UDC 547.772

SYNTHESIS AND CONVERSION OF PYRAZOLE DERIVATIVES

A.R. Karayeva

Institute of Polymer Materials
National Academy of Sciences of Azerbaijan
A3 5004, Sumgait, S.Vurgun Str, 124; e-mail: ipoma@science.az

Received 05.08.2019

Abstract: *The new representatives of functionally substituted pyrazoles were synthesized and their interactions with secondary amines studied. It found that the interaction of 3,4-bis(diethylamino)but-2-en-1-ones with hydrazine hydrate gave rise to 3-alkyl-5-(diethylaminomethyl)pyrazoles. Appropriate 1-acetyl and 1-(2-chloromethyl carbonyl)pyrazoles were synthesized through the acylation of the last products with acetyl- and monochloroacetyl chloride in the presence of triethylamine. It revealed that 1-(2-chloromethyl carbonyl)pyrazoles react with twofold quantity of diethylamine and morpholine under mild reaction conditions to form new polyfunctional pyrazole derivatives. The composition and structure of the synthesized compounds were confirmed by IR- and NMR ^{1}H-spectroscopy. It established that 3-methyl- and 3-ethyl-5-(diethylaminomethyl) pyrazoles were biologically active substances out of synthesized functionally pyrazole derivatives.*

Keywords: *hydrazine hydrate, 3-alkyl-5-(diethylaminomethyl)pyrazoles, acylation, 3-alkyl-1-acetyl-5-(diethylaminomethyl)pyrazoles, 3-alkyl-1-(2-chloromethylcarbonyl)-5-(diethylamino-methyl) pyrazoles, secondary amines, antimicrobial activity.*

DOI: 10.32737/2221-8688-2019-4-584-590

Introduction

As is known, the compounds containing pyrazole ring in its composition have a wide spectrum of pharmacological effect. For example, "antipyrine", "analgin", "amidopyrine" are successfully used in the medical practice as anti-inflammatory and antipyretic agent; "pyramidon" – as analgesic agent; "celebrex" as a pain relief in joints, etc. [1-5]. In addition, the pyrazole derivatives are also used in fine organic synthesis, supra-molecular and polymer chemistry; in the preparation of liquid crystals and agrochemical preparations [6-9].

It should be noted that effective methods of preparation of functionally substituted pyrazoles were developed: for ex., 3-alkyl pyrazoles [10] were obtained by interaction of 2-chlorvinyl ketones with alkyl hydrazines; 1,3-disubstituted 5-chloropyrazoles [11] were synthesized from 2,2-dichlorovinyl alkyl ketones and alkyl- or 1,1-dialkyl hydrazines, the reaction of 1-alkyl(aryl)-3,4-bis(dimethylamino)but-2-en-1-ones with hydrazine hydrate led to the preparation of 3-alkyl(aryl)-5-(dimethylaminomethyl) pyrazoles [12-13], etc.

Continuing investigations in the field of development of the methods for synthesis of the pyrazoles on the basis of unsaturated ketones the heterocyclization of aminoketones under action of hydrazine hydrate has been studied.

Experimental

Synthesis technique

The initial 3,4-bis(diethylamino)but-2-en-1-ones (I, II) were obtained from 3,4-dichlorobut-2-en-1-ones and diethylamine on method [14]. The physical-chemical constants of aminoketones (I, II) are identical with data presented in work [14].

3-Alkyl-5-(diethylaminomethyl)pyrazoles (III, IV). 4.4 ml (0.1 mol) of hydrazine hydrate at 20-25°C in stirring was added on dropwise to a solution of 22.6 g (0.1 mol) of 1-methyl-3,4-bis(diethylamino) but-2-en-1-

ones (I) in 30 ml of ethanol. The reaction mixture was stirred at 50-55°C for 5 h. After cooling, the solvent was distilled off, and the residue distilled in vacuum.

