelating ability. Here, an efficient and easy method of vinylation of azoles in the presence of chitosan-supported mercury(II) acetate heterogenous catalytic system is reported. As a result, several products were synthesized in high yields. The developed procedure is easy to perform, requires less amount of catalyst, shortens reaction time, excludes the formation of side products, and provides higher selective yields of vinylated products, reduces water contamination with mercury salts. Furthermore, it is possible to recover the catalyst from the reaction mixture and recycle this catalytic system more than four times.

Key words: vinylation, azoles, polymer-supported catalyst, chitosan, vinyl acetate

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INTRODUCTION

Many biologically active compounds contain five-membered heterocyclic systems. Pyrazoles are known for their wide range of applications, especially in medicinal chemistry [1-4]. Chemosensors containing a pyrazole are currently known, which are used to obtain qualitative or quantitative data of a number of molecules or ions [3]. Imidazole and triazole rings are also important fragments in other compounds with various applications [5, 6].

The vinylation of azoles to obtain N-vinylazoles opens new fields for applications. These vinylated compounds are monomers of various widely used synthetic polymers [7, 8] and can be found in many biologically active compounds [9, 10]. Moreover, copolymers of N-vinylazoles can be used as anionic membranes [11-14].

There are two main mechanisms (radical and cationic) for polymerization of N-vinylazoles products [15-17]. The different methods for synthesis of N-vinylazoles are known [18-35].

For vinylation of heterocycles with two and more nitrogen atoms, the mercury (II) acetate is usually used as a catalyst in the presence of an acid [36, 37]. The main problem with these methods is use of mercury, which is considered dangerous for ecology and contaminates water.

Therefore, the optimization of vinylation reaction and the development of a safe and eco-friendly method is highly demanded. Polymer-supported systems are used in various fields, for example, analytical and synthetic chemistry, and in material science as well [38-40]. The use of catalysts on the polymeric carrier has important significance for applications. It enables to increase reaction yields and makes the catalyst recyclable, which allows to avoid the additional waste of catalyst and to reduce its ecological risks. There are many studies based on different catalysts synthesized on the polymeric carriers, and they are used in many important reactions, such as Heck, Sonogashira, Biginelli, and others [41-46].

Chitosan is a D-glucosamine natural polymer, which is obtained from the deacetylation of chitin [47]. There is a large spectrum of applications of chitosan in material science, medicinal chemistry and other fields [48-51]. It is also widely used as a catalyst in organic synthesis. In the last decades, many catalysts were created, based on metal complexation with chitosan and its modified derivatives [52, 53]. Chitosan and its modified derivatives are effective organocatalysts for Knoevenagel, Michael, aldol condensation, and other reactions [54-58]. Many works are known where the adsorption of mercury by different chitosan derivatives for different purposes has been investigated [59, 60].

EXPERIMENTAL PART

General Information

IR spectroscopy analysis was performed via “Nicolet Avatar 330 FT-IR” spectrometer. TG analysis was performed via “STA 449 F3 Jupiter” analyzer. TG analysis spectrum and IR spectrum of ChHg complex can be found in Supporting Information. Reactions were monitored by TLC and GC, yields were detected via “GC/MS Bruker EM 640”. ^1H and ^{13}C NMR spectra were recorded by “Varian Mercury 300” and “Bruker Avance Neo 400” spectrometers (300, 400 and 75, 125 MHz) in $\text{DMSO-}d_6/\text{CCl}_4$ (1/3) or CDCl_3 . Spectra were processed by Mestre Nova. ^1H and ^{13}C NMR spectra of all obtained compounds are collected in Supporting Information.

Synthesis of ChHg complex. To a flask, containing 30 ml of toluene, 7.4 g of high molecular weight chitosan (degree of deacetylation 90%) and 10 g of mercury oxide, 30 ml acetic acid was added. The mixture was stirred and refluxed for 2 h. Reaction mixture was filtered and washed several times with benzene. Obtained ChHg complex 25.4 g (yellowish powder was dried under vacuum), in which amount of $\text{Hg}(\text{OAc})_2$ is 72%.

