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LETTERS TO THE EDITOR

PREPARATION OF 3-CYANO-1-(2-PYRIDYL)ISOQUINOLINES BY USING ARYNE INTERMEDIATES

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While the isoquinoline system serves as a structural foundation of many natural product molecules, such as certain alkaloids [1], isoquinolines also have intrinsic biological activity [2] and play an important role as fragments in natural and synthetic drugs. Besides that, 1-(2-pyridyl)isoquinolines present interest as ligands for transition metal cations [3]. The introduction of a cyano group at position 3 of isoquinoline ring in such compounds opens a broad range of possibilities for obtaining various derivatives through subsequent functionalization. Unfortunately, no effective methods are currently known for the synthesis of 3-cyano-isoquinolines. For example, direct cyanation of isoquinoline *N*-oxides occurs exclusively at position 1, while the few cases of direct 3-cyanation of isoquinolines gave low yields [4] or required special reaction conditions [5]. Besides, 3-cyanoisoquinolines can be obtained through various variants of heterocyclization [6, 7] and by the decomposition of 2,3-substituted diazidonaphthaline – in that case 3-cyanoisoquinoline was formed in mixture with by-products [8]. Finally, the 3-cyano group in isoquinoline may be created by chemical transformations of other functional groups, such as substitution of a chlorine atom [9].

In this report, we propose a convenient method for the synthesis of 3-cyano-1-(2-pyridyl)isoquinolines based on the available 5-cyano-3-(2-pyridyl)-1,2,4-triazines **1a-c** [10] by using a known effective method for the synthesis of various pyridine derivatives from 1,2,4-triazine analogs [11]. It has been established that the interaction of 1,2,4-triazines with enamines followed by oxidation [12], or with *in situ* generated arynes [13] allows to obtain substituted isoquinolines effectively, even avoiding the aromatization step in the case of arynes [14]. We have previously demonstrated that 3-(2-pyridyl)-1,2,4-triazines substituted with aryl groups at positions 5 and/or 6 [15] react with 1,2-dehydrobenzene forming 10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles. However, 5-cyano-3-(2-pyridyl)-1,2,4-triazines have never before been used as starting materials in these reactions.

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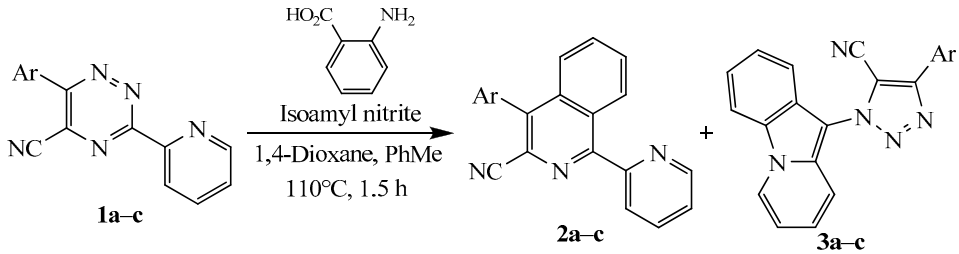
We have established that, unlike in the case of 5,6-aryl-substituted 1,2,4-triazines, the reaction of 5-cyanotriazines **1a-c** with 1,2-dehydrobenzene generated *in situ* from isoamyl nitrite and anthranylic acid, generally leads to moderate yields of the 3-cyano-1-(2-pyridyl)isoquinolines **2a-c**, while the 10-(4-aryl-5-cyano-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles **3a-c** are formed only in trace quantities (< 5% according to ^{1}H NMR spectroscopy data).

Compound **3b** could be isolated and characterized, while the products **3a**,**c** were identified by mass spectrometry. The structure of 3-cyanoisoquinolines **2a-c** was proved by ^{1}H and ^{13}C NMR, as well as by IR spectroscopy, mass spectrometry, and elemental analysis. All the spectral characteristics of compound **3b** were substantially similar to those of pyrido[1,2-*a*]indoles previously described by us, which did not contain a cyano group [15].



a Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** 4-BrC_6H_4

Thus, we have proposed a new and convenient method for the synthesis of 3-cyano-1-(2-pyridyl)-isoquinolines, based on available 5-cyano-1,2,4-triazines. Only minor amounts of the 10-(4-aryl-5-cyano-1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indole by-products were formed.

IR spectra were recorded on a Bruker Alpha FTIR spectrometer with an ATR accessory (ZnSe). ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance II instrument (400 and 100 MHz, respectively) in $CDCl_3$ (unless indicated otherwise), internal standard – TMS. Mass spectra were recorded on a MicrOTOF-Q II mass spectrometer (Bruker Daltonics) with electrospray ionization. Elemental analysis was performed on a PE 2400 II CHN-analyzer (Perkin Elmer). Melting points were determined on a Boetius apparatus.