3-Alkyl-1-acetyl-5-(diethylaminomethyl)-(V,VI) and 3-alkyl-5- diethylamino-methyl)-1(chloromethylcarbonyl)pyrazoles (VII,VIII). For synthesis of compounds (V,VI) 4 g (0.05 mol) of chloranhydride of acetic acid in stirring was added on drop wise to a solution of 8.35 g (0.05 mol) of 5-(diethylaminomethyl)-3-methylpyrazole (III) in 50 ml of anhydrous ether and 7 ml (0.05 mol) of triethylamine at a temperature of 0÷5°C and for synthesis of compounds (VII,VIII) 5.6 g (0.05 mol) of chloranhydride of monochloroacetic acid with stirring on dropwise was added to above-mentioned solution. Then the reaction mass was again stirred for 4-6 h at 15÷20°C and washed (100 ml) with 2% aqueous solution of the sodium carbonate, the ether layer was separated and the aqueous layer treated with 50 ml ether while the combined ether extracts were dried over $MgSO_4$. After distillation of solvent the residue was distilled in vacuum.

3-Alkyl-5-(diethylaminomethyl)-1-(2-dialkylaminomethylcarbonyl)pyrazoles (IX-XII). 3.7 g (0.05 mol) of diethylamine or 4.4 g (0.05 mol) of morpholine at temperature 20-25ºC in stirring was added on dropwise to a solution of 6 g (0.025 mol) of 5-(diethylaminomethyl)-1-(2-chloromethylcarbonyl)-3-methylpyrazole (VII) in 50 ml of anhydrous ether. The reaction mixture was intensively stirred for 5 h at a temperature of 30-35ºC. After cooling, the reaction mass was washed with diluted aqueous soda solution; the ether layer was separated and aqueous layer extracted with ether. The combined ether extracts were dried over $MgSO_4$. After distillation of solvent the residue was distilled in vacuum.

Physical-chemical indices of the synthesized pyrazoles (III-XII) are presented in Table 1.

Table 1. Physical-chemical indices of the compounds (III-XII).

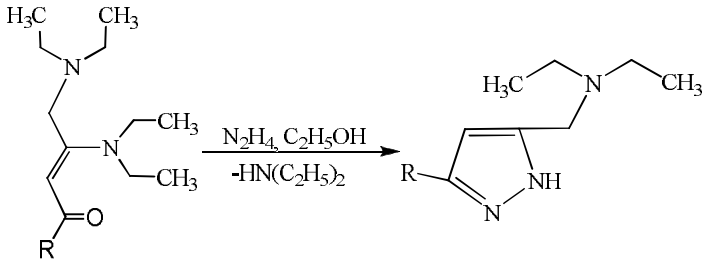
№	Formula	B.p., °C/mm.merc.c	n_D^{20}	d_4^{20}	Found,% / Calculated,%			Yield,%
					C	H	N	
III	$C_9H_{17}N_3$	130-131º/2mm	1.5010	0.9760	64.00 / 64.61	10.35 / 10.10	24.95 / 25.10	76
IV	$C_{10}H_{19}N_3$	133-134º/2mm	1.4965	0.9615	65.84 / 66.29	11.61 / 10.49	23.28 / 23.20	73
V	$C_{11}H_{19}N_3O$	101-102º/3mm	1.4930	1.0005	63.39 / 63.15	10.30 / 9.09	20.39 / 20.10	73
VI	$C_{12}H_{21}N_3O$	114-115º/2mm	1.4865	0.9878	63.85 / 64.57	9.02 / 9.41	18.50 / 18.83	69
VII	$C_{11}H_{18}ClN_3O$	139-141º/3mm	1.4945	1.0670	54.71 / 53.39	7.39 / 7.87	17.24 / 16.97	68
VIII	$C_{12}H_{20}ClN_3O$	150-151º/3mm	1.4910	1.0735	55.92 / 56.35	7.77 / 7.23	16.32 / 16.15	64
IX	$C_{15}H_{28}N_4O$	148-149º/2mm	1.4905	0.9640	64.28 / 64.95	10.00 / 9.58	20.00 / 20.22	64
X	$C_{16}H_{30}N_4O$	160-161º/2мм	1.4865	0.9710	65.30 / 64.85	10.20 / 10.48	19.04 / 20.02	66
XI	$C_{15}H_{26}N_4O_2$	150-151º/2mm	1.4995	1.0400	61.62 / 61.65	8.84 / 8.28	19.04 / 20.25	65
XII	$C_{16}H_{28}N_4O_2$	156-158º/2mm	1.5045	1.0560	62.33 / 62.65	9.09 / 8.86	18.18 / 19.05	67

