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Features of Reactions of (*E*)-1-(β-Aroylvinyl)pyridinium Bromides with Binucleophiles

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Abstract—Regardless of pH and a solvent nature the reactions of (*E*)-1-(β-aroylvinyl)pyridinium bromides with hydrazine led to the formation of pyrazole derivatives. The salts reacted with thiourea via intermediate formation of 4-arylpyrimidine-2-thiol to give (*Z*)-2-[(β-aroylvinyl)sulfanyl]-4-arylpyrimidines. In the case of *N,N'*-diphenylthiourea the reaction provided 6-aryl-3-aroyl-1-phenylpyridinium bromides. Pyridine hydrobromide liberated in the reaction course has a major influence on the process chemoselectivity.

Keywords: (*E*)-1-(β-aroylvinyl)pyridinium bromide, pyrimidine thiol, elimination, addition

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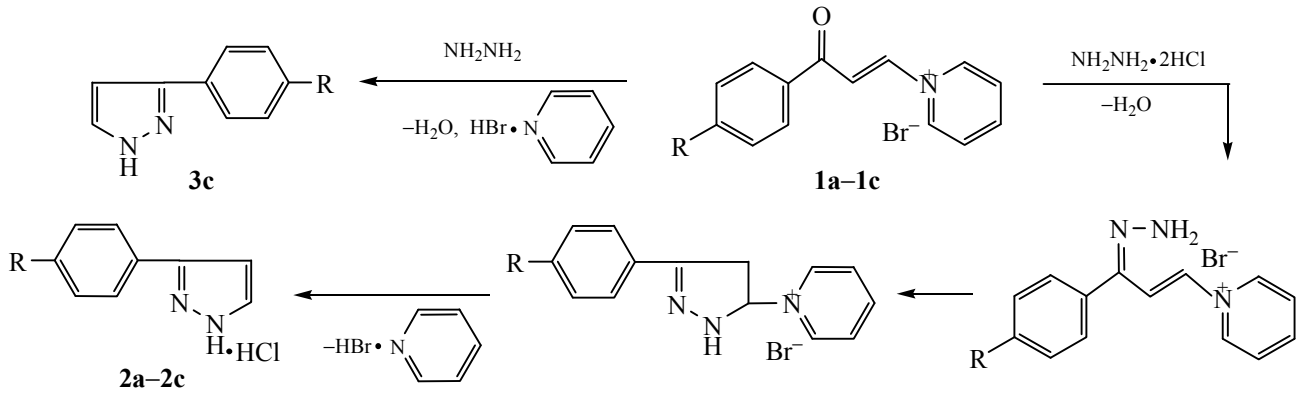
(*E*)-β-Aroylacrylic acids and (*E*)-1-(β-aroylvinyl)-pyridinium bromides **1a–1c** [1] have been known to react with hydroxylamine hydrochloride in different ways [2]. Data on reactions of (*E*)-1-(β-aroylvinyl)-pyridinium bromide **1a–1c** with binucleophiles are absent. In order to further functionalization of these salts and to obtain new heterocyclic compounds we studied their interaction with such binucleophiles as hydrazine and thioureas.

Depending on the pH value of the medium the reaction of β-aroylacrylic acids with hydrazine may proceed in a different manner. Thus, in alcohol or acetic acid the reaction led to the formation of adducts across the double bond, while in the presence of sulfuric or hydrochloric acid hydrazones or pyrazolinecarboxylic acid derivatives formed [3, 4].

