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Single-Pot Synthesis Method of 2-Hydroxybenzylidene-4-[(aza, thio)xanthenyl]anilines and Their Plant Growth Regulator Activity

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Abstract—The synthesis of 2-hydroxybenzylidene-4-[(aza, thio)xantenyl]anilines has been carried out via the reaction of 2-hydroxybenzaldehyde, aniline, and (aza, thio)xanthydrol in acetic acid or ethanol medium. Two competing pathways leading the formation of 2-hydroxybenzylidene-4-[(aza, thio)xantenyl]anilines have been revealed by means of chromato–mass spectrometry. The growth-regulating activity of 2-hydroxybenzylidene-4-(5*H*-benzopyrano[2,3-*b*]-pyridin-5-yl)aniline towards spring wheat (Gornouralskaya variety) has been studied.

Keywords: 4-heterylacetanilides, 2-hydroxybenzylidene-4-[(aza, thio)xantenyl]anilines, aromatic imines, plant growth regulators

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The interest to *N*-benzylideneaniline is due to their diverse biological activity. The species exhibiting antioxidant [1], antituberculous [2], and antibacterial activity [3] are known among this class of compounds. Some aromatic imines are used in agriculture as plant growth regulators [4–9].

The known methods of synthesis of aromatic imines include direct interaction between benzaldehyde and aniline (or their derivatives) in the medium of toluene [10–11], ethanol [13–16], methanol [17], ethanol–acetic acid [18, 19], or in the absence of any solvent [20]. *N*-Benzylideneanilines (imines) can be also obtained via the condensation of benzyl alcohol with aniline in toluene in the presence of molecular oxygen and catalysts based on Au, Pd, Ru [21], or via condensation of aromatic nitroso compounds with the species containing activated methylene group [22]. The formation of derivatives of *N*-benzylideneanilines in the reactions of dehydrogenation of the corresponding tertiary amines has been demonstrated [23, 24].

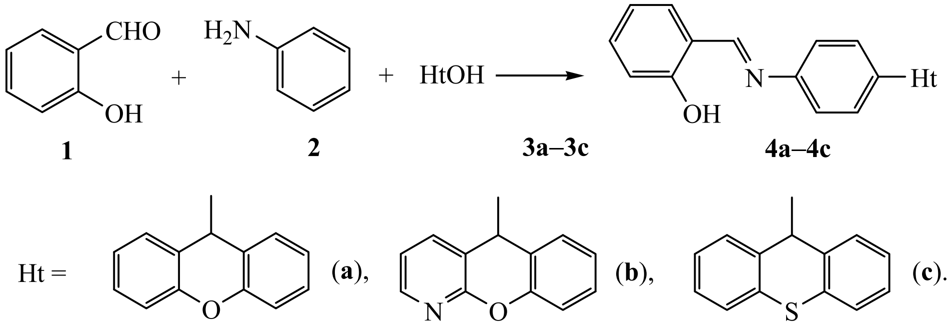
We have earlier elaborated a synthetic method allowing the preparation of *para*-substituted *N*-benzylideneanilines the aniline part of which contains a heterocyclic substituent (9*H*-xanthene, 9*H*-thioxanthene, or 1-azaxanthene) in acetic acid medium [25] and have investigated antimicrobial activity of some of them [26].

This study aimed to elucidate the effect of the solvation factor on the direction of a single-pot synthesis of 2-hydroxybenzylidene-4-[(aza,thio)xanthenyl]-anilines and investigate their utilitarian properties.