(VII) Cl-14.57/15.17%; (VIII) Cl-13.78/14.05%

Results and discussion

It has been established that the heterocyclization of 1-alkyl-3,4-bis(diethylamino)but-2-en-1-ones (I,II) proceeds in a medium of ethanol at

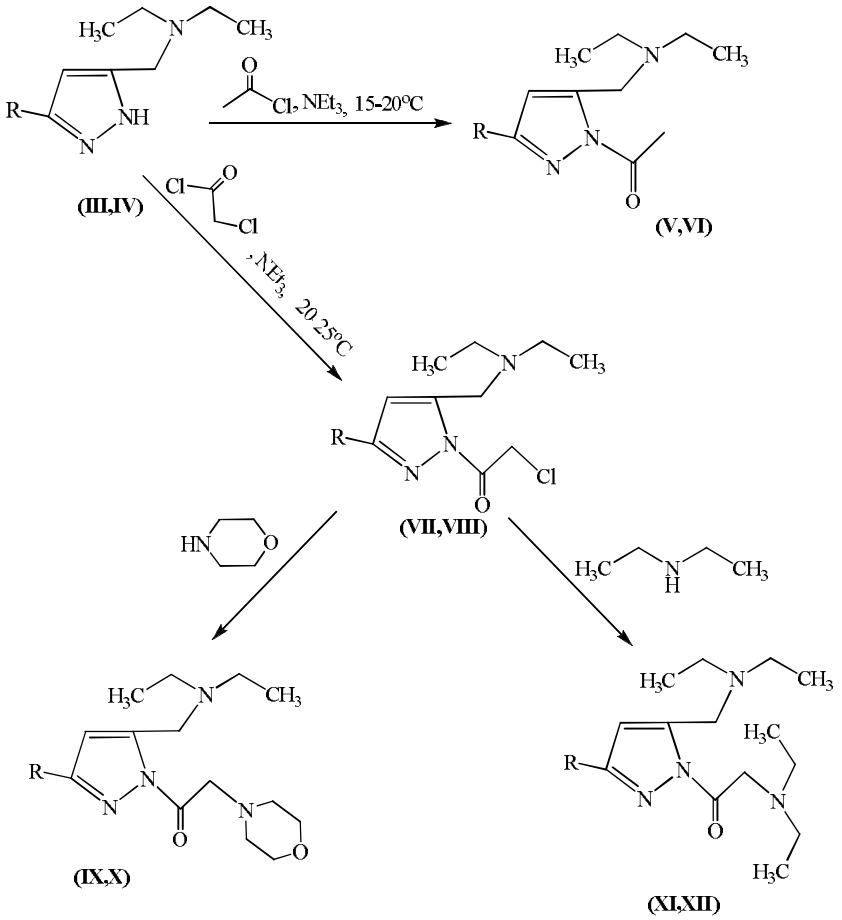
temperature 50-55ºC and leads to the preparation of 3-alkyl-5-(diethylaminomethyl)pyrazoles (III,IVThe yield of the synthesized pyrazoles (III, IV) was 73-76%.



(I,II) **(III,IV)**

I,III R=CH_3; **II,IV** R=C_2H_5.