Vinylation Reactions (The general preparation procedure for 3a-m). 1 mmol of corresponding azole (**1a-k**), was dissolved in 1 ml of vinyl acetate (**2**). Then, 24 mg (72% $\text{Hg}(\text{OAc})_2$) of ChHg catalyst was added, after that 4 μl of TFA (CF_3COOH) or H_2SO_4 was dissolved, and then hydroquinone was added and reaction mixture was stirred at 70 °C for 1-3 h and cooled to room temperature. The catalyst was collected by filtration. On the filtrate 80 mg of sodium carbonate and 40 μl of water were added, and the mixture was left to neutralize overnight. Afterwards solid was filtrated and excess of vinyl acetate was removed from the reaction mixture to obtain crude product. The residue was purified by flash chromatography (EA:hexanes as eluent).

3(5)-methyl-4-nitro-1-vinyl-1H-pyrazole (3d) White crystals, 92% yield, m. p. 33 °C, b. p. 119-121 °C (3 mm Hg), mixture of 2 isomers (9:1). ^1H NMR (400 MHz, $\text{DMSO-}d_6/\text{CCl}_4$ 1/3): 8.88 (0.9H, s, =CH), 8.10 (0.1H, s, =CH), 7.20 (0.1H, dd, $J_1 = 15.0$, $J_2 = 8.7$, -CH=CH₂), 7.09 (0.9H, dd, $J_1 = 15.6$, $J_2 = 8.7$, -CH=CH₂), 5.87 (0.1H, d, $J = 15.0$, =CH₂, trans), 5.80 (0.9H, dd, $J_1 = 15.6$, $J_2 = 0.6$, =CH₂, trans), 5.13 (0.1H, d, $J = 8.7$, =CH₂, cis), 5.01 (0.9H, dd, $J_1 = 8.6$, $J_2 = 0.6$, =CH₂, cis), 2.70 (0.3H, s, CH₃) 2.49 (2.7H, s, CH₃). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6/\text{CCl}_4$ 1/3): 145.4, 136.5 (=CH), 133.6, 131.7 (=CH), 129.5 (=CH), 128.8 (=CH), 105.5 (=CH₂), 103.2 (=CH₂), 12.8 (CH₃), 9.7 (CH₃). Found, %: C 47.12; H 4.42; N 27.48. $\text{C}_6\text{H}_7\text{N}_3\text{O}_2$. Calculated, %: C 47.06; H 4.61; N 27.44.

4-chloro-3(5)-methyl-1-vinyl-1H-pyrazole

(*3e*) Colorless liquid, 83% yield, $n_d^{20} = 1.5220$, b. p. 52 °C (1 mm Hg), mixture of 2 isomers (2,3:1). ^1H NMR (400 MHz, $\text{DMSO-}d_6/\text{CCl}_4$ 1/3): 7.90 (0.7H, s, =CH), 7.41 (0.3H, s, =CH), 7.03 (0.3H, dd, $J_1 = 15.2$, $J_2 = 8.8$, -CH=CH₂), 6.95 (0.7H, dd, $J_1 = 15.7$, $J_2 = 8.9$, -CH=CH₂), 5.65 (0.3H, d, $J = 15.2$, =CH₂, trans), 5.46 (0.7H, d, $J = 15.7$, =CH₂, trans), 4.86 (0.3H, d, $J = 8.8$, =CH₂, cis), 4.72 (0.7H, d, $J = 8.9$, =CH₂, cis), 2.25 (0.9H, s, CH₃) 2.21 (2.1H, s, CH₃). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6/\text{CCl}_4$ 1/3): 145.50 137.3 (=CH), 134.2, 132.4 (=CH), 129.6 (=CH), 125.7 (=CH), 110.0 (=CH), 108.8 (=CH), 100.8 (=CH₂), 98.2 (=CH₂), 10.4 (CH₃), 8.1 (CH₃). Found, %: C 50.58; H 4.51; Cl 24.89; N 19.67. $\text{C}_6\text{H}_7\text{ClN}_2$. Calculated, %: C 50.54; H 4.95; Cl, 24.86; N 19.65.

