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SYNTHESIS OF β-AMINOETHYL-SUBSTITUTED PYRAZOLES

O. V. Kokoreva[1], E. B. Averina[1], O. A. Ivanova[1], S. I. Kozhushkov[2], and T. S. Kuznetsova[1]

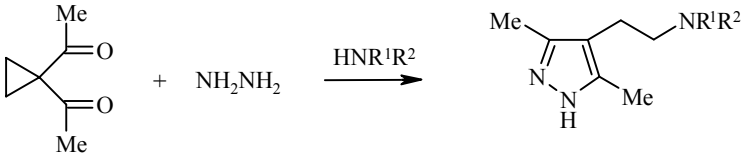
Methods have been developed for the synthesis of 3,5-dimethyl-4-(2-N-mono- and -disubstituted and also unsubstituted aminoethyl)pyrazoles from 1,1-diacetylcyclopropane.

Keywords: 3,5-dimethyl-4-(2-mono-substituted aminoethyl)pyrazole, 3,5-dimethyl-4-(2-disubstituted aminoethyl)pyrazoles, 3,5-dimethyl-(2-aminoethyl)pyrazoles.

We previously found a new effective method of synthesizing β-X-ethyl substituted pyrazoles by the nucleophilic opening of the three-membered ring in 1,1-diacetylcyclopropanes by the action of hydrazine and its derivatives [1-3].

We studied various aspects of this unusual reaction [2,3], its mechanism [4], and also synthesized a large number of diverse β-X-ethyl-substituted pyrazoles [1-4]. However β-aminoethylpyrazoles, which are potentially biologically active compounds, remained unknown. The present work fills this gap and is devoted to the development of synthetic approaches to the preparation of 4-(2-aminoethyl)-3,5-dimethylpyrazoles from 1,1-diacetylcyclopropane (**1**) by the reaction previously found by us [1-4].

We found that the reaction of diketone **1** with hydrazine hydrate in the presence of N-substituted amines, such as diethylamine, piperidine, and cyclohexylamine, in aqueous medium at room temperature with a molar ratio of starting materials of 1:1.05:1.1 leads smoothly to the corresponding 3,5-dimethyl-4-(2-N-substituted aminoethyl)pyrazoles **2-4** in high yield.



1 **2**–**4**

2 $R^1 = R^2 =$ Et; **3** $R^1 - R^2 = -(CH_2)_5-$; **4** $R^1 =$ H, $R^2 =$ 

The composition and structure of the pyrazoles **2-4** were confirmed by data of elemental analysis and ^{1}H NMR spectra (see Table 1).

The one-step method proposed by us for the synthesis of β-N-substituted aminoethylpyrazoles from the available 1,1-diacetylcyclopropane [5] may be used in preparative organic chemistry.

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[1] M. V. Lomonosov Moscow State University, Moscow 119899, Russia; e-mail: koko@org.chem.msu.ru, elaver@org.chem.ru. [2] Institute of Organic Chemistry, Georg-August-University of Göttingen, Tammannstrasse 2, D-37077, Göttingen, Germany; e-mail: skozhus@gwdg.de. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 906-911, July, 2001. Original article submitted August 30, 1999.

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TABLE 1. Characteristics and Spectral Properties of the Synthesized Compounds