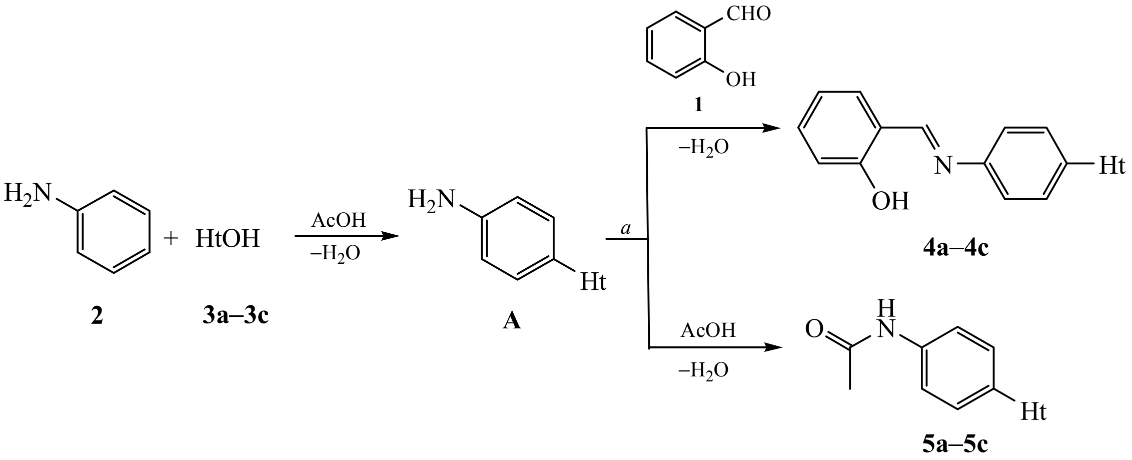
Single-pot synthesis of 2-hydroxybenzylidene-4-[(aza,thio)xanthenyl]anilines **4a**–**4c** was performed via the interaction of 2-hydroxybenzaldehyde **1**, aniline **2**, and the corresponding hydrols (9*H*-xanthen-9-ol **3a**, 5*H*-benzopyrano[2,3-*b*]pyridin-5-ol **3b**, or 9*H*-thioxanthen-9-ol **3c**) in 43% acetic acid or 96% ethanol in the presence of hydrochloric acid(Scheme 1). When acetic acid was used as solvent, the yield of the target product was of 47–60%, being of 45–84% in the case of ethanolic medium.

Several competing pathways of the reaction can often be operative in multicomponent systems. Detailed investigation of the influence of the solvent nature on the course of the considered reaction was performed by means of chromato–mass spectrometry (Table 1). The obtained data revealed two directions of

Scheme 1.



Scheme 2.



the formation of 2-hydroxybenzylidene-4-[(aza,thio)-xanthenyl]anilines **4a**–**4c**. In detail, the acylation of intermediate **A** affording 4-heterylacetanilides **5a**–**5c** was found competing with the formation of the final products **4a**–**4c** in the acetic acid medium, hence, the reaction occurred via pathway *a* (Scheme 2).

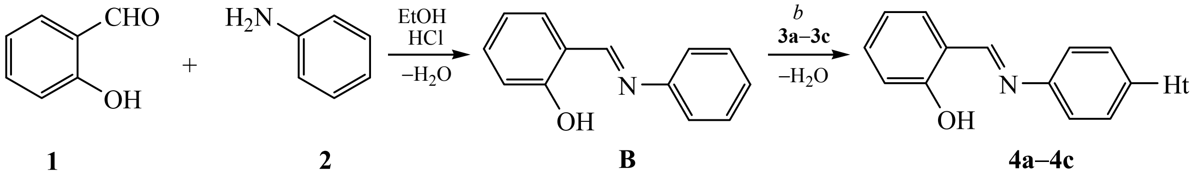
The reaction involving azaxanthydrol **3b** in ethanolic medium occurred predominantly through the formation of intermediate **B** detected in the reaction mass. The low content of compound **4b** was likely related to low rate of heterylation (pathway *b*, Scheme 3). In the case of xanthydrol **3a**, the yield of the target product **4a** was high, but intermediate **B** was not detected, probably due to fast heterylation.

Analysis of the reaction mixture during the process involving thioxanthydrol **3c** revealed approximately equal contents of 4-thioxanthenylacetanilide **5c** and intermediate **B**, pointing at the formation of compound

Table 1. The effect of solvent on the composition of reaction mixture during synthesis of 2-hydroxybenzylidene-4-[(aza,thio)-xanthenyl]anilines **4a**–**4c**

Reaction mixture component	Content, %					
	3a		**3b**		**3c**	
	AcOH	EtOH	AcOH	EtOH	AcOH	EtOH
Intermediate **A**	–	5.06	10.16	0.32	0.25	–
Intermediate **B**	–	–	57.94	26.36	20.22	–
4a–**4c**	99.06	94.94	27.23	73.32	63.07	100
5a–**5c**	0.94	–	4.67	–	16.46	–

Scheme 3.



