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First Synthesis of 2-Amino-5-hydroxy-4*H*-chromene-3-carbonitriles from 4-(2-Pyridylazo)resorcinol

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Abstract—4-(2-Pyridylazo)resorcinol (PAR) sodium salt reacts with aromatic aldehydes and malononitrile in aqueous ethanol to form 2-amino-4-aryl-5-hydroxy-6-(2-pyridylazo)-4*H*-chromene-3-carbonitriles.

Keywords: 4-(2-pyridylazo)resorcinol (PAR), malononitrile, 2-amino-4*H*-chromene-3-carbonitriles, 6-(2-pyridylazo)chromenes

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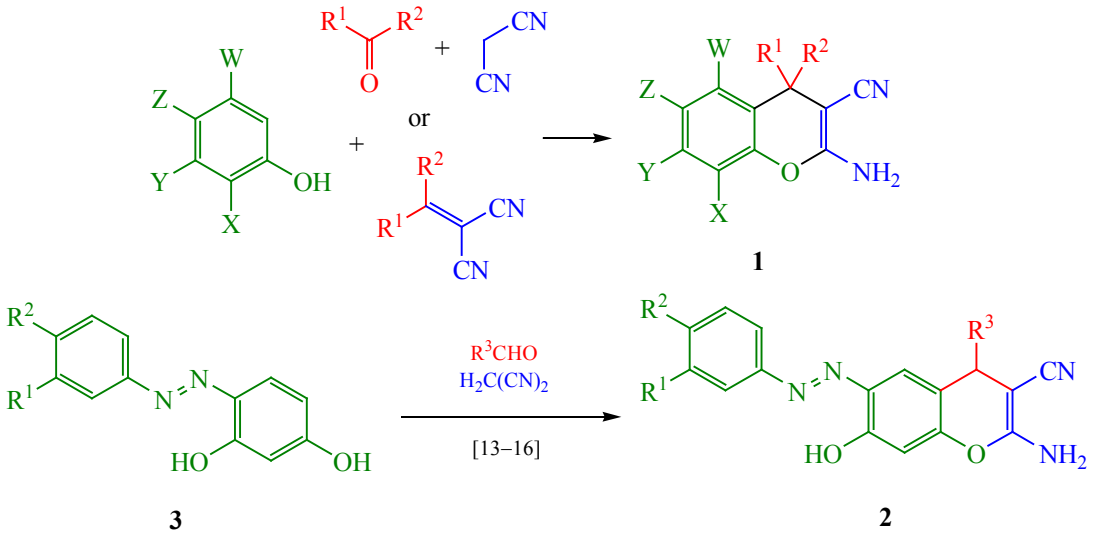
2-Amino-4*H*-chromene-3-carbonitriles **1** are an important class of organic compounds [1–6] due to their biological activity. Among them, antitumor agents, herbicides, samples with anticonvulsant, antituberculosis, fungicidal, bactericidal effect, etc. were found (for reviews, see [1, 3–6]). Interest in chromenes **1** is also due to their preparative availability: these compounds are easily obtained from activated phenols, carbonyl compounds, and malononitrile under a widely varied range of conditions (Scheme 1). Resorcinol and some of its derivatives are often used as activated phenols [7–12]. Over the past 5 years, a number of works have appeared [13–16] describing the preparation of 6-(arylazo)-2-amino-4*H*-chromenes **2** from 4-(arylazo)resorcinols **3**. Arylazochromenes **2** are of interest primarily as complexing agents and azo dyes [17]. In addition, some of compounds **2** showed antitumor [13, 14], antimicrobial [15–18], and antioxidant [18] activity.

