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Synthesis, Structure and Chemical Transformations of 4-Aminobenzaldehyde

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Abstract—A possibility of nucleophilic substitution of the fluorine atom in 4-fluorobenzaldehyde with amines (morpholine, piperidine or cytisine) under convection heating and microwave irradiation was shown. Reactions of 4-morpholinyl- and 4-piperidinylbenzaldehyde with hydrazides of isonicotinic and salicylic acids afford the corresponding hydrazones. The structure of the synthesized compounds was confirmed by IR, ^{1}H NMR spectroscopy, mass spectrometry, and X-ray analysis data.

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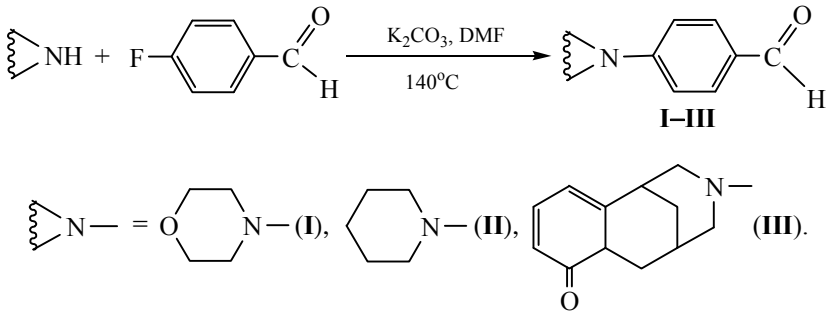
It is known that aldehydes are important synthons for the synthesis of various classes of organic compounds including heterocycles [1–3]. According to [4], amino-substituted aromatic aldehydes can be obtained by reacting the corresponding amines (morpholine, piperidine) and *o*-fluorobenzaldehydes under reflux in DMF in the presence of potassium carbonate. Synthesized amino-substituted aromatic aldehydes are used further for the synthesis of important heterocyclic quinolines spiro derivatives. These reactions with halogenated aldehydes are interesting because the lone pair of the fluorine atom is ρ,π-conjugated with the double bond or with a π-electronic system of the ring. It should also be noted that in the nucleophilic substitution of alkyl halides the iodide and bromide ions are better leaving groups, and the fluoride ions are the most difficult leaving groups. In the S_NAr reactions an opposite sequence is often observed: fluorine-derived substrates react with higher rate (if the ring contains the electron-acceptor substituents in the *ortho*- and *para*-positions). These features of the electronic structure of fluorobenzaldehydes are of particular scientific interest. In this regard, we were interested in the synthesis of aromatic aldehydes containing a biologically active amino moiety in the *para*-position of the aromatic ring.

By analogy with the method described in [4], we performed the substitution of the fluorine atom in 4-fluorobenzaldehyde by the amino moiety (morpholine, piperidine or cytisine). We found that the heterocyclic amines react with 4-fluorobenzaldehyde under reflux in DMF in the presence of potassium carbonate within 20 h to give 4-aminobenzaldehydes **I**–**III**. The reaction probably occurs by an addition-elimination mechanism.

Synthesis of 4-aminobenzaldehydes is a long process (over 20 h). Furthermore, yields of the reaction depend on the structure of amines.

Use of microwave activation is known to significantly reduce the reaction time: from several hours or days to few minutes. The reaction rate is increased 10–100 times. The use of microwave irradiation allows also performing many syntheses, which failed to occur in standard conditions, and also leads to a change in the reaction selectivity and direction [1, 3]. In order to intensify the process of the synthesis of aldehydes **I**–**III**, we studied the preparation of compound **I** under the microwave activation.