3-Alkyl-5-(diethylaminomethyl)pyrazoles (III, IV) contain highly mobile hydrogen in molecules and are easily acylated with chloranhydrides of carboxylic acids An interaction of the synthesized pyrazoles (III, IV) with chloranhydride of acetic acid in the presence of triethylamine (for binding of isolated HCl) in a medium of anhydrous ether proceeds at temperature 15-20°C and for 4 h leads to the preparation of 3-alkyl-1-acetyl-5-(diethylaminomethyl)pyrazoles (V, VI) with yields 66-75%.



(III,IV) **(V,VI)** **(VII,VIII)** **(IX,X)** **(XI,XII)**

III,V,VII,IX,XI R=CH_3;
IV,VI,VIII,X,XII R=C_2H_5.

In case of chloranhydride of monochloro-acetic acid at 20-25°C for 6 h, the reaction leads to the preparation 3-alkyl-5-(diethylaminomethyl)-1-(2-chloromethyl-carbonyl)pyrazoles (VII,VIII) with yields 63-67% which contain mobile chlorine atom in a molecule. Therefore, the reaction of 1-(2-chloromethylcarbonyl)pyrazoles (VII,VIII) was studied with nucleophilic reagents to establish that they could easily be substituted by secondary amines. The reaction of pyrazoles (VII,VIII) with diethylamine and morpholine with nucleophilic substitution of the chlorine atom for dialkylamine group leads to the preparation 3-alkyl-5-(diethylaminomethyl)¬-1-(2-dialkylamino-methylcarbonyl)pyrazoles (IX-XII) with yields 63-72%.

The structure of the obtained pyrazoles (III-XII) was confirmed by means of IR- and NMR ^{1}H-spectroscopy methods, their purity was controlled by TLC method on plates «Silufol UV-254», and their composition was established by elemental analysis data. Typical IR and NMR ^{1}H spectra of the synthesized pyrazole derivatives were well agreed with literature data [15] presented in Figs.1-3.

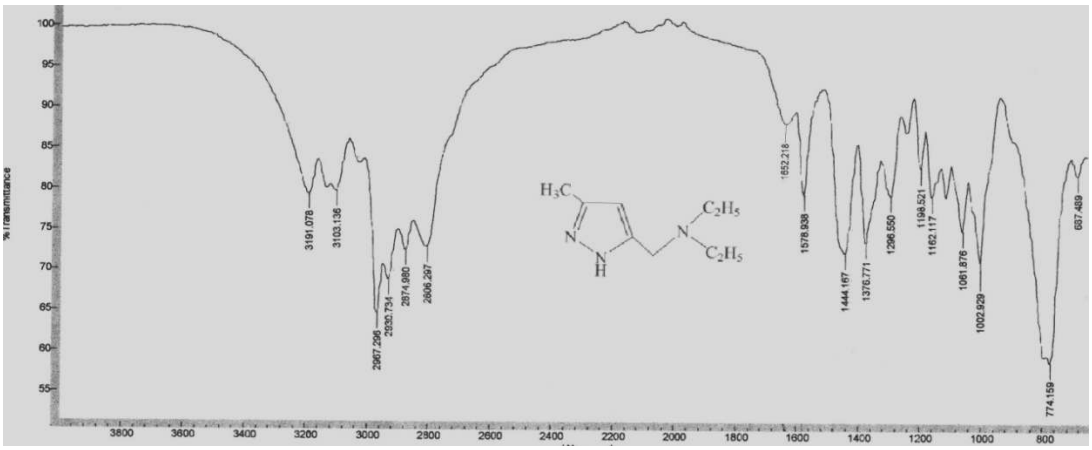


Fig. 1. IR spectrum of 5-(diethylaminomethyl)-3-methylpyrazole (comp. III)

In the IR spectra (ν, cm^{-1}) of the pyrazoles (III,IV) [R_f=0.61 (benzene:ethanol – 4:1)], the absorption bands of N-H fragment in the field of 3200-3100 cm^{-1}, fragment -CH= at frequency 2930-2967, double carbon bond C=C at 1578-1652 cm^{-1} and fragment C=N at 1376-1444 cm^{-1} (Fig. 1.) were observed.