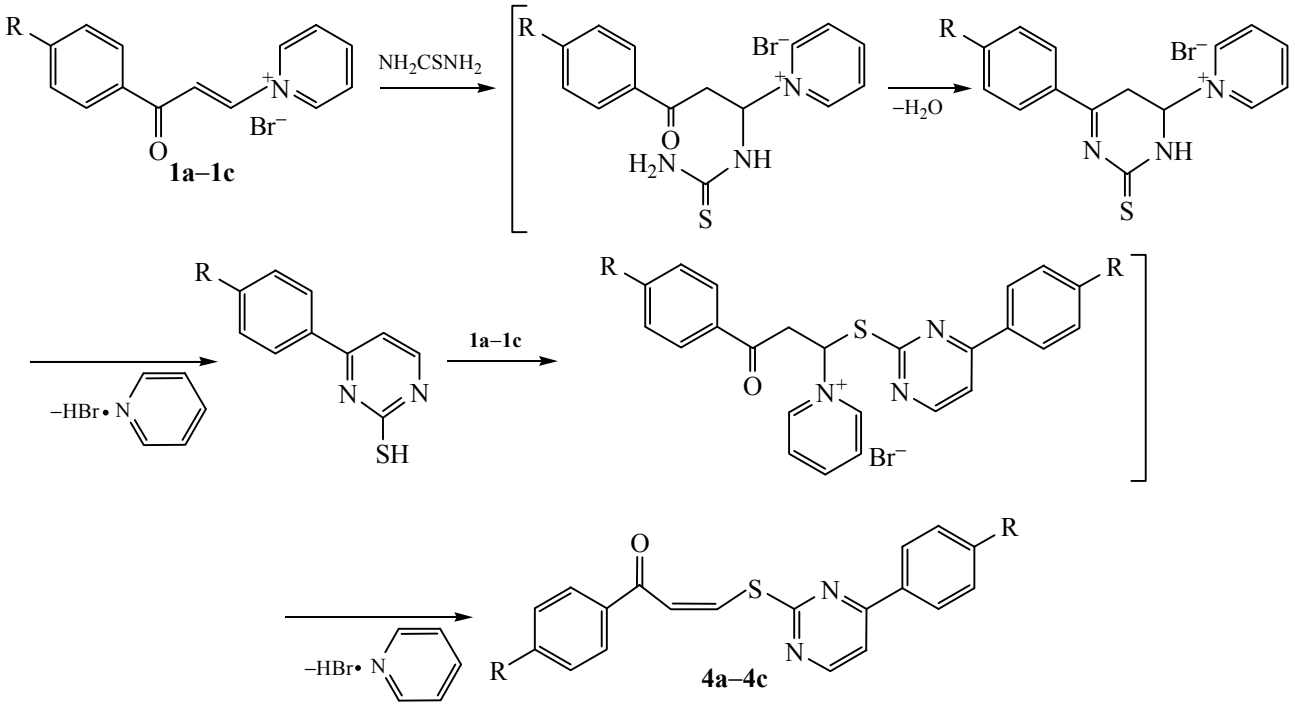
The reaction of (*E*)-1-(β-aroylvinyl)pyridinium bromides **1a–1c** with hydrazine hydrate and hydrochloride in aqueous acetonitrile or ethanol afforded pyrazole derivatives. In the case of hydrazine hydrochloride the corresponding hydrochlorides were obtained (Scheme 1).

Scheme 1.



R = CH_3 (**a**), Cl (**b**), Br (**c**).

Scheme 2.



R = CH_3 (**a**), Cl (**b**), Br (**c**).

The reaction probably occurs via initial condensation of compounds **1a**–**1c** with hydrazine involving the carbonyl group followed by intramolecular nucleophilic addition of NH_2 group across the double bond with the elimination of pyridine. However, an alternative reaction pathway including initial nucleophile attack on the double bond should not be excluded.

It has been found previously that depending on the reaction temperature and the nature of the solvent and the catalyst the reaction of (*E*)-β-aroylacrylic acids with thiourea may provide salts of β-aroylacrylic acids with thiourea, 2-iminothiazolidinone derivatives, thiohydantoins, thiazolidinediones, and *N*,*N*'-substituted thioureas [5–7].

A different pattern was observed when reacting (*E*)-1-(β-aroylvinyl)pyridinium bromides **1a**–**1c** with thiourea. According to ^1H and ^{13}C NMR data, in acetonitrile and toluene the reaction led to the formation of (*Z*)-4-aryl-2-[(β-aroylvinyl)sulfanyl]pyrimidines **4a**–**4c** instead of the expected 1-hydro-2-sulfanylpyrimidine derivatives (Scheme 2).

