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Reaction of 4,5-Dimethoxy-1,2-dehydrobenzene with 3-(Pyridin-2-yl)-1,2,4-triazines

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Abstract—Reaction of 3-(pyridin-2-yl)-1,2,4-triazines with aryne intermediate, 4,5-dimethoxy-1,2-dehydrobenzene generated *in situ*, was investigated. As a result of the interaction products of the 1,2,4-triazine transformation are produced: 2,3-dimethoxy-10-(1*H*-1,2,3-triazol-1-yl)-pyrido[1,2-*a*]indoles, and also the products of Diels-Alder aza-reaction, 6,7-dimethoxy-1-(pyridin-2-yl)isoquinolines.

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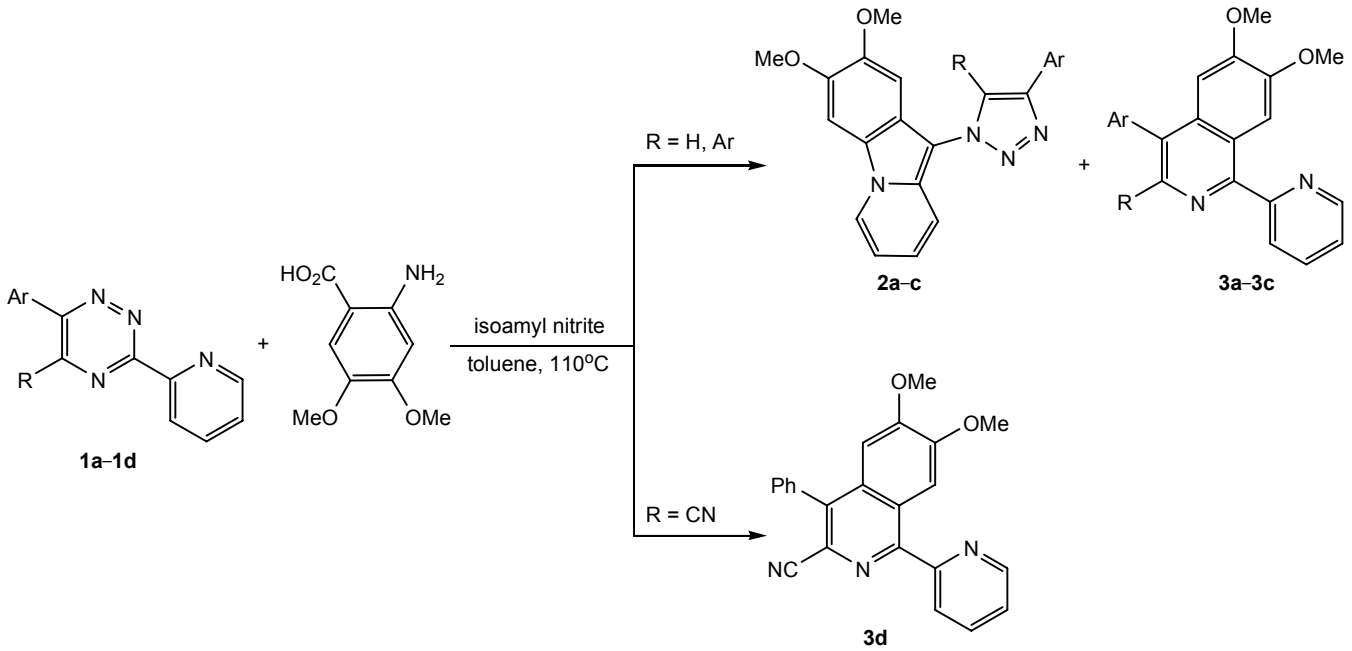
Isoquinolines and pyrido[1,2-*a*]indoles are known by their biological and practical properties. In particular, they are present in the composition of natural physiologically active compounds [1, 2]. Synthetic analogs of isoquinolines and pyridoindoles show a wide range of bioactivity [3, 4], including antimalarial [5], antiviral [6], also anti-HIV [7, 8], and antitumor action [2, 9]. Some isoquinolines are included in photoluminescence sensors of the explosives [10].

Pyridinyl-substituted isoquinolines may be obtained by many synthetic methods [11, 12], while the methods of direct construction of pyrido[1,2-*a*]indole structure are quite limited [13–15]. Only recently the methods of one-stage preparation of such systems by the reaction of arynes generated *in situ* with (benzo)-pyridine synthons were described [16, 17]. In the series of 1,2,4-triazines such reaction [18, 19] may result in generation of isoquinolines [20–24] in addition to pyrido[1,2-*a*]indoles [24, 25]. The direction of the reaction depends on the conditions of the process, the aryne electrophilicity, and also on the nature of the substituents in 1,2,4-triazine ring. In reactions of 5-*R*-3-(pyridin-2-yl)-1,2,4-triazines with highly electrophilic dehydrobenzene or with 4,5-difluorodehydrobenzene (R = H or Ar) the main products are pyrido[1,2-*a*]indoles formed as a result of the attack of pyridine nitrogen atom [24, 25] on the aryne. At R = CN main products of the reaction are isoquinolines [26].