4-bromo-3(5)-methyl-1-vinyl-1H-pyrazole (3f)

Colorless liquid, 76% yield, $n_d^{20} = 1.5550$, b. p. 70-73 °C (1 mm Hg), mixture of 2 isomers (1:1). ^1H NMR (400 MHz, $\text{DMSO-}d_6/\text{CCl}_4$ 1/3): 7.93 (0.5H, s, CH), 7.44 (0.5H, s, CH), 7.05 (0.5H, dd, $J_1 = 15.2$, $J_2 = 8.9$, -CH=CH₂), 6.97 (0.5H, dd, $J_1 = 15.7$, $J_2 = 8.9$, -CH=CH₂), 5.65 (0.5H, dd, $J_1 = 15.2$, $J_2 = 1.0$, =CH₂, trans), 5.48 (0.5H, dd, $J_1 = 15.7$, $J_2 = 1.0$, =CH₂, trans), 4.85 (0.5H, d, $J = 8.9$, =CH₂, cis), 4.75 (0.5H, d, $J = 8.9$, =CH₂, cis), 2.33 (1.5H, s, CH₃) 2.214 (1.5H, s, CH₃). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6/\text{CCl}_4$ 1/3): 147.5, 139.3 (=CH), 136.0, 133.0 (=CH), 129.6 (=CH), 128.1 (=CH), 101.0 (=CH₂), 98.4 (=CH₂), 94.9 (=CH), 93.1 (=CH), 11.3 (CH₃), 9.0 (CH₃). Found, %: C 38.59; H 3.88; Br, 42.83; N, 14.99. $\text{C}_6\text{H}_7\text{BrN}_2$. Calculated, %: C 38.53; H 3.77; Br 42.72; N 14.98.

4-Iodo-3(5)-methyl-1-vinyl-1H-pyrazole (3g)

Colorless liquid, 68% yield, $n_d^{20} = 1.6220$, b. p. 89-92 °C (1 mm Hg), mixture of 2 isomers (9:1). ^1H NMR (400 MHz, CDCl_3): 7.59 (0.9H, s, CH), 7.54 (0.1H, s, CH), 6.97 (0.1H, dd, $J_1 = 15.3$, $J_2 = 8.8$, =CH-), 6.92 (0.9H, dd, $J_1 = 15.7$, $J_2 = 8.9$, -CH=CH₂), 5.72 (0.1H, d, $J = 15.3$, =CH₂, trans), 5.43 (0.9H, d, $J = 15.7$, =CH₂, trans), 4.89 (0.1H, d, $J = 8.8$, =CH₂, cis), 4.79 (0.9H, d, $J = 8.9$, =CH₂, cis), 2.36 (0.3H, s, CH₃), 2.29 (2.7H, s, CH₃). ^{13}C NMR (100 MHz, CDCl_3): 152.8, 145.0, 132.8 (=CH), 132.7 (=CH), 130.1 (=CH), 102.6 (=CH₂), 99.7 (=CH₂), 96.5 (=CH), 62.6, 61.8, 14.0 (CH₃), 11.7 (CH₃). Found, %: C 30.81; H 3.1; I 54.42; N 11.98. $\text{C}_6\text{H}_7\text{IN}_2$. Calculated, %: C 30.79; H 3.01; I 54.22; N 11.97.

Methyl 4-nitro-1-vinyl-1H-pyrazole-3(5)-carboxylate (3l) White crystals, 82% yield, m. p. 86-89 °C, mixture of 2 isomers (3:1). ^1H NMR (400 MHz, $\text{DMSO-}d_6/\text{CCl}_4$ 1/3): 9.22 (0.25H, s, =CH), 8.25 (0.35H, s, =CH), 7.31 (0.75H, ddd, $J_1 = 15.1$, $J_2 = 8.7$, $J_3 = 0.4$, -CH=CH₂), 7.24 (0.25H, dd, $J_1 = 15.5$, $J_2 =$

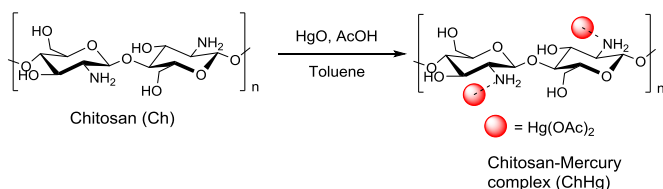
8.7, $-\underline{\text{C}}\text{H}=\text{CH}_2$), 5.99 (0.75H, dd, $J_1 = 15.1$, $J_2 = 0.8$, $=\text{CH}_2$, trans), 5.97 (0.25H, dd, $J_1 = 15.5$, $J_2 = 1.5$, $=\text{CH}_2$, trans), 5.27 (0.75H, dd, $J_1 = 8.7$, $J_2 = 0.8$, $=\text{CH}_2$, cis), 5.19 (0.25H, d, $J = 8.7$; 1.6, $=\text{CH}_2$, cis), 4.03 (2.25H, s, CH_3), 3.95 (0.75H, s, CH_3). ^{13}C NMR (100 MHz, $\text{DMSO-d}_6/\text{CCl}_4$ 1/3): 159.7 (C=O), 157.4 (C=O), 138.6, 135.8 ($=\text{CH}$), 134.4 ($=\text{CH}$), 133.7, 131.8, 129.6 ($=\text{CH}$), 107.3 ($=\text{CH}_2$), 105.4 ($=\text{CH}_2$), 53.4 (CH_3), 52.2 (CH_3). Found, %: C 45.11; H 5.24; N 19.78. $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_4$. Calculated, %: C 45.07; H 5.20; N 19.71.