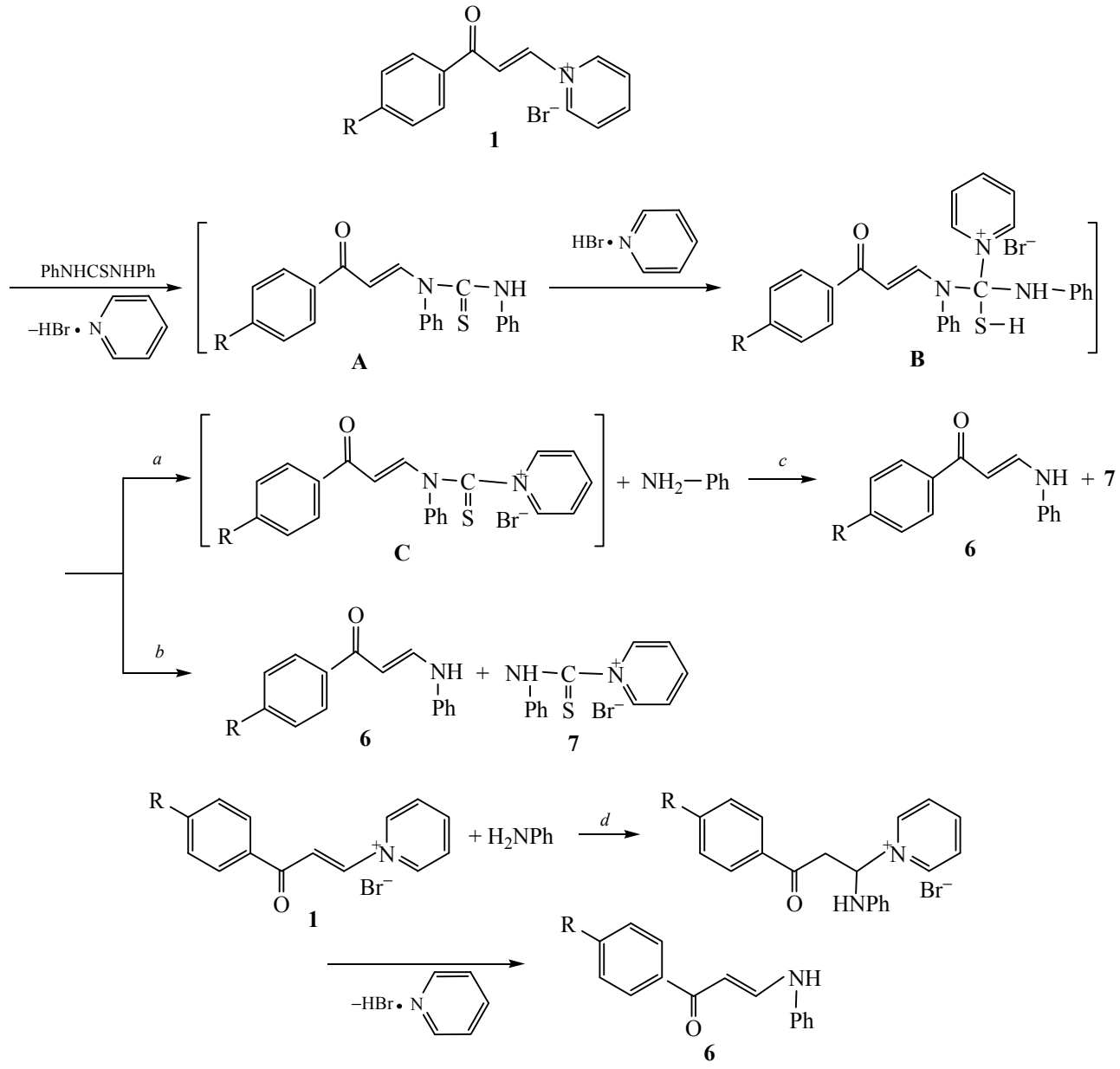
The reaction presumably starts with the attack of amino group at the double bond of salt **1**, and then condensation happens with the second amino group and subsequent cleavage of pyridine. Prototropic isomerization leads to the formation of the intermediate sulfanylpyrimidine, which adds the second molecule of the original salt followed by elimination of pyridine hydrobromide.

The reactions of *N*,*N*'-diphenylthiourea with the salts **1a**–**1c** resulted in the formation of 2-aryl-5-aroyl-1-phenylpyridinium bromides **5a**–**5c**, as well as enamine ketones **6a**–**6c** and 1-(phenylcarbamothioyl)-pyridinium bromide **7** as the minor reaction products (Scheme 3).

Most likely, the attack of *N*,*N*'-diphenylthiourea takes place only at the double bond of the original salt **1**, and the nitrogen atom is a nucleophilic site. Subsequent cleavage of pyridine hydrobromide results in the formation of intermediate **A**, which transforms into compound **B** by attaching pyridine hydrobromide at the C=S bond. Under the reaction conditions the intermediate **B** eliminates aniline to form compound **C** (pathway *a*) or is converted into enaminoketone **6** and 1-(phenylcarbamothioyl)pyridinium bromide **7** (pathway *b*).

Aminolysis of the intermediate **C** with aniline (pathway *c*) and reacting the liberated aniline with the

Scheme 3.