In this article in order to study the possibility to apply the "aryne" method to the targeted preparation of heterocyclic systems containing methoxy groups we investigated the reaction of 3-(pyridin-2-yl)-1,2,4-triazines **1** with 4,5-dimethoxy-1,2-dehydrobenzene generated *in situ* from 2-aminoveratric acid.

Unlike the previously described reaction of 3-(pyridin-2-yl)-1,2,4-triazines with 1,2-dehydrobenzene and its difluoroderivative [24, 25] the reaction of triazines **1** with less electrophilic 4,5-dimethoxy-1,2-dehydrobenzene results in a mixture of two compounds: products of transformation of 1,2,4-triazine ring, 2,3-dimethoxy-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles **2** in up to 44% yield, and products of the Diels-Alder aza-reaction, isoquinolines **3**. Only compound **3c** was isolated, products **3a** and **3b** were detected in the mass spectra. The additional introduction of a cyano group into the position *5* of 1,2,4-triazine ring inhibits its ability to transform, and isoquinoline-3-carbonitrile **3d** has been obtained as the single reaction product, but due to a significant tarring of the reaction mixture its yield is only 10%.

Hence the lowering of the aryne electrophilicity by introducing into it electron-donor groups decreases its affinity to nucleophilic attack by pyridine nitrogen atom in reactions with 3-(pyridin-2-yl)-1,2,4-triazines reducing the amount of reaction products **2** and raising the quantity of Diels-Alder aza-reaction products **3** in the reaction mixture.



Ar = Ph, R = H (**a**); Ar, R = biphenyl-2,2'-yl (**b**); Ar = R = Ph (**c**); Ar = Ph, R = CN (**d**).

Structure of compounds **2** and **3** was confirmed by the ^{1}H and ^{13}C NMR spectroscopy data, mass spectrometry, their composition was proved by the elemental analysis. Spectral characteristic of reaction products **2** are very similar to previously described compounds without methoxy groups [24, 25]. In ^{1}H NMR spectra of compounds **3** two singlets are present from protons in positions *5* and *8* of isoquinoline, proton signals of the pyridine ring appear as multiplets in the range 7.30–8.80 ppm. In mass spectra the peaks of molecular ions are present.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a spectrometer Bruker DRX-400 (400 and 100 MHz respectively) in $CDCl_3$, reference TMS. Mass spectra (ESI-MS) were obtained on a mass spectrometer MicrOTOF-Q II (Bruker Daltonics). Elemental analysis was carried out on a CHN analyzer PE 2400, series II Perkin Elmer. Melting points were measured on a Boetius heating block. TLC analysis was performed on Merck silica gel 60F254 plates, development in UV light.

Initial 1,2,4-triazines **1a** [27], **1b** [28], **1c** [29], and **1d** [30] were obtained by described methods.

Reaction of 1,2,4-triazines (1a–1d) with 1,2-dehydrobenzene. In 130 mL of anhydrous toluene 3 mmol of the corresponding triazine **1** was dispersed, and 1.61 mL (12 mmol) of isoamyl nitrite was added. To the boiling reaction mixture while stirring in an argon atmosphere was added dropwise during 30 min a solution of 2.36 g (12 mmol) of 3,4-dimethoxyanthranilic acid in 15 mL of anhydrous 1,4-dioxane. The mixture was stirred while boiling for 1 h, then cooled to room temperature, washed with 3 M aqueous solution of NaOH (3 × 75 mL). The organic layer was dried with anhydrous Na_2SO_4, solvents were distilled off at a reduced pressure. The reaction products were isolated by column chromatography on silica gel. Samples for analysis were obtained by recrystallization from ethanol.

2,3-Dimethoxy-10-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (2a). Yield 0.28 g (25%), colorless crystals, mp. 189–191°C. R_f 0.8 (CH_2Cl_2–AcOEt, 3 : 1). ^{1}H NMR spectrum, δ, ppm: 3.98 s (3H, OMe), 4.05 br.s. (3H, OMe), 6.46–6.83 br.s. (2H), 7.00 br.s. (1H), 7.30–7.41 m (2H), 7.49 m (3H, Ph), 8.00 m (2H, Ph), 8.17–8.40 br.s (2H). ^{13}C NMR spectrum, δ, ppm: 56.3, 56.4, 93.1, 97.8, 103.1, 109.1, 115.9, 117.3, 121.1, 121.7, 122.5, 123.3, 125.8, 128.3, 129.0, 129.1, 130.7, 146.9, 147.5, 149.0. Mass spectrum, *m/z* (I_{rel}, %): 371 $[M + H]^+$ (100). Found, %: C 71.30; H 4.81; N 15.02. $C_{22}H_{18}N_4O_2$. Calculated, %: C 71.34; H 4.90; N 15.13.