Methyl 5-nitro-1-vinyl-1H-pyrazole-3-carboxylate (3m) White crystals, 86% yield, m. p. 102-104 °C. ^1H NMR (400 MHz, $\text{DMSO-d}_6/\text{CCl}_4$ 1/3): 8.04 (1H, dd, $J_1 = 15.3$, $J_2 = 8.6$, $-\underline{\text{C}}\text{H}=\text{CH}_2$), 7.48 (1H, s, $=\text{CH}$), 6.09 (1H, d, $J = 15.3$, $=\text{CH}_2$, trans), 5.3 (1H, d, $J = 8.6$, $=\text{CH}_2$, cis), 3.95 (3H, s, CH_3). ^{13}C NMR (100 MHz, $\text{DMSO-d}_6/\text{CCl}_4$ 1/3): 157.5 (C=O), 154.4, 133.2, 130.1 ($=\text{CH}$), 107.4 ($=\text{CH}$), 107.2 ($=\text{CH}_2$), 52.4 (CH_3). Found, %: C 42.71; H 3.60; N 21.35. $\text{C}_7\text{H}_7\text{N}_3\text{O}_4$. Calculated, %: C 42.65; H 3.58; N 21.31.

RESULTS AND DISCUSSION

Here we suggest to use chitosan-supported mercury(II) catalyst to ensure the reuse of catalyst.

In this study we have synthesized a new chitosan-mercury complex. Mercuric oxide was immobilized on chitosan in the presence of acetic acid (Scheme 1).



Scheme 1. Synthesis of chitosan-mercury complex
Схема 1. Синтез комплекса хитозан-ртуть

Inclusion of mercury acetate to the chitosan was monitored by the FTIR spectroscopy. Spectra of chitosan, mercury acetate and resulting complex are presented in Fig. 1. The immobilization of mercury acetate on the chitosan can be clearly seen on the spectrum of the complex through absorptions of C=O (1537 cm^{-1}) bond of acetate anion, as well as Hg-O (617 cm^{-1}) and Hg-N (684 cm^{-1}) bonds.

Synthesized chitosan-supported mercury(II) catalyst was used for vinylation reactions of azoles with vinyl acetate as a vinyl source in the presence of different acids (CF_3COOH (TFA) and H_2SO_4) (Scheme 2).

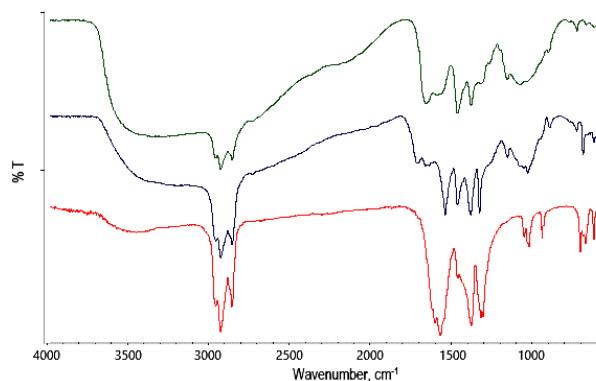
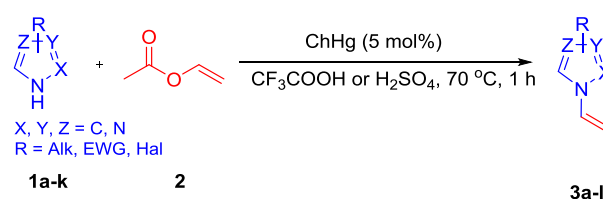


Fig. 1. Comparison of FTIR spectra of chitosan (green), mercury(II) acetate (red) and synthesized complex (blue)
Рис. 1. Сравнение ИК спектров хитозана (зеленый), ацетата ртути (II) (красный) и синтезированного комплекса (синий)



Scheme 2
Схема 2

Yields of obtained vinylazoles with ChHg catalyst in the presence of acid are shown in Table.