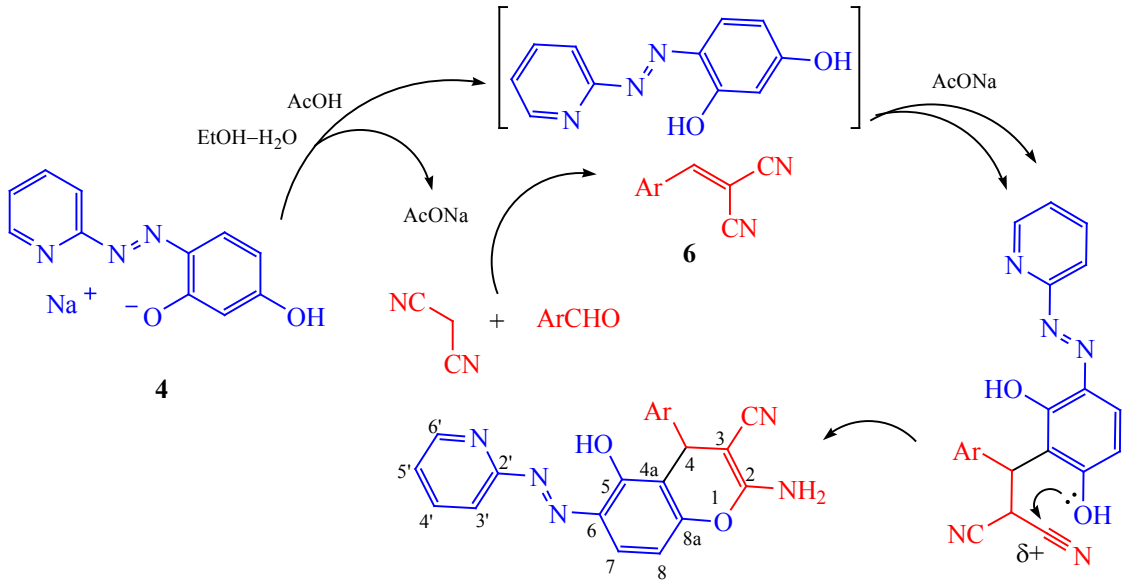
4-(2-Pyridylazo)resorcinol (PAR, **4**), available in the form of sodium salt monohydrate, has long been actively used in analytical chemistry as a non-selective tridentate complexing agent for the extraction and concentration of heavy metal ions, as a metallochromic indicator for complexometric titration, reagent for the photometric determination of analytes (for reviews, see [19–23]). In recent years, PAR has been actively used to create optical sensors and test materials for the determination and extraction of heavy metals [24–27], spectrophotometric analysis of transition metals in catalysts [28], extraction of Rh^{3+} [29], Ga^{3+} [30], Ir^{4+} [31], and Co^{2+} ions [32], obtaining charge-transfer complexes with aromatic nitro compounds [33], etc. However, as far as we know, 4-(2-pyridylazo)resorcinol has not yet been used as a reagent for fine organic synthesis. Possible products of the reaction of PAR with aldehydes and malononitrile with the expected structure of 6-(2-pyridylazo)-4*H*-chromenes are promising as new metallochromic indicators, reagents for the extraction of heavy metals from the organic phase, or as biologically active compounds by analogy with the available data [18, 34, 35]. In continuation of our studies in the chemistry of 4*H*-pyrans and 4*H*-chromenes [36–39], herein we reported the possibility of using PAR in organic synthesis, and in particular, for the preparation of 2-amino-4*H*-chromene-3-carbonitriles.

We found that PAR sodium salt monohydrate **4** reacts with aromatic aldehydes and malononitrile in the presence of a small amount of AcOH in aqueous alcohol to form new 2-amino-6-(2-pyridylazo)-4*H*-chromenes **5a** and **5b** (Scheme 2). The base required for the Knoevenagel condensation between aldehydes and malononitrile and subsequent Michael addition to arylidenemalononitriles **6** is sodium acetate, which is formed *in situ* after the addition of acetic acid.

Scheme 1.



Scheme 2.



Ar = 4-ClC_6H_4 (**a**), 3,4-$(MeO)_2C_6H_3$ (**b**).

It should be specially noted that, in the case of unsubstituted resorcinol [7–12] and 4-(arylazo)-resorcinols [13–16], the condensation products are 7-OH-chromenes, while in the case of PAR, 5-OH isomers **5** are formed. 5-Hydroxy-4*H*-chromenes have been previously observed in the case of orcin (5-methylresorcinol) [40, 41] or resorcinols having a strong acceptor substituent in position 4 [42–44]. In the ^{1}H NMR spectra of compounds **5**, two characteristic [42–44] doublets of the protons H^7 (δ 7.71–7.72 ppm) and H^8 (δ 6.78 ppm)

with spin-spin coupling constant ^3J 9.2 Hz are found, while in the spectra of 7-OH-isomers, one would expect the appearance of two singlets.

The resulting 2-amino-6-(2-pyridylazo)-4*H*-chromenes represent a new class of promising complexing agents and indicators. The reaction described above is the first example of the use of PAR as a reactant in a heterocyclic synthesis. Structural features of new compounds, possibilities and limitations of the reaction, spectral features and aspects of the possible application of 2-amino-6-(2-pyridylazo)-4*H*-chromenes in analytical chemistry will be the subject of further research.

EXPERIMENTAL

IR spectra were recorded on a Bruker Vertex 70 spectrophotometer with an ATR attachment by the method of frustrated total internal reflection on a diamond crystal, error ±4 cm^{-1}. NMR spectra were recorded on a Bruker Avance III HD 400 MHz spectrometer [400.17 (^{1}H), 100.63 MHz (^{13}C)] in DMSO-d_6 solution. The reaction progress and individuality of obtained compounds were monitored by TLC on Sorbfil-A plates (OOO Imid, Krasnodar), eluting with acetone–hexane (1 : 1) or EtOAc, developing with iodine vapor or UV detector. Melting points were measured in a capillary on a PTP instrument.

4-(2-Pyridylazo)resorcinol **4** is a commercially available reagent.