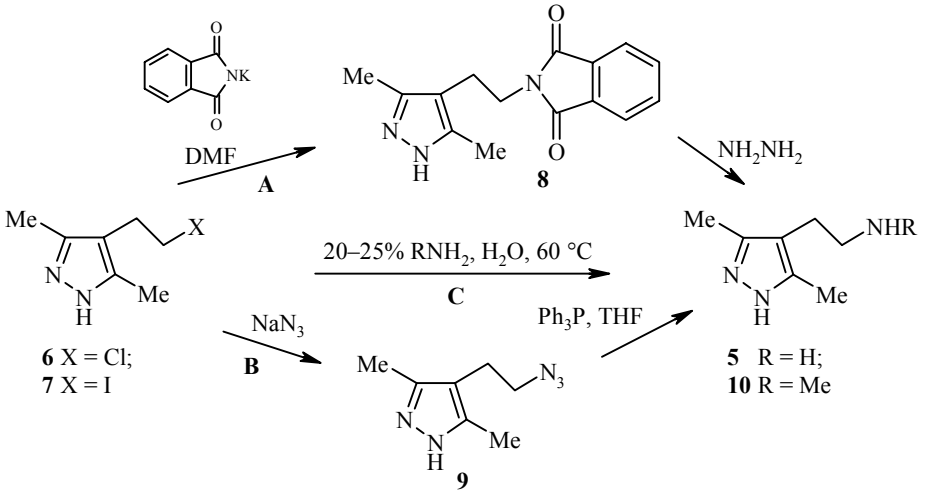
Compound	Empirical formula	Found, % / Calculated, %			mp, °C [bp, °C (gPa)]	^{1}H NMR spectrum, DMSO-d_6, δ, ppm (SSCC, *J*, Hz)	^{13}C NMR spectrum, DMSO-d_6, δ, ppm	Yield, %
		C	H	N				
1	2	3	4	5	6	7	8	9
2	$C_{11}H_{21}N_3$	67.52 / 67.75	10.71 / 10.84	21.30 / 21.51	[165-167 (5.3)]	0.98 (6H, t, $2CH_3$, *J* = 7.3); 2.17 (6H, s, $2CH_3$); 2.44 (4H, m, $2CH_2$); 2.56 (4H, q, $2CH_2$, *J* = 7.3), 12.12 (H, br. s, NH)		60
3	$C_{12}H_{21}N_3$	69.30 / 69.52	10.43 / 10.21	20.54 / 20.27	51-54 [150-154 (2.7)]	1.5 (6H, m, $3CH_2$, ring); 2.13 (6H, s, $2CH_3$); 2.40 (8H, m, $4CH_2$); 11.21 (H, br. s, NH)		56
4	$C_{13}H_{23}N_3$	70.30 / 70.54	10.54 / 10.47	19.23 / 18.98	67-68 [150-156 (2.7)]	0.85-1.90 (10H, m, 5 CH_2); 2.06 (6H, s, $2CH_3$); 2.39 (2H, m, CH_2); 2.57 (2H, m, CH_2); 2,61 (H, m, CH); 5.60 (H, br. s, N-H)	11.76 (2S, $2CH_3$); 23.85, 25.01 ($2CH_2$, cyclohexyl); 24.94 ($2CH_2$, cyclohexyl); 36.51 (CH_2, pyrazole); 56.62 (CH); 112.54 (C); 141.86 (2C)	81
5	$C_7H_{13}N_3$				[153-156 (4)]	2.08 (6H, s, $2CH_3$); 2.36 (2H, br. t, CH_2); 2.58 (2H, br. t, CH_2)	10.11 ($2CH_3$); 27.50 (CH_2); 43.00 (CH_2); 113.00 (C); 142.00 (2C)	81
5·2HCl	$C_7H_{15}Cl_2N_3$	39.77 / 39.64	7.23 / 7.13	19.80 / 19.81	260-270	2.34 (6H, s, $2CH_3$); 2.78 (2H, m, CH_2); 2.89 (2H, m, CH_2); 8.41 (5H, br. s, NH_3^+, NH_2^+)	9.54 ($2CH_3$); 19.84 (CH_2); 38.47 (CH_2); 113.48 (C); 143.32 (2C)	62

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
8	$C_{15}H_{15}N_3O_2$				191	2.02 (6H, s, $2CH_3$); 2.60 (2H, br. t, CH_2, J = 4.0); 3.60 (2H, br. t, CH_2, J = 4.0); 7.8 (4H, br. s, C_6H_4);	10.38 ($2CH_3$); 21.65 (CH_2); 37.71 (CH_2); 110.49 (C, pyrazole); 123.05 (2CH, arom.); 131.56 (2C, arom.); 134.49 (2CH, arom.); 141.16 (2C, pyrazole); 167.75 (2C, CO)	80
9	$C_7H_{11}N_5$				145	2.15 (6H, s, $2CH_3$); 2.57 (2H, br. t, CH_2); 3.33 (2H, br. t, CH_2); 11.95 (H, br. t, NH)		97
10	$C_8H_{15}N_3$	$\frac{62.67}{62.75}$	$\frac{9.70}{9.80}$	$\frac{27.75}{27.45}$	[156-158 (4)]	2.31 (6H, s, $2CH_3$); 2.63 (2H, m, CH_2); 2.69 (2H, m, CH_2); 2.73 (3H, br. d, N-CH_3)	11.11 ($2CH_3$, pyrazole); 23.56 (CH_2); 36.50 (CH_2); 53.00 (CH_3, N-CH_3); 112.50 (C); 141.00 (2C)	82
10·2HCl	$C_8H_{17}Cl_2N_3$				255-260	2.31 (6H, s, $2CH_3$); 2.51 (3H, m, N-CH_3); 2.82 (2H, m, CH_2); 2.93 (2H, m, CH_2); 9.2 (H, br. s, NH)		91