Table
Obtained compounds with corresponding yields
Таблица. Полученные соединения с соответствующими выходами

 3a 78%	 3b 84%	 3c 87%	 3d 92%
 3e 83%	 3f 76%	 3g 68%	 3h 75%
 3i 65%	 3j 60%	 3k-1 and 3k-2 84%	 3l 82%
 3m 65%			

1-vinyl-3(5)-methyl-4-nitropyrazole (**3d**) was obtained in high yield. The main reason is the higher acidic nature of this compound due to electron-withdrawing effect of nitro- group. Results show that for the series of pyrazoles the reaction yields (temperature 70 °C) decrease when we introduce donor groups, whereas the yields increase when we use acceptor groups (Fig. 2).

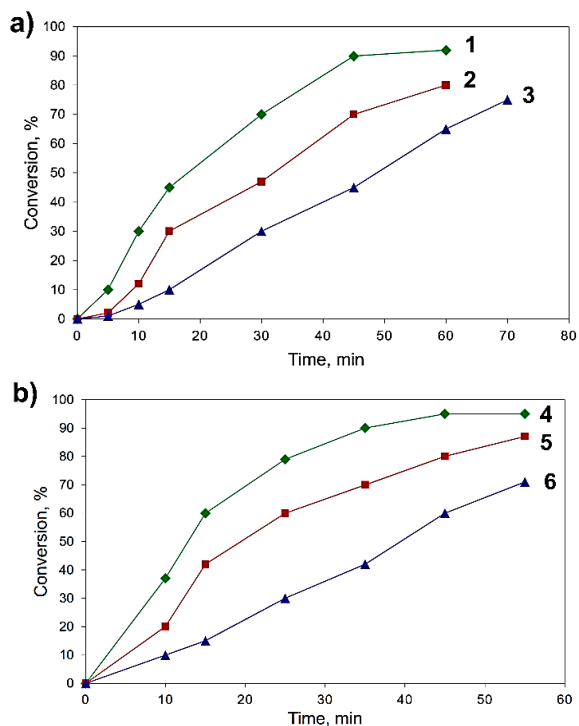
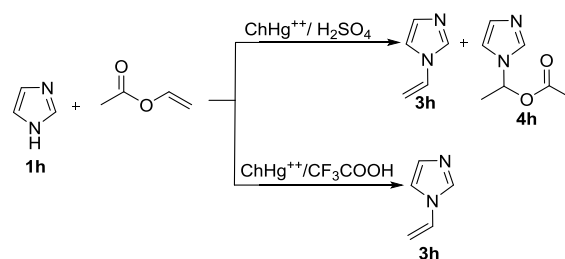


Fig. 2. The curves of vinylation kinetics for (a) **1** - pyrazole (**3c**), **2** - 3(5)-methylpyrazole (**3b**), **3** - 3,5-dimethylpyrazole (**3a**), (b) **4** - 4-chloro-3(5)-methylpyrazole (**3e**), **5** - 4-bromo-3(5)-methylpyrazole (**3f**) and **6** - 4-iodo-3,5-dimethylpyrazole (**3g**).
Рис. 2. Кривые кинетики винилирования (a) **1** - пиразола (**3c**), **2** - 3(5)-метилпиразола (**3b**), **3** - 3,5-диметилпиразола (**3a**), (b) **4** - 4-хлор-3(5)-метилпиразола (**3e**), **5** - 4-бром-3(5)-метилпиразола (**3f**) и **6** - 4-йод-3,5-диметилпиразола (**3g**)