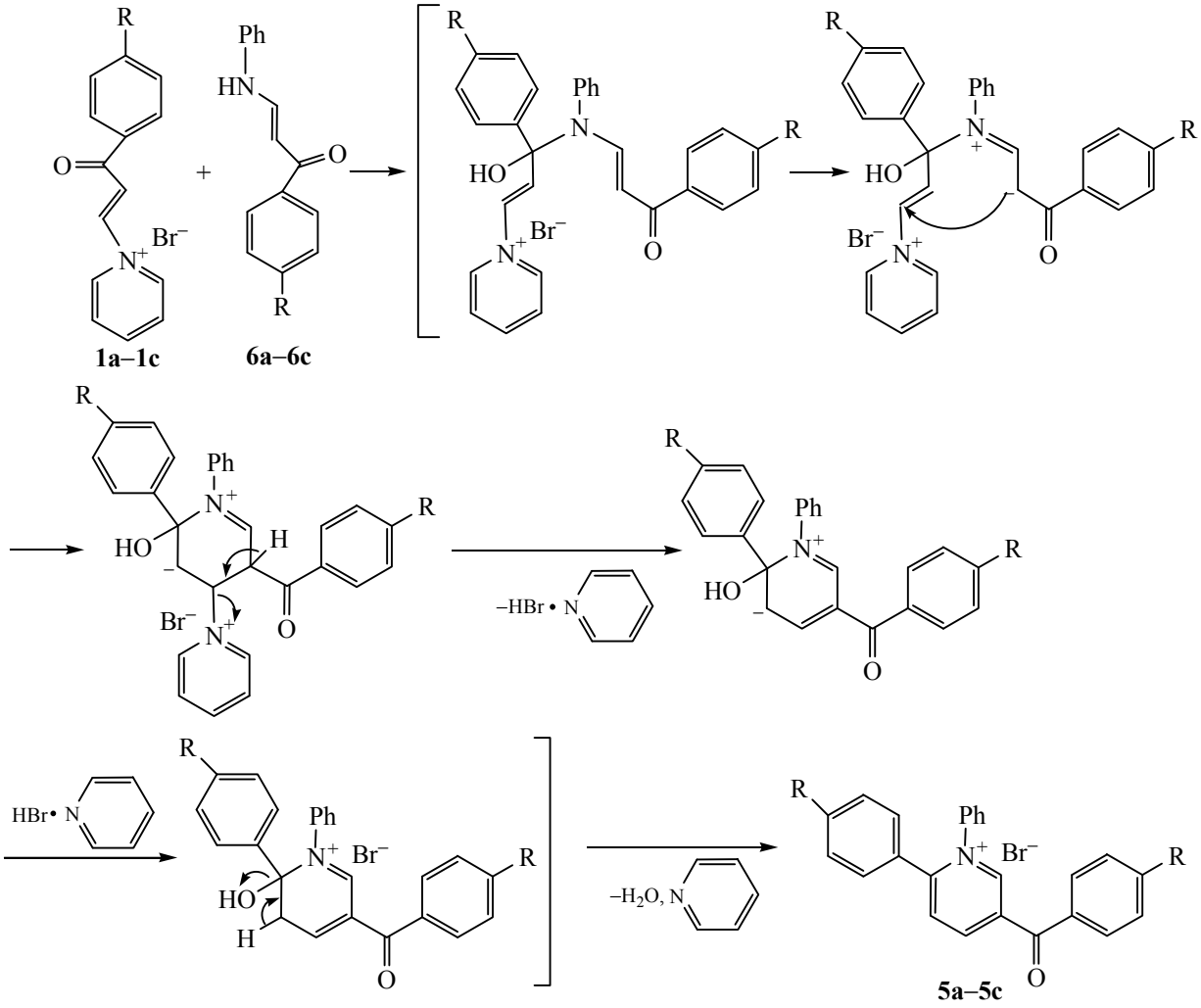
initial salts **1a**–**1c** (pathway *d*) may also provide compounds **6a**–**6c**.

The data obtained confirmed clearly that the formation of 2-aryl-5-aroyl-1-phenylpyridinium bromides results from the reaction of β-aroylvinylanilines **6a**–**6c** with the original salts **1a**–**1c**.

As can be seen from the scheme below, compounds **6a**–**6c** do react across the double bond, but at the carbonyl group of the starting salts **1a**–**1c**. Probably, the intermediate enamines undergo rearrangement into imines. Next, betaine intermediate carbanion attacks electrophilic carbon atom in the α-position relative to the pyridinium cation, followed by eliminating pyridinium bromide. Subsequent dehydration results in the formation of salts **5a**–**5c** (Scheme 4).

Aniline and compounds **6a**–**6c** reacted with the salts **1a**–**1c** under the same conditions in a ratio of 2 : 1 and 1 : 1, respectively, that supported the proposed reaction pathway.

Scheme 4.



R = CH_3 (**a**), Cl (**b**), Br (**c**).