In addition the preparation of 4-(2-aminoethyl)-3,5-dimethylpyrazole (**5**), the simplest amino derivative in the series of pyrazoles studied, using the reaction of diketone **1** with hydrazine in aqueous ammonia proved to be ineffective due to the formation of polymeric products. We have therefore studied other approaches to the synthesis of pyrazole **5** from 4-(2-chloro and iodoethyl)-3,5-dimethylpyrazoles **6** and **7**. The latter are readily formed by the reaction of diketone **1** with hydrazine in solutions of ammonium chloride or iodide respectively [2,3].

Application of the classical method of synthesizing primary amines (the Gabriel reaction [6]) to the iodide **7** (route A) leads smoothly to the preparation of the desired aminopyrazole **5**.



The phthalimidoethylpyrazole **8** is formed in 80% yield. Hydrazine hydrate is used for its decomposition with subsequent addition of hydrochloric acid. This stage requires careful control for the completeness of decomposition of adduct **8**. Such control was effected by TLC and ^{1}H NMR spectroscopy. Amine **5** was isolated by crystallization from ethanol (96%) as the dihydrochloride. The characteristics and spectral properties of the compounds **5** and **8** obtained are given in Table 1.

Although method A is satisfactorily efficient and was used by us to obtain significant quantities of amine **5**, it is fairly laborious and the overall yield of the desired pyrazole **5** did not exceed 40%.

We found that a scheme based on the Staudinger reaction [7,8] is more convenient for synthesizing it (route B). Reaction of the initial iodide **7** with sodium azide in DMSO leads to 4-(2-azidoethyl)-3,5-dimethyl-pyrazole (**9**) in practically quantitative yield. Under the action of triphenylphosphine in moist THF compound **9** is converted into aminopyrazole **5** in 80% yield as the double salt with a high degree of purity.

However the most convenient preparative method of obtaining amine **5** is the direct alkylation of ammonia with haloethylpyrazoles **6** and **7** (route C). Heating chloride **6** or iodide **7** with 20% ammonia solution (threefold excess) in a sealed ampule at 60°C for 10-15 h leads to the desired amine **5** in high yield.

We have found that route C is also optimal for obtaining the N-methyl derivative of amine **5**. 3,5-Dimethyl-4-(2-N-methylaminoethyl)pyrazole (**10**) was obtained by the reaction of chloroethylpyrazole **6** with 25% aqueous methylamine at 60°C. The characteristics of amine **10** and of its dihydrochloride are given in Table 1.

In view of the preparative availability of the initial haloethylpyrazoles **6** and **7** and also the fact that their reactions with ammonia and methylamine under these conditions proceed exclusively as monoalkylation processes, it is possible to consider this approach as the simplest and most effective method of obtaining unsubstituted amino- and N-monosubstituted aminoethylpyrazoles.

EXPERIMENTAL

A check on the progress of reactions and the homogeneity of substances was effected by TLC on Silufol UV 254 plates. The ^{1}H and ^{13}C NMR spectra were obtained on a Varian VXR 400 spectrometer in DMSO-d_6, internal standard was TMS. The characteristics of the compounds synthesized are given in Table 1.

Diacetylcyclopropane (1) was synthesized from acetylacetone and dibromoethane in the presence of potassium carbonate by the procedure of [5].

4-(2-Chloroethyl)-3,5-dimethyl- (6) and 4-(2-Iodoethyl)-3,5-dimethyl)- (7) pyrazoles were obtained by methods developed previously by us in [2].

