INTERACTION OF 1-VINYLPYRAZOLES WITH ALKANETHIOLS

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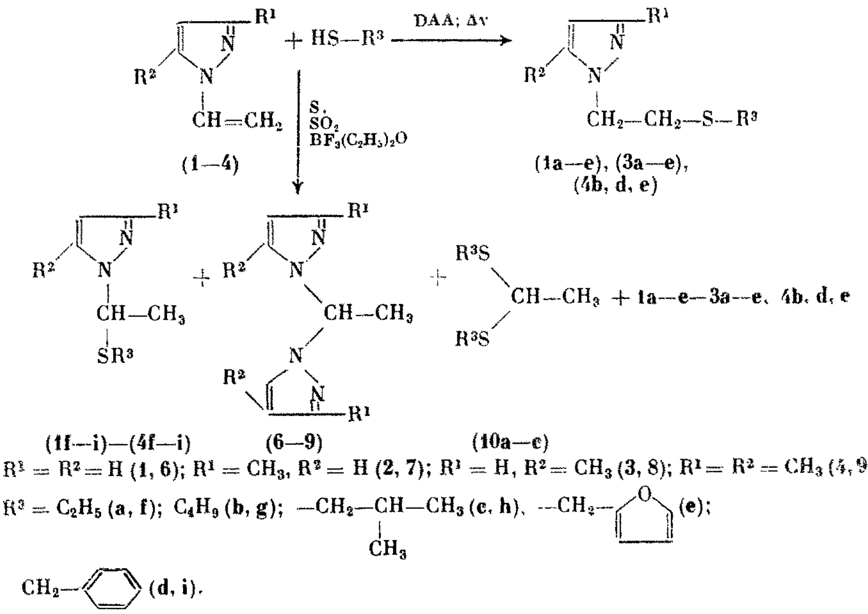
It was found that vinylpyrazoles react with thiols both according to ionic and according to free-radical mechanisms, with the formation of products of α- and β-addition. Radical thiylation of 1-vinylpyrazoles is a convenient method of synthesis of pyrazoles with sulfur-containing substituents.

Keywords: *vinylpyrazoles, vinylimidazole, alkanethiols, α-, β-addition, free-radical, ionic initiation, photoinitiation, disproportionation.*

Derivatives of nitrogen-containing heterocycles containing sulfur atoms exhibit biological activity and are used as drugs [1-4]. One accessible and convenient method of fabricating sulfur-containing compounds containing a heterocyclic fragment is addition of thiols to vinylic derivatives of indoles, imidazoles [5], and pyrroles [6], which can be conducted against or according to the Markovnikov rule (β- and α-addition).

We investigated the reaction of 1-vinylpyrazole (**1**) and its alkyl-substituted derivatives 1-vinyl-3-methylpyrazole (**2**), 1-vinyl-5-methylpyrazole (**3**), and 1-vinyl-3,5-dimethylpyrazole (**4**) with alkanethiols to synthesize sulfur-containing pyrazoles and to determine the direction of the reaction in different catalytic and temperature conditions in comparison to the previously investigated closest analog, 1-vinylimidazole (**5**) [5]. Ethane- (**a**), 1-butane- (**b**), 2-methyl-1-propane- (**c**), phenylmethane- (**d**), and 2-furylmethane- (**e**) thiols were used in the reaction. It was found that 1-vinylpyrazoles can react with thiols both according to ionic and according to free-radical mechanisms.



(1—4)

(1a—e), (3a—e), (4b, d, e)

(1f—i)—(4f—i) (6—9) (10a—c)

R¹ = R² = H (**1, 6**); R¹ = CH₃, R² = H (**2, 7**); R¹ = H, R² = CH₃ (**3, 8**); R¹ = R² = CH₃ (**4, 9**).

R³ = C₂H₅ (**a, f**); C₄H₉ (**b, g**); —CH₂—CH(CH₃)—CH₃ (**c, h**), —CH₂— (**e**); CH₂— (**d, i**).