4c via the pathway *a* or *b*. When the solvent was changed to ethanol (thus excluding the competing acylation process), the formation of compounds **4a**–**4c** occurred via pathway *b,* the target products yield being slightly improved.

We further assessed the growth regulation activity of the heterylated imines towards spring wheat (Gornouralskaya) via a known method [27]. We selected compound **4b** for that study, since it contained two potentially physiologically active fragments (azomethine and azaxanthene) capable of growth regulation [4–9, 28].

According to the data in Table 2, compound **4b** applied in concentration of 0.001% enhanced the number of productive plants by 5%, and the total number of stems was increased by 7–13% over the entire concentration range studied. When applied in concentrations 0.001 and 0.0005%, it induced the increase in the average height of the plants by 8 and 6%, respectively, the straw mass was increased by 22–23% at the compound concentration 0.005 and 0.0001%, and the ear mass was increased by 5–12% (Table 3).

A distinct feature of the action of compound **4b** was significant (by 98%) increase in the wheat roots mass when applied in concentration of 0.001%, which enhanced the intensity of nutritive materials consumption by the plant.

When applied in concentration of 0.005 and 0.001%, the tested compound increased the number of grains per raceme by 2–3%, and biological productivity of the wheat was increased by 0.13–0.15 t/ha with respect to the control experiment as well as the reference active compound (Table 4).

In summary, the change of the solvent (acetic acid to ethanol) in the synthesis of 2-hydroxybenzylidene-4-[(aza,thio)xanthenyl]anilines led to slight increase in the yield of the target products and avoided the formation of the side products (acetanilides). The agrochemical experiments revealed positive effect of 2-hydroxybenzylidene-4-(5*H*-benzopyrano[2,3-*b*]pyridin-5-yl)aniline on the growth and productivity of the Gornouralskaya spring wheat, the active component concentration being 0.005 or 0.001%.

EXPERIMENTAL

^{1}H NMR spectra were recorded using a Mercury 300BB instrument (Varian, USA) (300 MHz, $CDCl_3$, HMDS as internal reference). Mass spectra were obtained using an Agilent Technologies 6890N/5975B chromato–mass spectrometer (USA); column HP-5ms (30 × 0.25 mm, 0.25 μm), helium as carrier gas,

Table 2. Growth of winter wheat (Gornouralskaya) affected by compound **4b**

Experiment	*c*, %	Number of plants				Number of stems			
		total		productive		total		productive	
		pc/m^2	change, +/–	pc/m^2	change, +/–	pc/m^2	change, +/–	pc/m^2	change, +/–
Control		290	–	290	–	348	–	338	–
Reference		258	–16	258	–16	356	+3	326	–6
4b	0.0050	290	0	282	–4	372	+12	338	+2
	0.0010	304	+7	304	+7	384	+17	326	+9
	0.0005	284	–4	218	–36	392	+21	338	+14
	0.0001	256	–17	256	–17	380	+15	326	+5

Table 3. Effect of compound **4b** on vegetative and generative parts of the wheat

Experiment	*c*, %	Average height		Straw mass		Ears mass		Roots mass	
		cm	change, +/–	g	change, +/–	g	change, +/–	g	change, +/–
Control		94.50	–	305.56	–	250.84	–	121.10	–
Reference		89.30	–5.17	354.98	+24.71	184.80	–33.02	195.04	+36.97
4b	0.0050	88.60	–5.90	371.58	+23.01	240.70	–5.07	239.34	+59.12
	0.0010	101.75	+7.25	356.42	+25.43	274.08	+11.62	130.36	+4.63
	0.0005	100.75	+6.25	314.18	+4.31	262.54	+5.85	164.36	+21.63
	0.0001	101.00	+6.50	374.92	+34.68	281.60	+15.38	159.92	+19.41

electron impact ionization at 70 eV, column temperature 100°C. The compounds purity was determined by means of TLC on Sorbfil PTSKh-P-A-UV plates.