4-(2-Diethylaminoethyl)-3,5-dimethylpyrazole (2), 3,5-Dimethyl-4-(2-piperidinoethyl)pyrazole (3), and 4-(2-Cyclohexylaminoethyl)-3,5-dimethylpyrazole (4). The reaction mixture of diketone **1** (0.04 mol), hydrazine hydrate (0.044 mol), and amine (diethylamine, piperidine, or cyclohexylamine) (0.048 mol) in water (200 ml) was stirred for 10 h at room temperature, and then extracted with chloroform (3 × 100 ml). The extract was dried with magnesium sulfate, the solvent distilled off, and the residue redistilled in vacuum.

3,5-Dimethyl-4-(2-phthalimidoethyl)pyrazole (8). Potassium phthalimide (3.9 g, 21 mmol) was added to iodide **7** (5 g, 20 mmol) in DMF (20 ml). The reaction was slightly exothermic, but after 5 min the temperature of the reaction mixture had fallen to room temperature. The mixture was stirred for a further 30 min, then water (100 ml) and chloroform (30 ml) were added, and the aqueous layer extracted. The chloroform solution was washed with 2 N NaOH (20 ml) and with water (20 ml). After evaporating the chloroform solution and drying in vacuum, white crystals (4.3 g, 80%) of phthalimidopyrazole **8** were obtained.

4-(2-Azidoethyl)-3,5-dimethylpyrazole (9). A mixture of iodide **7** (24 g, 0.097 mol) and sodium azide (6.5 g, 0.1 mol) in DMSO (130 ml) was stirred at 60°C for 3 h. Water (50 ml) was added to the reaction mixture, and the mixture was extracted with dichloromethane (3 × 50 ml). The extract was washed repeatedly with small quantities of ice water, and dried with $MgSO_4$. After removing the solvent, azide **9** (16 g) was obtained as a white crystalline substance.

4-(2-Aminoethyl)-3,5-dimethylpyrazole Dihydrochloride (5). A. Hydrazine hydrate (0.18 ml, 3.74 mmol) was added to phthalimidopyrazole **3** (1.01 g, 3.74 mmol) in ethanol (10 ml), and the mixture stirred while boiling for 2.5 h (after 15 min a white solid began to precipitate). The reaction mixture was then cooled, the precipitated solid filtered off, and washed with cold ethanol (10 ml). Conc. HCl (about 0.3 ml) was added to the ethanolic solution to give a strongly acid reaction, after which more white solid precipitated (for a more complete precipitation the reaction mixture was stored overnight in the refrigerator). The solid was filtered off, washed with a small quantity of cold ethanol, and dried in vacuum to constant weight. Amine dihydrochloride **5** (4.9 g, 62%) was obtained.

B. A solution of Ph_3P (2.62 g, 10 mmol) in THF (20 ml) was added to a solution of azide **9** (1.65 g, 10 mmol) in THF (20 ml) (the reaction was accompanied by the evolution of nitrogen). After 10 min water (3.6 ml) was added to the reaction mixture, which was then stirred for 15 h until evolution of nitrogen had completely finished. The reaction mixture was concentrated and the product extracted with 10% HCl solution (2 × 80 ml). The extract was then washed with dichloromethane (2 × 50 ml) and concentrated under reduced pressure. The residue was dried in vacuum and amine dihydrochloride **5** (2 g) was obtained.

C. A mixture of iodide **7** (2 g, 8 mmol) in 20% aqueous ammonia (10 ml) was heated for 15 h at 60°C in a sealed ampule. The reaction mixture was concentrated in vacuum, the residue treated with NaOH solution (0.96 g, 24 mmol in 2.4 ml water), and then extracted with chloroform (3 × 10 ml). For the best extraction it was salted out with potassium carbonate. The desired amine **5** (0.9 g) was obtained as a colorless oil, which crystallized after distillation. Treatment of the obtained amine **5** with a threefold excess of hydrochloric acid gave the dihydrochloride salt **5**.

3,5-Dimethyl-4-(2-methylaminoethyl)pyrazole (10). A mixture of iodide **7** (7.5 g, 30 mmol) in 25% aqueous methylamine solution (10 ml) was heated at 60°C for 15 h in a sealed ampule. The reaction mixture was concentrated in vacuum, the residue treated with NaOH solution (3.6 g, 90 mmol in 9 ml water), and then

extracted with chloroform (3 × 10 ml). For the best extraction it was salted out with potassium carbonate. The desired amine **10** (3.76 g) was obtained as a yellowish oil, which crystallized on distillation.

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