1-(2,3-Dimethoxypyrido[1,2-*a*]indol-10-yl)-1*H*-phenanthro[9,10-*d*][1,2,3]triazole (2b). Yield 0.60 g

(44%), light-yellow crystals, mp 210–212°C. R_f 0.8 (CH_2Cl_2–AcOEt, 3 : 1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.72 s (3H, OMe), 4.00–4.15 br.s (3H, OMe), 6.70 br.s (1H), 6.75 br.s (1H), 6.90–7.00 br.s (1H), 7.12–7.20 br.s (1H), 7.20–7.28 m (1H), 7.47 s (1H), 7.57–7.65 m (2H), 7.72–7.80 t.d (1H, ^3J 8.5, 7.5, ^4J 1.5), 7.80–7.87 t.d (1H, ^3J 7.5, 7.5, ^4J 1.0), 8.39 br.s (1H), 8.68–8.71 d.d (1H, ^3J 8.4, ^4J 1.0), 8.71–8.74 d.d (1H, ^3J 8.4, ^4J 1.0), 8.93–9.00 d.d (1H, ^3J 8.0, ^4J 1.0). ^{13}C NMR spectrum, δ, ppm: 56.1, 56.5, 93.4, 97.9, 102.1, 109.4, 116.0, 119.2, 120.6, 122.1, 122.9, 122.9, 123.0, 123.4, 123.5, 124.0, 125.2, 127.1, 127.3, 127.8, 128.2, 129.1, 130.2, 131.1, 131.6, 141.3, 146.9, 149.2. Mass spectrum, *m/z* (I_{rel}, %): 445 $[M + H]^+$ (100). Found, %: C 75.56; H 4.56; N 12.50. $C_{28}H_{20}N_4O_2$. Calculated, %: C 75.66; H 4.54; N 12.60.

2,3-Dimethoxy-10-(4,5-diphenyl-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole (2c). Yield 0.35 g (26%), colorless crystals, mp 201–203°C, R_f 0.6 (CH_2Cl_2–AcOEt, 3 : 2). ^{1}H NMR spectrum, δ, ppm: 3.78 s (3H, OMe), 4.00 br.s (3H, OMe), 6.58 br.s (1H), 6.69 br.s (1H), 6.79–6.92 br.s (1H), 7.12–7.29 m (7H), 7.30–7.42 m (3H), 7.72 m (2H), 8.18 br.s (1H). Mass-spectrum, *m/z* (I_{rel}, %): 447 $[M + H]^+$ (100). Found, %: C 75.26; H 4.89; N 12.53. $C_{28}H_{22}N_4O_2$. Calculated, %: C 75.32; H 4.97; N 12.55.

6,7-Dimethoxy-1-(pyridin-2-yl)-4-phenylisoquinoline (3a). Mass spectrum, *m/z* (I_{rel}, %): 343 $[M + H]^+$ (100).

12,13-Dimethoxy-10-(pyridin-2-yl)dibenzo[*a,c*]-phenanthridine (3b). Mass spectrum, *m/z* (I_{rel}, %): 417 $[M + H]^+$ (100).

6,7-Dimethoxy-1-(pyridin-2-yl)-3,4-diphenylisoquinoline (3c). Yield 0.05 g (4%), colorless crystals, mp 182–184°C, R_f 0.4 (CH_2Cl_2–AcOEt, 3 : 2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.78 s (3H, OMe), 3.99 s (3H, OMe), 6.96 s (1H, $H^8_{isoquinoline}$), 7.12–7.22 m (3H, Ph), 7.23–7.32 m (2H, Ph), 7.32–7.44 m (6H, Ph, H^5_{Py}), 7.88–7.95 d.d.d (1H, H^4_{Py}, ^3J 7.7, 7.7, ^4J 2.0), 8.21–8.25 d.d (1H, H^3_{Py}, ^3J 7.7, ^4J 1.0), 8.30 s (1H, $H^5_{isoquinoline}$), 8.80 d.d (1H, H^6_{Py}, ^3J 4.8, ^4J 2.0). Mass spectrum, *m/z* (I_{rel}, %): 419 $[M + H]^+$ (100). Found, %: C 80.29; H 5.35; N 6.61. $C_{28}H_{22}N_2O_2$. Calculated, %: C 80.36; H 5.30; N 6.69.

6,7-Dimethoxy-1-(pyridin-2-yl)-4-phenylisoquinoline-3-carbonitrile (3d). Yield 0.10 g (10%), colorless crystals, mp 171–173°C, R_f 0.3 (CH_2Cl_2–AcOEt, 3 : 1). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.82 s (3H, OMe), 4.00 s (3H, OMe), 7.00 s (1H, $H^8_{isoquinoline}$), 7.42–7.47 d.d.d (1H, H^5_{Py}, ^3J 4.8, 7.7, ^4J 1.0), 7.50–7.70 m (5H, Ph), 7.95–8.03 d.d.d (1H, H^4_{Py}, ^3J 7.7, 7.7, ^4J 2.0), 8.20–8.23 d.d (1H, H^3_{Py}, ^3J 7.7, ^4J 1.0), 8.46 s (1H, $H^5_{isoquinoline}$), 8.80 d.d (1H, H^6_{Py}, ^3J 4.8, ^4J 2.0). Mass spectrum, *m/z* (I_{rel}, %): 368 $[M + H]^+$ (100). Found, %: C 75.18; H 4.57; N 11.48. $C_{23}H_{17}N_3O_2$. Calculated, %: C 75.19; H 4.66; N 11.44.

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