Compounds 4a–4c (*general procedure*). A mixture of equimolar (1 mmol each) of 2-hydroxybenzaldehyde **1**, aniline **2**, and the corresponding hydrol **3a–3c** in 7 mL of 43% acetic acid (or 7 mL of 96% ethanol with 1 drop of 36% hydrochloric acid) was heated during 10 min at 90°C. The reaction mass was cooled and neutralized with 25% ammonia solution. The crystalline precipitate was washed with water and recrystallized from ethanol.

2-Hydroxybenzylidene-4-(9*H*-xanthen-9-yl)-aniline (4a). Yield 0.18 g (49%, AcOH), 0.32 g (84%, EtOH + HCl), light-yellow crystals, mp 177–178°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 5.27 s (1H, C^{9}H, Ht), 6.85–7.37 m (16H, Ar + Ht), 8.54 s (1H, CH=N), 13.20 br. s (1H, OH). Mass spectrum, *m/z* (I_{rel}, %): 377 (69) $[M]^+$, 360 (1), 271 (1), 257 (10), 196 (1.1), 181 (100), 120 (0.6), 76 (1.7).

2-Hydroxybenzylidene-4-(5*H*-benzopyrano[2,3-*b*]pyridin-5-yl)aniline (4b). Yield 0.22 g (60%, AcOH), 0.17 g (45%, EtOH + HCl), yellow crystals, mp 194°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 5.34 s (1H, C^{5}H, Ht), 6.89–7.44 m (15H, Ar + Ht), 8.20–8.21 m (1H, CH=N, Ht), 8.56 s (1H, CH=N), 13.14 br. s (1H, OH). Mass spectrum, *m/z* (I_{rel}, %): 378 (78) $[M]^+$, 361 (1), 260 (14), 258 (10.5), 196 (1.5), 182 (100), 120 (1), 76 (2.5).

2-Hydroxybenzylidene-4-(9*H*-thioxanthen-9-yl)-aniline (4c). Yield 0.35 g (47%, AcOH), 0.28 g (74%,

Table 4. Effect of compound **4b** on the wheat crop productivity

Experiment	*c*, %	Number of productive stems		Number of grains in raceme		Mass of 1000 grains		Productivity of raceme		Biological productivity	
		pc/m^2	change, +/–	pc	change, +/–	g	change, +/–	g	change, +/–	t/ha	change, +/–
Control		338	–	14.08	–	35.23	–	0.50	–	1.69	–
Reference		326	–6	14.33	+0.25	34.44	–0.79	0.49	–0.01	1.60	–0.09
4b	0.0050	338	+2	14.43	+0.35	33.33	–1.90	0.48	–0.02	1.64	–0.05
	0.0010	326	+9	14.53	+0.45	35.05	–0.18	0.51	+0.01	1.82	+0.13
	0.0005	338	+15	14.28	+0.20	35.32	+0.09	0.50	0	1.84	+0.15
	0.0001	326	+6	14.53	+0.45	34.66	–0.57	0.50	0	1.75	+0.06

EtOH + HCl), yellow crystals, mp 150°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 5.35 s (1H, C^9H, Ht), 6.84–7.64 m (16H, Ar + Ht), 8.51 s (1H, CH=N), 13.21 br. s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 393 (64) $[M]^+$, 376 (0.7), 288 (0.6), 273 (6.8), 197 (100), 182 (100), 196 (4.2), 120 (0.6), 76 (2).

***N*-[4-(9*H*-Xanthen-9-yl)phenyl]acetamide (5a)** could not be isolated in the individual form. Mass spectrum, m/z (I_{rel}, %): 315 (41.0) $[M]^+$, 257 (7.0), 181 (100), 152 (8.2).

***N*-[4-(5*H*-Chromeno[2,3-*b*]pyridin-5-yl)phenyl]-acetamide (5b)** could not be isolated in the individual form. Mass spectrum, m/z (I_{rel}, %): 316 (37.7) $[M]^+$, 273 (16.4), 182 (100), 43 (12.5).

***N*-[4-(9*H*-Thioxanthen-9-yl)phenyl]acetamide (5c)** could not be isolated in the individual form. Mass spectrum, m/z (I_{rel}, %): 331 (31.6) $[M]^+$, 288 (7.9), 197 (100), 165 (10.5).

CONFLICT OF INTERESTS

No conflict of interest was declared by authors.

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