Table 1. Yields, melting points and elemental analysis data of compounds **2**–**6**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N (Br)
2a	69	168–169	61.72	5.60	14.38	$C_{10}H_{11}ClN_2$	61.69	5.65	14.39
2b	73	202–203	50.19	3.77	13.08	$C_9H_8Cl_2N_2$	50.23	3.72	13.02
2c	75	170–171	41.65	2.98	10.73	$C_9H_8BrClN_2$	41.61	3.08	10.78
4a	89	199–200	72.78	5.24	8.13	$C_{21}H_{18}N_2OS$	72.83	5.20	8.09
4b	90	224–225	58.86	3.14	7.22	$C_{19}H_{12}N_2Cl_2OS$	58.91	3.10	7.23
4c	94	226–227	47.91	2.50	5.84	$C_{19}H_{12}N_2Br_2OS$	47.89	2.52	5.88
5a	41 (*a*), 90 (*b*), 89 (*c*)	254–255	70.25	4.89 (18.00)	3.18	$C_{26}H_{22}NOBr$	70.27	4.95	3.15 (18.02)
5b	43 (*a*)	220–221	61.39	3.47 (17.02)	2.95	$C_{24}H_{16}NOBrCl_2$	61.41	3.41	2.99 (17.06)
5c	46 (*a*), 86 (*b*), 91 (*c*)	230–231	49.97	2.66 (41.85)	2.41	$C_{24}H_{16}NOBr_3$	50.17	2.79	2.44 (41.81)
6a	17		81.05	6.30	4.96	$C_{16}H_{15}NO$	81.01	6.33	5.91
6b	11.5		69.79	4.71	5.38	$C_{15}H_{12}NOCl$	69.90	4.66	5.44
6c	7		58.98	4.01	4.56	$C_{15}H_{12}NOBr$	59.60	3.97	4.64