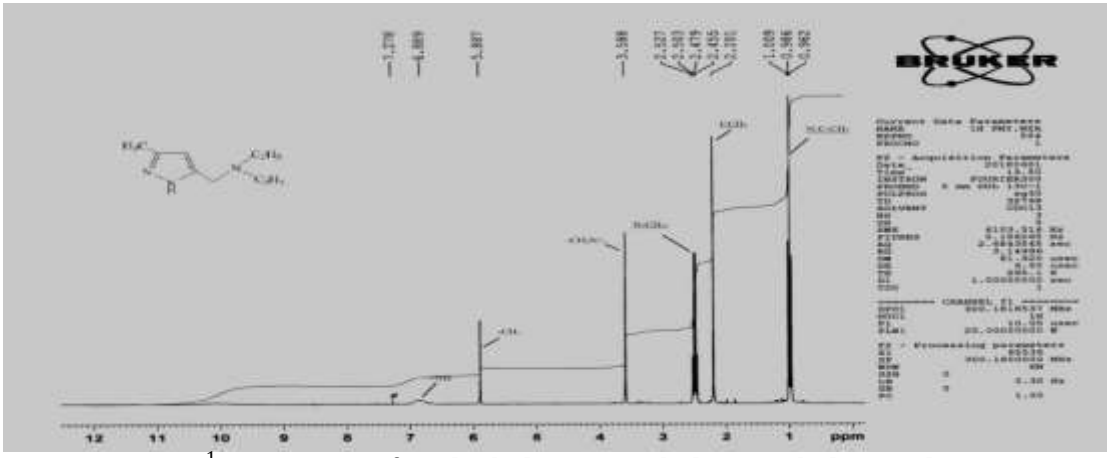


Fig. 2. NMR ^{1}H spectrum of 5-(diethylaminomethyl)-3-methylpyrazole (comp. III)

In the NMR ^{1}H spectrum of 5-(diethylaminomethyl)-3-methyl pyrazole (III), the characteristic signals of the protons of diethyl radical (δ, ppm): triplet 0.98 [6H, N(-C-CH_3)$_2$] and quadruplet 2.45-2.52 [2H, N(-CH_2-)$_2$], methyl radical – singlet 2.20 (3H, CH_3), pyrazole nucleus 5.88 – singlet [1H, (CH, H-4)] and broadened signal of N-H proton at 6.88 ppm were established (Fig. 2.).

In the IR spectrum (ν, cm^{-1}) of pyrazoles (V-XII), the absorption bands of N-H fragment disappear and in this case the characteristic signal of carbonyl group in the field of 1700-1735 cm^{-1} appeared. In the IR spectrum of 5-(diethylaminomethyl)-1-(2-chloromethylcarbonyl)-3-methylpyrazole (VII,VIII) [R_f=0.68 (benzene:ethanol– 6:1)] besides the absorption bands of C=O group the absorption bands of C-Cl bond at frequencies 710-740 cm^{-1}, and also 3026-3103 (–CH=), 1700-1725 (C=O), 1605-1629 (C=C), 1452-1496 (C=N) and deformation valence vibrations of the pyrazole ring of fragment –CH= in the frequencies 758-784 cm^{-1} were detected.

In the NMR ^{1}H-spectra of the pyrazoles (V-VIII), the signals of proton of N-H fragment disappear and the singlet signals for compounds (V,VI) $COCH_3$ (δ=2,46-2,66 ppm), for pyrazoles (VII,VIII) $COCH_2Cl$ (δ=3.85-4.15 ppm) were observed.

In the NMR ^{1}H spectrum of the compound (VII), the characteristic signals [3H, N(-C-CH_3)$_2$] 1.00 ppm triplet and [4H, N(-CH_2-)$_2$] 2.52 ppm multiplet, (3H, CCH_3) 2.22 ppm singlet, (2H, CH_2N) 3.60 ppm singlet, (2H, CH_2Cl) 3.85 ppm singlet and one proton of pyrazole ring [1H, (CH, H-4)] 5.90 ppm singlet (Fig. 3.) were detected.