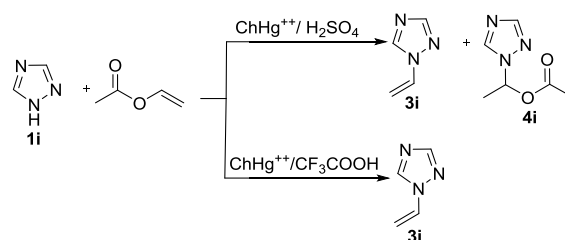
The effects of substituent for the series of pyrazoles on the reaction kinetics and the product yields were also studied. The various factors affecting the reaction were studied by GC-analysis. We compared the kinetics of vinylation of pyrazole (**3c**), 3(5)-methylpyrazole (**3b**) and 3,5-dimethylpyrazole (**3a**) (Fig. 2a). Results show that donation and steric effects of methyl groups decrease reaction yield. Then the study was performed by changing halogen substituents in the 4th position of pyrazole ring (Fig. 2b). The results imply that the vinylation of 4-chloro-3(5)-methylpyrazole (**3e**) undergoes easier compared to 4-bromo-3(5)-methylpyrazole (**3f**) and 4-iodo-3,5-dimethylpyrazole (**3g**). Thus, the nature of halogen substituent is an important factor for the kinetics of vinylation.

Reaction of other azoles (**1h** and **1i**) with vinyl acetate in the presence of ChHg with sulfuric acid usually leads to obtaining besides vinylated product also addition products (**4h** and **4i**). Thus, for example, when we move from pyrazoles to imidazoles and triazoles together with vinylation products we obtain addition products (adducts) (Scheme 3, 4).

When instead of sulfuric acid the TFA is used, vinylated products of imidazoles and triazoles are obtained chemoselectively. During of vinylation of 3(5)-methylpyrazole the mixture of two isomers with different ratios (3Me:5Me with prevalence of 3Me isomer) is obtained due to tautomerization of 3(5)-substituted pyrazoles [61, 62].



Scheme 3
Схема 3



Scheme 4
Схема 4

Methyl 1H-pyrazole-3-carboxylate (**1k**) vinylation products **3k-1** and **3k-2** can be isolated by vacuum distillation since their boiling points are varying in a wide temperature range. The reason behind is the intramolecular hydrogen bond [63] in **3k-2**, which decreases boiling point of **3k-2** compared with **3k-1**. Therefore, we isolated those isomers and identified their structure by 2D NMR spectroscopy. In the case of vinylation of methyl 3,5-nitro-1H-pyrazole-3-carboxylate (**1m**) only one isomer (methyl 5-nitro-1-vinyl-1H-pyrazole-3-carboxylate, **3m**) was obtained. This isomer was also isolated and the structure was identified by 2D NMR spectroscopy. In particular, in ¹H-¹⁵N HMBC spectra one of the nitrogen atoms of the pyrazole ring has cross peaks with all the protons of the vinyl group and the pyrazole proton, while the second nitrogen atom has cross peaks with only the α-proton of the vinyl group. The downfield shift of the ¹H signal

of the α -proton of the vinyl group also verifies the structure of this isomer. Probably the observed high regioselective vinylation occurs due to strong coordination of nitro group to mercury [64, 65].

The reuse of catalyst was studied on an example of vinylation of 3(5)-methyl-4-nitropyrazole (**1g**).

Experiment shows that Ch Hg catalyst can be reused more than four times in the presence of acid and the difference in product yields of the 4th and 1st reactions is 15% (Fig. 4).

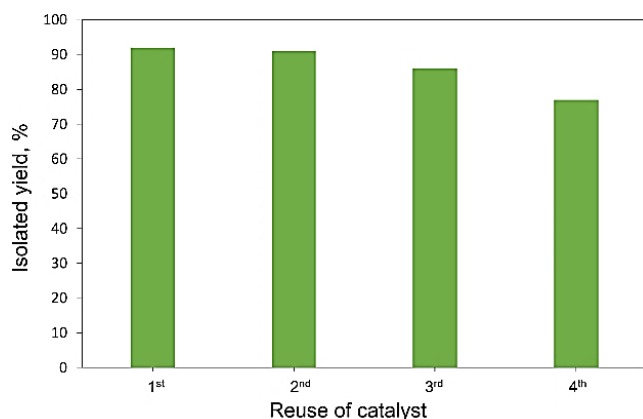


Fig. 3. Recycling of ChHg
Рис. 3. Повторное использование ChHg

CONCLUSION

Thus, we have successfully developed new method of vinylation of azoles with catalytic system based on chitosan and mercury(II) acetate with heterogeneous nature, which allows to use it more than four times and develop practical protocol for industry. Various azoles were vinyolated under the same conditions. For certain azoles, the formation of addition products was excluded. The proposed method reduces wastes of mercury(II) and its ecological damages and decreases reaction time and waste of catalyst. However, despite reducing water contamination with mercury salts, currently this method does not solve the problem completely.

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