Table 2. NMR spectral data (DMSO-d_6–CCl_4, 1 : 3) for compounds **2**–**6**

Comp no.	δ, ppm (*J*, Hz)
2a	δ_H: 6.60 d (1H, H^4, pyrazole, *J* = 2.2), 7.18–7.22 m (2H, C_6H_4), 6.62–7.75 m (1H, H^5, pyrazole; 2H, C_6H_4), 9.00 br. S (2H, $H^{1,2}$, pyrazole)
2b	δ_H: 6.60 d (1H, H^4, pyrazole, *J* = 2.2), 7.33–7.38 m (2H, C_6H_4), 7.63 d (1H, H^5, pyrazole, *J* = 2.2), 7.74–.79 m (2H, C_6H_4), 8.68 br.s (2H, $H^{1,2}$, pyrazole)
2c	δ_H: 6.63 d (1H, H^4, pyrazole, *J* = 2.2), 7.50–7.55 m (2H, C_6H_4), 7.64 d (1H, H^5, pyrazole, *J* = 2.2), 7.78–7.80 m (2H, C_6H_4), 9.20 br.s (2H, $H^{1,2}$, pyrazole)
4a	δ_H: 2.45 s (3H, CH_3), 2.46 s (3H, CH_3), 7.28–7.35 m (4H, C_6H_4), 7.42 d (1H, SCH=CH, *J* = 10.0), 7.72 d (1H, CH=CHN, *J* = 5.3), 7.88–7.95 m (2H, C_6H_4), 8.07–8.13 m (2H, C_6H_4), 8.70 d (1H, CH=CHN, *J* = 5.3), 8.86 d (1H, SCH=CH, *J* = 10.0) δ_C: 20.9 (CH_3), 21.0 (CH_3), 113.2 (CH=CHN), 116.8 (SCH=CH), 126.8, 127.8, 128.8, 129.1, 132.5, 134.6, 141.0, 142.4, 142.5 (SCH=CH), 157.7 (CH=CHN), 163.4 168.4, 187.2 (CO).
4b	δ_H: 7.59–7.65 m (5H, C_6H_4 + pyrimidine), 7.98 d (1H, CH=CHN, *J* = 5.3), 7.08–8.12 m (2H, C_6H_4), 8.26–8.31 m (2H, C_6H_4), 8.85 d (1H, CH=CHN, *J* = 5.3), 8.90 d (1H, SCH, *J* = 9.9)
4c	δ_H: 7.53 d (1H, SCH=CH, *J* = 10.0), 7.68–7.74 m (4H, C_6H_4), 7.91 d (1H, CH=CHN, *J* = 5.3), 7.97–8.02 m (2H, C_6H_4), 8.17–8.22 m (2H, C_6H_4), 8.80 d (1H, CH=CHN, *J* = 5.3), 8.90 d (1H, SCH=CH, *J* = 10.0)
5a	δ_H: 2.36 s (3H, CH_3), 2.50 s (3H, CH_3), 7.15–7.20 m (2H, C_6H_4), 7.37–7.50 m (7H, C_6H_5 + C_6H_4), 7.76–7.80 m (2H, C_6H_4), 8.02–8.06 m (2H, C_6H_4), 8.39 d (1H, $C_5H_3N^+$, *J* = 8.2), 8.95 d.d (1H, $C_5H_3N^+$, *J* = 8.2, 1.8), 9.19 d (1H, $C_5H_3N^+$, *J* = 1.8) δ_C: 20.8 (CH_3), 21.2 (CH_3), 126.6, 128.6, 128.7, 128.8, 129.2, 129.7, 130.0, 130.3, 130.5, 132.3, 135.3, 140.4, 141.9, 144.5, 145.3, 146.9 (NCH), 156.9, 189.2 (CO)
5b	δ_H: 7.37–7.42 m (2H, C_6H_4), 7.48–7.55 m (3H, C_6H_5), 7.65–7.70 m (4H, C_6H_5 + C_6H_4), 7.88–7.99 m (4H, ClC_6H_4CO), 8.52 d (1H, $C_5H_3N^+$, *J* = 8.2), 9.09 d.d (1H, $C_5H_3N^+$, *J* = 8.2, 1.7), 9.60 d (1H, $C_5H_3N^+$, *J* = 1.7)
5c	δ_H: 7.35–7.40 m (2H, C_6H_4), 7.48–7.55 m (3H, C_6H_5), 7.61–7.65 m (2H, C_6H_5), 7.65–7.70 m (2H, C_6H_4), 7.87–7.95 m (4H, BrC_6H_4CO), 8.51 d (1H, $C_5H_3N^+$, *J* = 8.2), 9.07 d.d (1H, $C_5H_3N^+$, *J* = 8.2, 1.8), 9.56 d (1H, $C_5H_3N^+$, *J* = 1.8)
6a (*Z* : *E* = 3 : 1)	δ_H: 2.2 s (3H, CH_3), 6.02 d (0.75H, =CHCO, *J* = 7.8), 6.37 d (0.25H, =CHCO, *J* = 12.5), 6.92 br.t (0.25H, Ph, *J* = 7.3), 7.02 br.t (0.75H, Ph, *J* = 7.3), 7.05–7.11 m (0.5H, Ar), 7.18–7.38 m (5.5H, Ar), 7.68 d.d (0.75H, =CHN, *J* = 12.1, 8.0), 7.76–7.79 m (0.5H, Ar), 7.80–7.83 m (1.5H, Ar), 8.03 d.d (0.25H =CHN, *J* = 12.9, 12.5), 9.80 br.d (0.25H, NH, *J* = 12.9), 12.10 br.d (0.75H, NH, *J* = 12.1)
6b (*Z* : *E* = 7 : 3)	δ_H: 6.10 d (0.7H, =CHCO, *J* = 7.8), 6.40 d (0.3H, =CHCO, *J* = 12.4), 7.04 br.t (0.3H, 4-H, Ph, *J* = 7.5), 7.12 br.t (0.7H, 4-H, Ph, *J* = 7.5), 7.18–7.20 m (0.6H, Ar), 7.27–7.40 m (3.4H, Ar), 7.56–7.60 m (2H, Ar), 7.81–7.85 d.d (0.7H, =CHN, *J* = 12.5, 7.8), 7.84–7.87 m (0.6H, Ar), 7.87–8.00 m (1.4H, Ar), 8.13 d.d (0.3H, =CHN, *J* = 13.1, 12.4), 10.20 br.d (0.3H, NH, *J* = 13.1), 12.10 br.d (0.7H, NH, *J* = 12.4)
6c (*Z* : *E* = 7 : 3)	δ_H: 6.02 d (0.7H, =CHCO, *J* = 7.8), 6.34 d (0.3H, =CHCO, *J* = 12.4), 6.95 br.t (0.3H, 4-H, Ph, *J* = 7.3), 7.04 br.t (0.7H, 4-H, Ph, *J* = 7.3), 7.09–7.14 m (0.6H, Ar), 7.19–7.37 m (3.4H, Ar), 7.55–7.60 m (2H, Ar), 7.76 d.d (0.7H, =CHN, *J* = 12.4, 7.8), 7.77–7.81 m (0.6H, Ar), 7.81–7.86 m (1.4H, Ar), 8.11 d.d (0.3H, =CHN, *J* = 13.1, 12.4), 9.92 br.d (0.3H, NH, *J* = 13.1), 12.14 br.d (0.7H, NH, *J* = 12.4)

Structure of compounds obtained was established by ^1H and ^{13}C NMR spectroscopy methods (Tables 1 and 2). Two-dimensional NOESY and HMQC techniques were used for assigning signals.

Structure of compound **5a** was confirmed by X-ray diffraction analysis (see figure). As show XRD data the unit cell contains two symmetrically nonequivalent molecules whose position with respect to each other is characterized by an inversion pseudocenter (0.97 0.62 0.24), which is an apparent cause of twinning. All cyclic fragments of compound **5a** are planar. The maximum deviation of the atoms from the average plane of the benzene ring does not exceed 0.0092(2) (Ph), 0.0051(3) (*p*-Tol), 0.0252(3) (Py) and 0.0210(2) Å [4-$CH_3C(O)Ph$].