2-Amino-4-aryl-5-hydroxy-6-(2-pyridylazo)-4*H*-chromene-3-carbonitriles (5a, 5b). To 300 mg (1.175 mmol) of PAR **4** was added 14 mL of an aqueous solution of ethanol (50% by volume) and stirred until dissolved, then acetic acid (0.07 mL, 1.22 mmol), malononitrile (78 mg, 1.175 mmol), and the corresponding aromatic aldehyde (1.175 mmol) were added. The reaction mixture was refluxed until the disappearance of PAR by TLC. The mixture was cooled, and kept for 12 h. The formed precipitate was filtered off and recrystallized from an EtOH–EtOAc mixture.

2-Amino-5-hydroxy-6-(2-pyridylazo)4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (5a). Yield 41%, mp 204°C, dark red powder. IR spectrum, ν, cm^{-1}: 3460 br. m, 3342 br. m (O–H, N–H), 2191 s (C≡N). ^{1}H NMR spectrum, δ, ppm: 4.76 s (1H, H^4), 6.78 d (1H, H^8, ^3J 9.2 Hz), 7.17 br. s (2H, NH_2), 7.23 d (2H, Ar, ^3J 8.5 Hz), 7.36 d (2H, Ar, ^3J 8.5 Hz), 7.46–7.49 m (1H, H^5-Py), 7.72 d (1H, H^7, ^3J 9.2 Hz), 7.92 br. d (1H, H^3-Py, ^3J 8.2 Hz), 7.96–8.01 m (1H, H^4-Py), 8.61–8.62 m (1H, H^6-Py), 13.19 br. s (1H, OH). ^{13}C NMR spectrum DEPTQ, δ_C, ppm: 35.9* (C^{4}H), 56.7 (C^3), 109.7* (C^{8}H), 112.4* (C^{7}H), 112.5 (C^{4a}), 120.0 (C≡N), 125.0* (C^{5}H-Py), 126.5* (C^{3}H-Py), 128.5* (2CH-Ar), 129.3* (2CH-Ar), 131.3 (C^{4}Cl-Ar), 134.7 (C^6), 138.9* (C^{4}H-Py), 143.9 (C^1-Ar), 149.3* (C^{6}H-Py), 153.6 (C^{8a}), 157.9 (C^5–OH), 159.4 (C^2-Py), 160.3 (C^2). Here and below, the *asterisk* denotes signals in antiphase. Found, %: C 62.35; H 3.63; N 17.30. $C_{21}H_{14}ClN_5O_2$. Calculated, %: C 62.46; H 3.49; N 17.34. *M* 403.82.

2-Amino-5-hydroxy-4-(3,4-dimethoxyphenyl)-6-(2-pyridylazo)-4*H*-chromene-3-carbonitrile (5b). Yield 51%, mp 189°C, dark red powder. IR spectrum, ν, cm^{-1}: 3389 br. m, 3321 br. m (O–H, N–H), 2189 s (C≡N). ^{1}H NMR spectrum, δ, ppm: 3.68 s (3H, MeO), 3.70 s (3H, MeO), 4.69 s (1H, H^4), 6.65 d. d (1H, H^6-Ar, ^4J 2.1, ^3J 8.3 Hz), 6.78 d (1H, H^8, ^3J 9.2 Hz), 6.82 d (1H, H^2-Ar, ^4J 2.1 Hz), 6.86 d (1H, H^5-Ar, ^3J 8.3 Hz), 7.08 br. s (2H, NH_2), 7.46–7.49 m (1H, H^5-Py), 7.71 d (1H, H^7, ^3J 9.2 Hz), 7.93 br. d (1H, H^3-Py, ^3J 8.1 Hz), 7.97–8.01 m (1H, H^4-Py), 8.61–8.63 m (1H, H^6-Py), 13.23 br. s (1H, OH). ^{13}C NMR spectrum DEPTQ, δ_C, ppm: 35.9* (C^{4}H), 55.48* (MeO), 55.52* (MeO), 57.4 (C^3), 109.7* (C^{8}H), 111.3* (C^{2}H-Ar), 112.0* (C^{5}H-Ar), 112.4* (C^{7}H), 113.3 (C^{4a}), 119.2* (C^{6}H-Ar), 120.2 (C≡N), 125.0* (C^{5}H-Py), 126.3* (C^{3}H-Py), 134.7 (C^6), 137.5 (C^1-Ar), 138.9* (C^{4}H-Py), 147.6 (C–OMe), 148.4 (C–OMe), 149.3* (C^{6}H-Py), 153.6 (C^{8a}), 157.8 (C^5–OH), 159.4 (C^2-Py), 160.3 (C^2). Found, %: C 64.25; H 4.59; N 16.22. $C_{23}H_{19}N_5O_4$. Calculated, %: C 64.33; H 4.46; N 16.31. *M* 429.43.

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CONFLICT OF INTERESTS

No conflict of interest was declared by the authors.

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