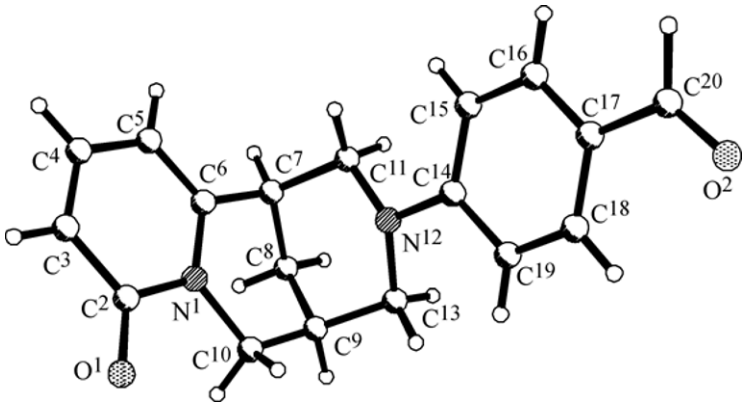
A special mode of syntheses under microwave irradiation includes the use of a solid support, i. e., a material, which is transparent in the microwave radiation region, but possesses catalytic properties. The elementary interaction acts occur on its surface [5–9]. For the reaction under study we used a specially prepared catalyst supported on a Silpearl silica gel, twice activated with potassium carbonate. For uniform distribution of potassium carbonate on silica gel, the latter was suspended into aqueous solution of K_2CO_3. Then water was evaporated, and the resulting dry residue was ground in a mortar and dried at 120°C.

Under microwave irradiation the synthesis of 4-(*N*-morpholyl)benzaldehyde **I** can be successfully carried out in 30 min in DMF using the above support. General procedure for the synthesis is given in the experimental part. Aldehyde **III** was prepared similarly.

In the ^{1}H NMR spectrum (DMSO-d_6, 500 MHz) of compound **I** the signals of methylene protons of morpholine fragment appear as two triplets at 3.36 and 3.72 ppm. Two doublets at 7.73 and 7.08 ppm correspond to *ortho*- and *meta*-protons of the phenyl moiety. Aldehyde proton is observed as a narrow singlet at 9.76 ppm.

In order to determine the spatial structure of the synthesized 4-aminobenzaldehydes **I**–**III** we performed X-ray diffraction analysis of 4-(*N*-cytisine)benzaldehyde **III**, a general view of whose molecule is shown in the figure.

The data obtained show that the bond lengths and angles in the structure of **III** are close to standard values, except for the bond angles at the atom N^{12} (Tables 1, 2) [1]. Sum of the bond angles at the trigonal planar atom N^{12} is 351.3°, which is caused by the conjugation of the unshared electron pair of the nitrogen atom with a π-system of the phenyl ring. Usually the coordination of this atom is close to pyramidal, such as in the molecule of *N*-methylcytisine [2] and *N*-cyanomethylcytisine [3]. Dihydropyridine ring in compound **III** is planar within the accuracy of ±0.005 Å, the atom O^1 is practically in the plane (the deviation is 0.021 Å). Tetrahydropyridine ring takes the conformation of near ideal *sofa* (ΔC_S^8 0.75°), the bridging atom C^8 is deviated from the mean plane of the remaining ring atoms by 0.758±0.006 Å. Piperidine ring has a distorted *chair* conformation (ΔC_S^8 3.9°) (torsion angles are shown in Table 3). Aldehyde group is in the plane of the phenyl ring (±0.01 Å), the torsion angle $C^{18}C^{19}C^{20}O^2$ is 0.6(5)°.



General view of the molecule of 4-(*N*-cytisinyl)benzaldehyde **III**.

Table 1. Bond lengths in the structure of **III**

Bond	*d*, Å	Bond	*d*, Å
O^1–C^2	1.245(4)	C^9–C^{13}	1.507(4)
O^2–C^{20}	1.214(4)	C^9–C^{10}	1.526(4)
N^1–C^6	1.379(3)	C^{11}–N^{12}	1.468(3)
N^1–C^2	1.398(4)	N^{12}–C^{14}	1.387(3)
N^1–C^{10}	1.474(4)	N^{12}–C^{13}	1.467(4)
C^2–C^3	1.425(5)	C^{14}–C^{15}	1.395(4)
C^3–C^4	1.350(5)	C^{14}–C^{19}	1.416(4)
C^4–C^5	1.388(4)	C^{15}–C^{16}	1.385(4)
C^5–C^6	1.345(4)	C^{16}–C^{17}	1.373(4)
C^6–C^7	1.501(4)	C^{17}–C^{18}	1.393(4)
C^7–C^8	1.514(4)	C^{17}–C^{20}	1.449(4)
C^7–C^{11}	1.523(4)	C^{18}–C^{19}	1.362(4)
C^8–C^9	1.507(4)		

The synthesized 4-aminobenzaldehydes **I**–**III** are reactive synthons for various chemical transformations, in particular, for condensation with hydrazides. Thus, reactions of the above aminoaldehydes **I**, **III** with hydrazides of isonicotinic and salicylic acids in alcoholic medium result in the corresponding hydrazones **IV**–**VII** in 74 and 82% yield, respectively.