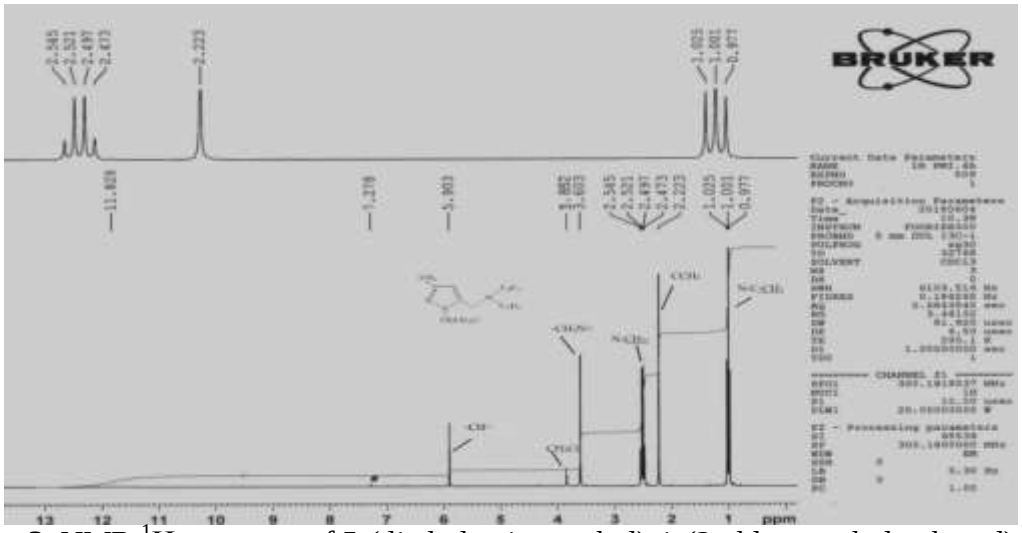


Fig. 3. NMR ^{1}H spectrum of 5-(diethylaminomethyl)-1-(2-chloromethylcarbonyl)-3-methylpyrazole (comp. VII.)

It found that signals of protons [6H, N(-C-CH_3)$_2$] (δ=0.98-1,08 triplet) and [2H, N(-CH_2-)$_2$] (2.45-2.52 quadruplet), and for compounds (XI,XII) triplet signals of protons of morpholine fragment [4H, N(CH_2)$_2$] (3.46 ppm) and [4H, (CH_2)$_2$O] (3.64 ppm), respectivelyin the NMR ^{1}H spectrum of the pyrazoles (IX, X) besides characteristic signals there are appeared the.

The study into antimicrobial activity of the pyrazoles (III, IV) was carried out by comparing them with well-known antimicrobial agents – ethanol, rivanol, furacilin and nitrofungin. 1% alcohol solutions of the tested pyrroles were used.

The antimicrobial activity of the pyrazoles (III,IV) was determined by means of serial successive dilutions in the sterile diethylated water in respect of gram-positive bacteria (Staphylococcus aureus, *S. aureus*), gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) and fungi

(*Candida, C. Albicans)*. MPa with pH 7,2 (for bacteria) and Saburo medium (for fungi) served as a nutrient medium for these microorganisms.

Dilution started with 500 mkg/ml depending on the activity of the compounds. Seeding was carried out in 10, 20, 40 and 60 min.; the incubation duration in a thermostat for bacteria at 37°C was 24 h and for fungi at 28°C - 48 h.