Regardless of the temperature (20-120°C) and use of an initiator (azobisisobutyronitrile — AIBN), the thiols react with 1-vinylpyrazoles forming products of β-addition — 1-(pyrazolyl-1)-2-(alkylthio)ethanes (**1a-e—3a-e, 4b, d, e**). The ease of radical addition of thiols to 1-vinylpyrazoles is a function of both the structure of both reactants and the conditions of the reaction, which takes place at ~20°C (Table 1). 1-Vinylpyrazole methyl derivatives **2-4** react more energetically than unsubstituted

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TABLE 1. Effect of the Reaction Conditions on the Yield of 1-(Pyrazolyl-1)-2-(alkylthio)ethanes

Compound	Synthesis conditions			Yield, %
	T, °C	time, min	AIBN, %	
	20–25	24 h		
	80	10–15		
1d				23
2d–4d				70–80
1b				8
2b–4b				20–30
4b	50	10		20
	70	10		49
	80	10	1	77
	80	30	1	85
2b, 3b	80	10	1	70–30
1b	80	60	1	85

TABLE 2. Characterization of the Compounds Synthesized

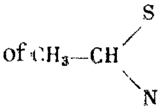
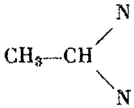
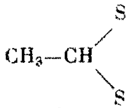
Compound	Bp, °C (p, mm Hg)	n_D^{20}	Found/Calculated, %				Empirical formula
			C	H	N	S	
1a	106(10)	1.5234	53,9 53.8	8.3 7.7	17.5 17.4	19.7 20.5	$C_7H_{12}N_2S$
2a	114(11)	1.5179	56.1 56.4	8.5 8.3	16.5 16.5	18.8 18.8	$C_8H_{14}N_2S$
3a	108–110(5)	1.5220	56.4 56.4	8.3 8.3	16.2 16.5	18.2 18.8	$C_8H_{14}N_2S$
1b	121(2)	1.5089	58.9 58.7	9.1 8.8	15.0 15.2	17.1 17.4	$C_9H_{16}N_2S$
2b	129–130(4)	1.5040	60.5 60.6	9.1 9.2	14.2 14.1	16.5 16.2	$C_{10}H_{18}N_2S$
3b	115(2)	1.5078	61.0 60.6	9.1 9.2	14.1 14.1	15.7 16.2	$C_{10}H_{18}N_2S$
4b	133–134(3)	1.5050	62.2 62.2	9.6 9.5	13.6 13.2	14.9 15.1	$C_{11}H_{20}N_2S$
2c	111–112(2)	1.5015	60.8 60.6	9.3 9.2	14.2 14.1	15.6 16.2	$C_{10}H_{16}N_2S$
3c	110–111(2)	1.5015	60.8 60.6	9.6 9.2	14.0 14.1	15.8 16.2	$C_{10}H_{18}N_2S$
4d	180(3)	1.5670	68.1 68.3	7.6 7.4	11.5 11.4	13.3 13.0	$C_{14}H_{18}N_2S$
1e	149–150(3)	1.5562	57.4 57.7	5.9 5.8	13.5 13.5	15.4 15.4	$C_{10}H_{12}N_2SO$
4e	168(3)	1.5451	60.2 61.0	6.9 6.8	11.9 11.9	13.3 13.6	$C_{12}H_{16}N_2SO$
4f	110–112(3)	1.5140	59.2 58.7	8.2 8.2	15.1 15.2	17.4 17.4	$C_9H_{16}N_2S$
2g	–	1.5070	60.0 60.6	9.1 9.2	14.2 14.1	16.0 16.2	$C_{10}H_{18}N_2S$
3g	–	–	60.0 60.6	8.8 9.2	13.7 14.1	15.5 16.2	$C_{10}H_{18}N_2S$
4g	105–106(2)	1.5025	62.1 62.2	9.3 9.5	13.3 13.2	14.9 15.1	$C_{11}H_{10}N_2S$
4h	–	1.5010	63.0 62.2	8.9 9.5	13.0 13.2	15.1 15.1	$C_{11}H_{10}N_2S$
4i	–	–	68.1 68.3	7.5 7.4	11.2 11.4	12.8 13.0	$C_{14}H_{18}N_2S$
10b	–	–	59.0 58.2	10.6 10.7	–	30.4 31.1	$C_{10}H_{22}S_2$
10c	–	–	57.7 58.2	10.0 10.7	–	31.1 31.1	$C_{10}H_{22}S_2$