Physicochemical characteristics and elemental analysis data of the synthesized aminoaldehydes **I**–**III** and hydrazones **IV**–**VII** are presented in Table 4.

Thus, we synthesized 4-aminobenzaldehydes and potentially bioactive hydrazones on their basis. A comparative study of the influence of convection and microwave heating on the yield of the target product was performed.

EXPERIMENTAL

The IR spectra were recorded on a NICOLET Avatar-320 Fourier transform spectrometer from KBr pellets. ^{1}H NMR spectra were registered on a Bruker DRX500 spectrometer (500 MHz, $CDCl_3$, DMSO-d_6), internal reference TMS. Melting points were measured on a Boetius instrument (measurement error ±0.1°C). TLC analysis was carried out on Silufol UV-254 and Sorbfil plates, detecting with iodine vapor.

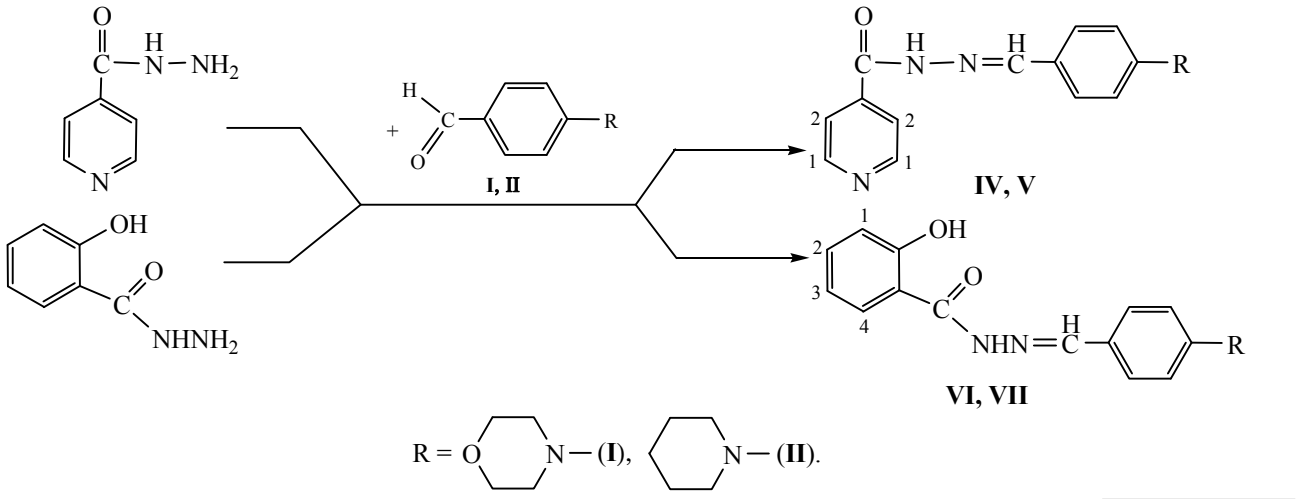
X-Ray diffraction analysis of compound III. Unit cell parameters and intensities of 2209 independent reflections were measured on a Xcalibur diffractometer (CuK_α, graphite monochromator, θ/2θ-scanning, $2\theta \leq 134°$). Crystals of **III** are rhombic; *a* 11.2684(6), *b* 11.511(4), *c* 11.815(3) Å, *V* 1471.5(8) Å^3, Z 4, $C_{18}H_{18}N_2O_2$; space group $P2_12_12_1$, d_{calc} 1.329 g cm^{-3}. The structure was solved by the direct method. The positions of the non-hydrogen atoms were refined by a full-matrix least-square method in an anisotropic approximation. Hydrogen atoms were placed into the geometrically calculated positions and included into the refinement in the *rider* model, except for the aldehyde hydrogen atom, which was revealed by the difference synthesis