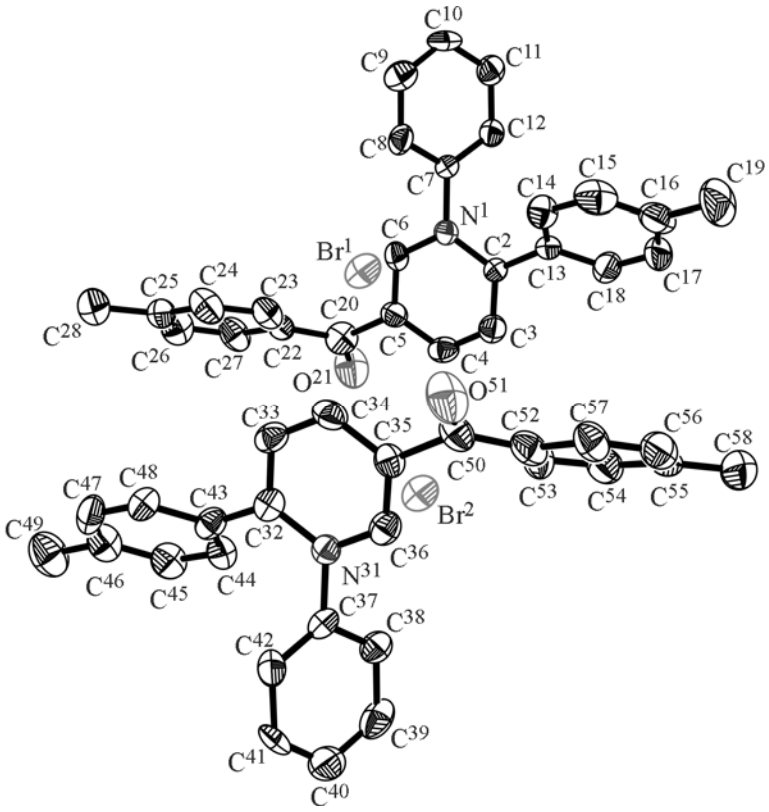


Fig. 1. General view of the molecule of compound **5a** in the crystal.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300 spectrometer (75.46 and 300.08 MHz, respectively) at 303 K. Chemical shifts are with respect to TMS signal.

Single-crystal X-ray diffraction measurements were performed at room temperature on an automatic diffractometer CAD-4 Enraf-Nonius (graphite monochromator, MoK_α-radiation, θ/2θ-scanning). Parameters of the monoclinic unit cell measured and refined by 24 reflections in a scanning range of $11.07 < \theta < 12.20$ were as follows: a = 7.2250(14), b = 13.697(3), c = 22.058(4) Å, β = 99.11(3)°, V = 2155.3(8) Å^3, space group *Pn*, Z 4, crystal size 0.35 × 0.30 × 0.22 mm. 6727 independent reflections were measured in the range of $0 \le h \le 10$, $0 \le k \le 19$, $0 \le l \le 30$, $\theta_{max} = 30°$. An array of experimental data contained 6727 symmetrically nonequivalent reflections, 3671 of them with $I > 2\sigma(I)$. Absorption was accounted by ψ-scanning method [T_{min} = 0.28996, T_{max} = 0.33174, μ(MoK_α) = 1.924 mm^{-1}] [8]. The structure was solved by the direct method and refined as a inversion twin (the ratio of volumes of the twin components of ~ 2 : 15). The coordinates of the hydrogen atoms were determined by geometric calculations and refined in a *rider* model, C–H = 0.93–0.96 Å, U_{iso}(H) = 1.2–1.5U_{eq}(C). The structure was refined by full-matrix least-squares method in anisotropic approximation for nonhydrogen atoms and in isotropic approximation for hydrogen atoms; the final divergence factors: R = 0.0708, wR^2 = 0.1789, S = 1.02. All calculations were performed using SHELXTL software [9]. The crystallographic data were deposited at the Cambridge Crystallographic Data Centre (CCDC 1,416,811).

(*E*)-1-(β-Aroylvinyl)pyridinium bromides **1a**–**1c** were synthesized as described in [1].

3-Aryl-1*H*-pyrazoles hydrochlorides (2a–2c). A solution of 0.95 g (0.009 mol) of hydrazine hydrochloride in a minimum amount of water was added to a saturated solution of 0.0015 mol of the salt **1a**–**1c** in acetonitrile (or ethanol). The reaction mixture was refluxed for 30 h, then cooled and poured into 200 mL of water. The reaction product was extracted with chloroform and reprecipitated with diethyl ether. The precipitate was filtered off, washed with ether, and dried in a vacuum.

3-(4-Bromophenyl)-1*H*-pyrazole (3c). A mixture of 0.55 g (0.0015 mol) of 1-[(*E*)-3-(4-bromophenyl)-3-oxoprop-1-en-1-yl]pyridinium bromide **1c** in acetonitrile and 0.44 mL (0.009 mol) of 65% hydrazine hydrate was refluxed for 8 h. The reaction mixture was poured into 100 mL of water, and the reaction product was extracted with chloroform. After removing the solvent, the residue was recrystallized from acetonitrile and dried in a vacuum. Yield 0.26 g (73%), mp 135°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ, ppm: 6.52 br.s (1H, H^4, pyrazole), 7.42–7.60 m (3H, C_6H_4 + H^5, pyrazole), 7.63–7.74 m (2H, C_6H_4), 12.74 br.s (0.75H, NH), 13.14 br.s (0.25H, NH). Found N, %: 12.60. $C_9H_7BrN_2$. Calculated N, %: 12.56.