1-vinylpyrazole 1. Increasing the temperature to 80°C and using AIBN (1%) reduces the time of the reaction of vinylpyrazoles with thiols to 0.5-2 h. The 1-(pyrazolyl-1)-2-(alkylthio)ethanes whose properties are reported in Table 2 were synthesized in these conditions with a yield of 80-85%.

It is reported in [5] that thiylation of 1-vinylimidazole **5** (70°C, AIBN, 1%) takes place after a relatively long time: 18 h. The reaction was conducted in conditions similar to those used in [7] for N-vinylpyrrolidone. It was found that 1-vinylimidazole, like 1-vinylpyrazole **1**, reacts with butylmercaptan at ~20°C, forming a product of β-addition (**5b**) with a yield of 9% and 45% after 24 and 72 h. At 80°C (AIBN, 1%), the yield of compound **5b** is 52% after 1 h.

The reaction of 1-vinylpyrazoles with thiols in conditions of photoinitiation has not been investigated previously. We showed for butanethiol that thiylation of vinylpyrazoles **1-4** and vinylimidazole **5** takes place energetically and is accompanied by an increase in the temperature to 80°C 5-10 min after irradiation begins (heating with a lamp by no more than 40-50°C after this time). The yield of products of β-addition **1b-5b** is 70-85% after 20-30 min.

Thiylation of 1-vinylpyrazoles in the presence of ionic initiators ($BF_3(C_2H_5)_2O$, SO_2, S) was conducted with heating. The reaction takes place in two competing directions with formation of products of both α- and β-addition, and the ratio is a function of the conditions used. The reaction mixture also contains 1,1-bis(pyrazolyl-1)ethanes (**6-9**) and 1,1-bis(R-thio)ethanes (**10**) obtained as a result of disproportionation of 1-(pyrazolyl-1)-1-(R-thio)ethanes (**1f-i**)-(**4f-i**). We isolated and characterized some products of α-addition **2g-4g**, **4f-i**, thioacetals (**10a-c**), and pyrazoles **6-9** (Table 2). The constants of pyrazoles **6-9** are in agreement with the constants of these compounds previously obtained in vinylation of pyrazoles [8]. Since the reaction mixtures were difficult to separate, some of them were analyzed by PMR.

In addition to the signals characterizing the pyrazole ring and the corresponding thiyl radical, R, all spectra contained "quartet–doublet" pairs in the 5.22-5.51 and 1.73-1.83 ppm region: 6.24-6.47 and 1.96-2.04 ppm; 3.85-4.11 and 1.53-1.55 ppm, indicating the presence of  $\mathrm{CH_3{-}CH}\genfrac{}{}{0pt}{}{\diagup S}{\diagdown N}$,  $\mathrm{CH_3{-}CH}\genfrac{}{}{0pt}{}{\diagup N}{\diagdown N}$,  $\mathrm{CH_3{-}CH}\genfrac{}{}{0pt}{}{\diagup S}{\diagdown S}$, groups belonging to products of α-addition **1f-i-4f-i** and the products of their disproportionation **6-9, 10**. The signals of the two triplets in the 3.94-4.19 and 2.78-2.90 ppm region correspond to $N-CH_2-CH_2-S$ fragments in pyrazoles **1a-e-3a-e** and **4b, d, e** (β-addition). It should be noted that the products of α-addition of thiols to 1-vinylimidazole are stable and did not disproportionate [5].