Table 2. Bond angles in the structure of **III**

Angle	ω, deg	Angle	ω, deg
$C^6N^1C^2$	122.7(3)	$C^{13}C^9C^{10}$	111.9(3)
$C^6N^1C^{10}$	123.1(2)	$N^1C^{10}C^9$	114.5(2)
$C^2N^1C^{10}$	114.2(2)	$N^{12}C^{11}C^7$	112.2(2)
$O^1C^2N^1$	119.3(3)	$C^{14}N^{12}C^{13}$	119.0(2)
$O^1C^2C^3$	125.6(3)	$C^{14}N^{12}C^{11}$	118.6(2)
$N^1C^2C^3$	115.2(3)	$C^{13}N^{12}C^{11}$	113.7(2)
$C^4C^3C^2$	121.8(3)	$N^{12}C^{13}C^9$	112.1(2)
$C^3C^4C^5$	120.1(3)	$N^{12}C^{14}C^{15}$	122.0(3)
$C^6C^5C^4$	120.8(3)	$N^{12}C^{14}C^{19}$	120.8(2)
$C^5C^6N^1$	119.5(3)	$C^{15}C^{14}C^{19}$	117.1(3)
$C^5C^6C^7$	121.7(3)	$C^{16}C^{15}C^{14}$	120.4(3)
$N^1C^6C^7$	118.8(2)	$C^{17}C^{16}C^{15}$	122.3(3)
$C^6C^7C^8$	109.9(2)	$C^{16}C^{17}C^{18}$	117.3(3)
$C^6C^7C^{11}$	110.2(2)	$C^{16}C^{17}C^{20}$	121.8(3)
$C^8C^7C^{11}$	112.1(2)	$C^{18}C^{17}C^{20}$	120.9(3)
$C^9C^8C^7$	106.1(2)	$C^{19}C^{18}C^{17}$	121.9(3)
$C^8C^9C^{13}$	110.4(3)	$C^{18}C^{19}C^{14}$	120.9(3)
$C^8C^9C^{10}$	111.5(2)	$O^2C^{20}C^{17}$	125.1(3)

Table 3. Some intracyclic torsion angles in the structure of **III**

Angle	τ, deg	Angle	τ, deg
$C^{10}N^1C^6C^7$	–1.2(4)	$C^{11}C^7C^8C^9$	59.4(3)
$N^1C^6C^7C^8$	33.7(4)	$C^7C^8C^9C^{13}$	–61.6(3)
$C^6C^7C^8C^9$	–63.5(3)	$C^8C^9C^{13}N^{12}$	58.8(4)
$C^7C^8C^9C^{10}$	63.3(3)	$C^{11}N^{12}C^{13}C^9$	–50.9(3)
$C^8C^9C^{10}N^1$	–32.1(3)	$C^7C^{11}N^{12}C^{13}$	47.8(3)
$C^6N^1C^{10}C^9$	0.2(4)	$C^8C^7C^{11}N^{12}$	–53.3(3)



of the electron density and its coordinates were isotropically refined. In the calculations 1502 reflections with $I \geq 2\sigma(I)$ were used. The final divergence factors are R_1 0.0411, wR_2 0.0893. The structure was solved and refined using the program packages SHELXS- 97 [4] and SHELXL- 97 [5]. The coordinates of the atoms are deposited at the Cambridge Crystallographic Data Center (CCDC 886090).

General procedure for the synthesis of aminoaldehydes I–III under standard conditions. To a solution of 0.02 mol of 4-fluorobenzaldehyde in 15 mL of DMF was added 0.022 mol of the appropriate amine (morpholine, piperidine, or cytisine) and 0.025 mol of potassium carbonate. The reaction mixture was heated on a glycerol bath to reflux at a temperature of 140–150°C for 20 h. Then to the reaction mixture was added 100 mL of water, and the product was extracted with ethyl acetate (3×60 mL). The combined solutions were dried over anhydrous Na_2SO_4 and evaporated to dryness. The resulting precipitate was recrystallized from 2-propanol.