It has been elucidated that the tested compounds show expressed antimicrobial activity in relation to bacteria *S. aureus* and fungi of type *C. Albicans.* Pyrazoles (III, IV) at 1:100 dilution exhibit higher antimicrobial activity to all tested test-cultures. These compounds indicated the antimicrobial action in the dilution 1:200 for 20 min. to bacteria *Ps. aereginosa* and for 40 min to *E-coli*. In the dilution 1:400 an exposition time to *Ps. aereginosa* and *E-coli* was 40 and 60 min., respectively. The tested compounds (III,IV) in the dilution 1:800 showed the antimicrobial action to *St. aureus* and *Cand. albicans* for 60 and 40 min.

The carried out investigations showed that the synthesized pyrazoles (III, IV) can be used in organic synthesis for preparation of practically useful and biologically active substances.

References

1. Hamad Elgazwy A.S., Nassar E., Zaki M.Y. Synthesis, biological evaluation of some 2,3-dihydropyrazoles and thiazoles as anti-inflammatory and antibacterial agents. *Organic Chem. Curr. Res.,* 2012, vol. 1, article 112.
2. Vicentini C.B., Romagnoli C., Andreotti E., Mares D. Synthetic pyrazole derivatives as growth inhibitors of some phytopathogenic fungi. *Jour. Agric. Food Chem.,* 2007, vol. 55, is. 25, pp. 10331-10338.
3. Rashad A.E., Hegab M.I., Abdel-Megeid R.E., Fathalla N. et al. Synthesis and anti HSV-1 evakution of some pyrazoles and fused pyrazolopyrimidines. *Eur. Jour. Med. Chem.,* 2009, vol. 44, pp. 3285-3292.
4. El Bordiny H.S., El Miligy M.M., Shaymaa E.K. et al. Design, synthesis, biological evaluation and docking studies of new 3-(4,5-dihydro-1H-pyrazol/izoxazol-5-yl)-2-phenyl-1H-indole derivatives as potent antioxidant and 15-lipoxygenase inhibitors. *Eur. Jour. of Med. Chem.,* 2018, vol. 145, pp. 594-605.
5. Janin Y.L. Preparation and chemistry of 3/5-halogenopyrazoles. *Chem. Rev.,* 2012, vol. 112, no. 7, pp.3924-3958.
6. Türkoglu G., Uldemolins C.P., Müller R., Hübner E. Bis(3,5-dimethyl-4-vinylpyrazol-1-yl)acetic acid. *Eur. J. Inorg. Chem.,* 2010, pp. 2962-2964.
7. Han L.C., Timmons R.B. Ring retention via pulsed plasma polymerization of heterotcyclic aromatic compounds. *Chem. Mater*., 1998, vol. 10, pp. 1422-1429.
8. Cavero E., Uriel S., Romero P. Tetrahedral Zinc complexes with liquid crystalline and luminescent properties. *J. Amer. Chem. Soc*., 2007, vol. 129, pp. 11608-11618.
9. Schimidt A., Dreger A. Recent advances in the chemistry of pyrazoles. *Curr. Org. Chem.,* 2011, vol. 15, pp. 1423-1463.
10. Nesmeyanov A.N., Kochetkov N.K. Synthesis of pyrazoles from β-chlorovinyl ketones *Uch.Zap MSU*, 1976, vol. 175, pp. 85-95.
11. Rudyakova E.B., Savosik B.A., Papernaya L.K., Albanov A.I. Synthesis and reactions of 4-formilpyrazoles. *Rus. J. Org. Chem.,* 2009, vol. 45, pp. 1053-1057.
12. Gadzhly R.A., Dikusar E.A., Aliyev A.G., Karayeva A.R. Synthesis and properties of 3-alkyl(aryl)-5-(dimethylaminomethyl)pyrazoles. *Rus. J. Org. Chem.,* 2015, vol. 51, pp. 530-533.
13. Karayeva A.R., Aliyev A.G., Gadzhly R.A., Mamedov B. A. Synthesis and properties of bis- and allyl 3-alkyl(aryl)-5-(dimethylaminomethyl)pyrazolines. *Chemical Problems*, 2018, no 2, pp. 250-255.