Thiylation in the presence of ionic initiators was studied in the most detail in vinylpyrazole **4** and 1-butanethiol **b**. It was found that in contrast to imidazole **5**, the process only occurs with the formation of the product of β-addition **4b** with *p*-toluenesulfonic acid (3%, 9%, 90°C, 8 h).

Elemental sulfur not only catalyzes addition of thiols to alkenes according to the Markovnikov rule, but is also an inhibitor of radical processes [9]. It was found that the total yield of products of thiylation of vinylpyrazole **4** (**4b** and **4g**) was no greater than 53% in the presence of 3, 9, and 15 mole % sulfur in heating for 14 h (90°C). When the reaction temperature was increased to 120°C, the yield of sulfides increased to 80-83%. The yield of products of the reaction for vinylpyrazoles **1-3** was 70-75% in similar conditions (120°C, 14 h, 9 mole %). The concentration of α- and β-products of addition in these conditions is 95:5-90:10. Increasing the amount of sulfur to 15% does not alter this ratio. When $BF_3(C_2H_5)_2O$ is used (9 mole %, 120°C, 14 h), competing β-addition predominates and the proportion of α-product **4g** is a total of 25%. Addition of radical process inhibitors to the reaction mixture — benzoquinone and hydroquinone (3-6%) — increases the concentration of α-products to 95-98% in all cases, but β-addition could not be completely suppressed (TLC monitoring).

The studies thus show that 1-vinylpyrazoles are convenient objects for synthesis of different compounds containing a pyrazole ring and sulfur atom. The method of radical thiylation is most rational, as it yields stable products, is easily and rapidly conducted not only with heating, catalysts, and irradiation with UV light, but also at 20°C without special initiation.

EXPERIMENTAL

The PMR spectra were recorded on a Tesla BS-497 spectrometer (100 MHz) in $CDCl_3$ solution. HMDS was the internal standard. Preparative GLC was conducted on a PAKhV-07 chromatograph, column 1 m long, 10 mm in diameter, 15% PFMS on Chesasorb (0.25-0.36 mm), 160°C. Brand 100/250 silica gel was used for the chromatographic columns, and benzene:chloroform:ethyl acetate (1:1:2) were used as the eluent for the compounds. The starting 1-vinylpyrazoles were prepared according to [8]. A DRT-230 lamp was the source of the UV radiation. The distance from the reaction flask (silica glass) was 6-7 cm.

Synthesis of 1-(Pyrazolyl-1)-2-(R-thio)ethanes (1a-e–3a-e, 4b, d, e). Equimolar amounts of vinylpyrazoles **1-4** and thiols **a-e** were held at ~20°C or heated in sealed ampuls at a defined temperature (50-120°C) with (1%) or without AIBN for 0.5-2 h. After the reaction ended, the product was immediately vacuum distilled, yielding the corresponding sulfide (Table 2).

Reaction of Vinylpyrazoles with Thiols in the Presence of Ionic Catalysts. A mixture of equimolar amounts of 1-vinylpyrazoles **1-4** and thiols **a-d** with a catalyst (S: 3, 9, 15 mole %; $BF_3(C_2H_5)_2O$: 9 mole %; SO_2: gas bubbled) with or without benzoquinone or hydroquinone (3-6%) was heated in a sealed ampul at 90 and 120°C for 8 and 14 h, respectively. The products formed were vacuum distilled. The unreacted vinylpyrazoles and thiols were collected in the first fraction and in a well-cooled trap. The corresponding 1,1-bis(pyrazolyl-1)ethanes **6** and **9** with mp = 58°C and 101°C (heptane) partially precipitated from the higher-boiling (80-180°C (2-4 mm)) fraction on standing in the case of vinylpyrazoles **1** and 4 [8]. After separation of the sediment, an oily liquid consisting of a mixture of products of α- and β-addition and products of disproportionation were separated into the individual compounds by GLC or in a column (Table 2).

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