4-(*N*-Morpholinyl)benzaldehyde (I). Yield 54%, mp 69–70°C. IR spectrum, ν, cm^{-1}: 1674 (C=O). ^1H NMR spectrum, δ, ppm: 3.36 t [4H, $N(CH_2)_2$, J_{HH} 4.0 Hz], 3.72 t [4H, $O(CH_2)_2$, J_{HH} 4.3 Hz], 7.08 d (1H, CH_{Ar}, J_{HH} 7.8 Hz), 7.73 d (1H, CH_{Ar}, J_{HH} 8.9 Hz), 9.76 s [1H, C(O)H]. Found, %: C 69.39; H 7.05; N 7.37. $C_{11}H_{13}NO_2$. Calculated, %: C 69.09; H 6.85; N 7.32.

4-(*N*-Piperidinyl)benzaldehyde (II). Yield 95%, mp 57–58°C. IR spectrum, ν, cm^{-1}: 1674 (C=O). ^1H NMR spectrum, δ, ppm: 1.60 br.m (6H, $CH_2CH_2CH_2$), 3.42 t (2H, NCH_2, J_{HH} 5.6 Hz), 7.01 d (1H, CH_{Ar}, J_{HH}

Table 4. Physicochemical characteristics and elemental analysis data of the compounds **I–VII**

Comp. no.	Yield, %[a]	mp, °C	Found, %		Formula	Calculated, %	
			C	H		C	H
I	54 (71)	69–70	69.39	7.05	$C_{11}H_{13}NO_2$	69.09	6.85
II	95	57–58	81.16	8.49	$C_{12}H_{15}NO$	76.16	7.99
III	35 (67)	244–245	78.29	7.03	$C_{19}H_{19}NO_2$	77.79	6.53
IV	80	256–257	70.79	6.35	$C_{17}H_{18}N_4O_2$	65.79	5.85
V	87	206–207	70.61	7.04	$C_{18}H_{20}N_4O$	70.11	6.54
VI	83	199–200	66.95	6.39	$C_{18}H_{19}N_3O_3$	66.45	5.89
VII	74	227–228	71.07	7.05	$C_{19}H_{21}N_3O_2$	70.57	6.55

[a] Yields of compounds obtained using microwave activation are given in parentheses.

7.2 Hz), 7.69 d (1H, CH_{Ar}, J_{HH} 8.9 Hz), 9.68 s [1H, C(O)H]. Found, %: C 76.32; H 8.15; N 7.45. $C_{12}H_{15}NO$. Calculated, %: C 76.16; H 7.99; N 7.40.

4-(*N*-Cytisinyl)benzaldehyde (III). Yield 42%, mp 244–245°C. IR spectrum, ν, cm^{-1}: 1674 (C=O), 1655 (C=O). ^1H NMR spectrum, δ, ppm: 1.96 br.t (2H, H^8), 2.57 br.s (1H, H^9), 3.08 br. d (1H, H^7, J 12.5 Hz), 3.15 d. d (1H, H^{11a}, $J_{11a,11e}$ 12.3, $J_{11a,9}$ 2.2 Hz), 3.25 br.d (1H, H^{13a}, $J_{13a,7}$ 2.3 Hz), 3.72 d. d (1H, H^{10a}, $J_{10a,9}$ 5.9, $J_{10a,10e}$ 15.5 Hz), 3.94 d (1H, H^{10e}, $J_{10e,10a}$ 15.4 Hz), 3.95 br.s (1H, H^{13e}), 4.14 br.d (1H, H^{11e}, $J_{11e,11a}$ 12.5 Hz), 6.15 d.d (1H, H^3, $J_{3,4}$ 9.0, $J_{3,5}$ 1.3 Hz), 6.22 d.d (1H, H^5, $J_{5,4}$ 6.9, $J_{5,3}$ 1.3 Hz), 6.91 d ($2H_{Ar}$, J 8.9 Hz), 7.32 d. d (1H, H^4, $J_{4,5}$ 6.9, $J_{4,3}$ 9.0 Hz), 7.62 d ($2H_{Ar}$, J 8.9 Hz), 9.66 s [1H, C(O)H]. Found, %: C 73.87; H 6.54; N 4.82. $C_{18}H_{18}N_2O_2$. Calculated, %: C 73.45; H 6.16; N 4.77.