14. Ibragimov I.I., Mamedov I.I., Aliyev A.G. Mekhtiyev T.S. Propenylation of secondary amines of 2,3-dihalogen-1-propenyl ketones. *Rus. J. Org. Chem.*, 1990, vol. 26, pp. 2503-2508.
15. Gordon A., Ford R. *Sputnik khimika*. Moscow: Mir Publ., 1976, pp. 271-312.

PİRAZOLLARIN SİNTEZİ VƏ ÇEVRİLMƏLƏRİ

A.R. Qarayeva

AMEA Polimer Materialları İnstitutu,
Az 5004, Sumqayıt ş., s.Vurğun küç., 124: e-mail: ipoma@science.az

Yeni funksionaləvəzli pirazol törəmələri sintez olunmuş və onların ikili aminlərlə reaksiyaları tədqiq olunmuşdur. Müəyyən olunmuşdur ki, 3,4-bis(dietilamino)-but-2-en-1-onların hidrazin hidratla qarşılıqlı təsirindən 3-alkil-5-(dietilaminometil)pirazollar alınır. Alınmış məhsulların sirkə və monoxlorsirkə turşusunun xloranhidridləri ilə trietilaminin iştirakı ilə asilləşməsindən 1-asetil- və 1-(2-xlormetilkarbonil)pirazollar sintez olunmuşdur. Öyrənilmişdir ki, 1-(2-xlormetilkarbonil)pirazollar ikiqat artıq miqdarda dietilamin və morfolinlə asan şərtlər altında reaksiyaya daxil olur və yeni polifunksional törəməli pirazollar əmələ gətirir. Sintez olunmuş birləşmələrin quruluşu İQ- və NMR ^{1}H- sprektoskopiya üsulu ilə öyrənilmişdir. Müəyyən olunmuşdur ki, 3-metil- və 3-etil-5-(dietilaminometil)pirazollar yüksək bioloji fəallığa malikdirlər.

Açar sözlər: *hidrazin hidrat, 3-alkil-5-(dietilaminometil)pirazollar, asilləşmə reaksiyası, 3-alkil-1-asetil-5-(dietilaminometil)pirazollar, 3-alkil-1-(2-xlormetilkarbonil)-5-(dietilaminometil)pirazollar, ikili aminlər, antimikrob fəallıq.*

СИНТЕЗ И ПРЕВРАЩЕНИЯ ПРОИЗВОДНЫХ ПИРАЗОЛА

А.Р. Караева

Институт полимерных материалов Национальной АН Азербайджана,
AZ 5004, Сумгаит, ул. С.Вургуна, 124; e-mail: ipoma@science.az

Синтезированы новые представители функционально замещенных пиразолов и изучены их взаимодействия с вторичными аминами. Установлено, что при взаимодействии 3,4-бис(диэтиламино)бут-2-ен-1-онов с гидразингидратом образуются 3-алкил-5-(диэтиламинометил)пиразолы. Ацилированием последних продуктов с ацетил- и монохлорацетилхлоридом в присутствии триэтиламина синтезированы соответствующие 1-ацетил и 1-(2-хлорметилкарбонил)пиразолы. Выяснено, что 1-(2-хлорметилкарбонил)пиразолы реагируют с двукратным количеством диэтиламина и морфолина при мягких условиях и образуют новые полифункциональные производные пиразолов. Состав и строение синтезированных соединений подтверждены ИК- и ЯМР ^{1}H-спектроскопией. Установлено, что из синтезированных функционально производных пиразолов 3-метил- и 3-этил-5-(диэтиламинометил)пиразолы являются биологически активными веществами.

Ключевые слова; *гидразингидрат, 3-алкил-5-(диэтиламинометил)пиразолы, ацилирование, 3-алкил-1-ацетил-5-(диэтиламинометил)пиразолы, 3-алкил-1-(2-хлорметилкарбонил)-5-(диэтиламинометил)пиразолы, вторичные амины, антимикробная активность.*