(*Z*)-1-Aryl-3-[(4-arylpyrimidin-2-yl)sulfanyl] prop-2-en-1-ones (4a–4c). A mixture of 0.0015 mol of salt **1a–1c**, 0.1 g (0.0015 mol) of thiourea in 10 mL of acetonitrile was heated for 17–20 h. The resulting precipitate was filtered off, repeatedly washed with hot acetonitrile, and dried in a vacuum.

2-Aryl-5-aroyl-1-phenylpyridine bromides (5a–5c). *a*. A mixture of 0.001 mol of salt **1a–1c**, 0.23 g (0.001 mol) of *N*,*N*'-diphenylthiourea, and 10–12 mL of acetonitrile was refluxed for 17–20 h. After cooling, the reaction mixture was filtered. The reaction product was precipitated with diethyl ether from the filtrate. The precipitate was filtered off, washed with diethyl ether, and dried in a vacuum. The precipitate obtained was additionally refluxed in benzene, filtered off, washed thoroughly with hot benzene, and dried in a vacuum.

Acetonitrile filtrate was evaporated, the residue was recrystallized from acetonitrile to yield compound **6a–6c** as a mixture of *Z*,*E*-isomers in the ratio of 3 : 1, 7 : 3, and 7 : 3, respectively.

After recrystallization of compound **6a–6c**, the acetonitrile filtrate was evaporated. The residue was dissolved in chloroform and reprecipitated with hexane to give 0.05 g (17%) of 1-(phenylcarbamothioyl)pyridinium bromide **7** of mp 89–90°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1 : 3), δ, ppm: 9.80 br.s (1H, NH), 7.62–8.00 m (10H, Ph, Py). Found, %: C 48.89; H, 3.51; N 9.48; Br 27.34. $C_{12}H_{10}BrN_2S$. Calculated, %: C 48.98; H 3.40; N 9.52; Br 27.21.

b. A mixture of 0.001 mol of the salt **1a** or **1c**, 0.05 mL (0.0005 mol) of aniline, and 12.10 mL of acetonitrile was refluxed for 15–17 h. Compounds **5a** and **5b** were isolated as described above.

c. A mixture of 0.0005 mol of the salt **1a** or **1c**, 0.0005 mol of compound **6a** or **6b**, and 7.5 mL of acetonitrile was refluxed for 14–15 h. The product was isolated as described above.

β-Aroylvinylanilines (6a–6c). A mixture of 0.001 mol of salt **1a** or **1c**, 0.037 mL (0.004 mol) of aniline and 0.2 mL (0.0001 mol) of 41% HBr solution in 5–7 mL of ethanol was refluxed for 2–3 h. The resulting precipitate was filtered off, washed with alcohol, dried in a vacuum, and recrystallized from acetonitrile.

REFERENCES

1. Khachikian, R.Dzh., Ovakimyan, Z.G., Panosyan, G.A., and Indzikyan, M.G., *Russ. J. Gen. Chem*., 2014, vol. 84, no. 3, p. 511. DOI: 10.1134/S1070363214030177.
2. Khachikian, R.Dzh., Ovakimyan, Z.G., Panosyan, G.A., Tamazyan, R.A., and Ayvazyan, A.G., *Russ. J. Gen. Chem*., 2015, vol. 85, no. 5, p. 1078. DOI: 10.1134/S1070363215050138.
3. Bougault, J. and Chabrier, P., *Compt. Rend. Chim*., 1949, vol. 228, p. 1952.
4. El'Kadi, M., El'Hashash, M.A., and Sayed, M.A., *Rev. Roum. Chem*., 1981, vol. 26, no. 8, p. 1161.
5. Abgalyan, S.G. and Khachikian, R.Dzh., *Arm. Khim. Zh.*, 1981, vol. 34, no. 7, p. 569.
6. Khachikian, R.Dzh., Atashyan, S.M., and Agbalyan, S.G., *Arm. Khim. Zh.*, 1984, vol. 37, no. 4, p. 237.
8. North, A.C.T., Phillips, D.C., and Mathews, F. S., *Acta Crystallogr. (A)*,1968, vol. 24, p. 351. DOI: 10.1107/S0567739468000707.
9. Sheldrick, G.M., *Acta Crystallogr. (A)*, 2008, vol. 64, p. 112. DOI: 10.1107/S0108767307043930.