General procedure for the synthesis of aminoaldehydes I, III under microwave irradiation. To a solution of 0.02 mol of 4-fluorobenzaldehyde in 15 mL of DMF was added 0.022 mol of the appropriate amine (morpholine or cytisine) and 0.025 g of potassium carbonate. The reaction mixture was irradiated in a microwave device LG MS2022G at irradiation power of 500 W for 30 min with minor interruptions. Then to the reaction mixture was added 100 mL of water, and the product was extracted with ethyl acetate (3×60 mL). The combined solutions were dried over anhydrous Na_2SO_4 and evaporated to dryness. The resulting precipitate was recrystallized from 2-propanol.

General procedure for the synthesis of hydrazones IV–VII. To a solution of 0.003 mol of aminobenzaldehyde **I, III** in 10 mL of ethanol was added 0.003 mol of the appropriate hydrazide (isonicotinylhydrazine, salicylic acid hydrazide). The reaction mixture was refluxed at 60–70°C for 2–2.5 h. The precipitate formed was filtered off, washed with ethanol, dried, and recrystallized from 2-propanol.

***N*-(4-Morpholinobenzylidene)isonicotinylhydrazide (IV).** Yield 80%, mp 256–257°C. IR spectrum, ν, cm^{-1}: 1680 (C=O). ^1H NMR spectrum, δ, ppm: 3.23 t [4H, $N(CH_2)_2$, J_{HH} 4.2 Hz], 3.74 t [4H, $O(CH_2)_2$, J_{HH} 4.5 Hz], 7.02 d (1H, CH_{arom}, J_{HH} 6.2 Hz), 7.61 d (1H, CH_{Ar}), 8.78 d (1H, CH^1), 7.80 d (1H, CH^2), 8.35 s (1H, CH=N), 11.85 br.s (1H, NH). Found, %: C 65.84; H 5.97; N 18.10. $C_{17}H_{18}N_4O_2$. Calculated, %: C 65.79; H 5.85; N 18.05.

***N*-[4-(Piperidin-1-yl)benzylidene]isonicotinylhydrazide (V).** Yield 87%, mp 206–207°C. IR spectrum, ν, cm^{-1}: 1682 (C=O). ^1H NMR spectrum, δ, ppm: 1.60 br.s (6H, $CH_2CH_2CH_2$), 3.30 t (2H, NCH_2, J_{HH} 5.4 Hz), 6.99 d (1H, CH_{Ar}, J_{HH} 6.4 Hz), 7.55 d (1H, CH_{Ar}, J_{HH} 8.8 Hz), 8.77 d (1H, CH^1, J_{HH} 6.6 Hz), 7.81 d (1H, CH^2), 8.35 s (1H, CH=N), 11.82 br.s (1H, NH). Found, %: C 70.26; H 6.65; N 18.22. $C_{17}H_{18}N_4O_2$. Calculated, %: C 70.11; H 6.54; N 18.17.

2-Hydroxy-*N*-(4-(piperidin-1-yl)benzylidene)-benzohydrazide (VII). Yield 74%, mp 227–228°C. IR spectrum, ν, cm^{-1}: 1662 (C=O). ^1H NMR spectrum, δ, ppm: 1.58 br.s (6H, $CH_2CH_2CH_2$), 3.36 s (2H, NCH_2), 6.98 d (1H, CH_{Ar}, J_{HH} 6.8 Hz), 7.56 d (1H, CH_{Ar}, J_{HH} 8.8 Hz), 7.43 t (1H, CH^2_{Ar}, J_{HH} 6.9 Hz), 6.95 d (1H, CH^3_{Ar}, J_{HH} 7.4 Hz), 7.90 d (1H, CH^4_{Ar}, J_{HH} 7.8 Hz), 8.33 s (1H, CH=N), 11.67 br.s (1H, OH), 12.08 br.m (1H, NH). Found, %: C 70.59; H 6.61; N 13.22. $C_{19}H_{21}N_3O_2$. Calculated, %: C 70.54; H 6.55; N 12.99.

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