The 6-aryl-5-cyano-3-(2-pyridyl)-1,2,4-triazines **1a-c** were obtained by a previously described method [10].

6-(4-Bromophenyl)-3-(2-pyridyl)-1,2,4-triazine-5-carbonitrile (1c). Yield 85%, yellow crystals, mp 172-174°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.55-7.59 (1H, m, H-5 Py); 7.78-7.83 (2H, m, H Ar); 8.00 (1H, td, ^3J = 7.8, ^4J = 2.0, H-4 Py); 8.04-8.09 (2H, m, H Ar); 8.71 (1H, dd, ^3J = 7.8, ^4J = 0.8, H-3 Py); 8.96 (1H, dd, ^3J = 4.8, ^4J = 2.0, H-6 Py). Mass spectrum, *m*/*z* (I_{rel}, %): 338 $[M+H]^+$ (100). Found, %: C 53.11; H 2.21; N 20.52. $C_{15}H_8BrN_5$. Calculated, %: C 53.28; H 2.38; N 20.71.

Interaction of 5-Cyano-1,2,4-triazines 1a-c with 1,2-Dehydrobenzene (General Method). The appropriate triazine **1a-c** (3 mmol) was suspended in anhydrous toluene (130 ml), and isoamyl nitrite (130 ml, 12 mmol) was added. The obtained mixture was stirred at room temperature under argon atmosphere with dropwise addition of an anthranylic acid (1.64 g, 12 mmol) solution in anhydrous 1,4-dioxane (15 ml) over 30 min. The mixture was further stirred at reflux for another 1 h, followed by cooling to room temperature. The reaction mixture was washed with aqueous 3 M NaOH solution (3×75 ml), the organic layer was dried over anhydrous Na_2SO_4, the solvents were removed by distillation at reduced pressure. The products were isolated by column chromatography (silica gel, eluent CH_2Cl_2–AcOEt, 7:5). Reference samples of these products were obtained by recrystallization from MeCN.

4-Phenyl-1-(2-pyridyl)isoquinoline-3-carbonitrile (2a). Yield 0.33 g (36%), light-yellow crystals, mp 171-173°C. R_f 0.6. IR spectrum, ν, cm^{-1}: 2227 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.53-7.60 (3H, m, H Ph); 7.62-7.69 (3H, m, H Ph, H-5 Py); 7.72-7.76 (1H, m, H-8); 7.82-7.87 (2H, m, H-6,7); 8.06 (1H, td, ^3J = 7.8, ^4J = 2.0, H-4 Py); 8.12 (1H, dd, ^3J = 7.8, ^4J = 0.8, H-3 Py); 8.80 (1H, dd, ^3J = 4.8, ^4J = 2.0, H-6 Py); 8.90–8.94 (1H, m, H-5). Mass spectrum, *m*/*z* (I_{rel}, %): 308 $[M+H]^+$ (100). Found, %: C 81.92; H 4.08; N 13.36. $C_{21}H_{13}N_3$. Calculated, %: C 82.07; H 4.26; N 13.67.

1-(2-Pyridyl)-4-(4-tolyl)isoquinoline-3-carbonitrile (2b). Yield 0.30 g (31%), light-yellow crystals, mp 196-198°C. R_f 0.6. IR spectrum, ν, cm^{-1}: 2224 (CN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.50 (3H, s, CH_3); 7.41-7.43 (4H, m, H Ar); 7.45-7.49 (1H, m, H-5 Py); 7.71-7.79 (2H, m, H-6,7); 7.81-7.85 (1H, m, H-8); 7.97 (1H, td, ^3J = 7.8, ^4J = 2.0, H-4 Py); 8.13 (1H, dd, ^3J = 7.8, ^4J = 0.8, H-3 Py); 8.80-8.86 (2H, m, H-5, H-6 Py). ^{13}C NMR spectrum, δ, ppm: 21.4; 117.8; 123.9; 125.4; 125.6; 126.6; 127.5; 128.5; 129.6; 130.0; 130.1; 130.7; 131.3; 136.0; 137.3; 139.4; 140.6; 148.6; 157.0; 158.0. Mass spectrum, *m*/*z* (I_{rel}, %): 322 $[M+H]^+$ (100). Found, %: C 82.05; H 4.54; N 12.93. $C_{22}H_{15}N_3$. Calculated, %: C 82.22; H 4.70; N 13.07.

4-(4-Bromophenyl)-1-(2-pyridyl)isoquinoline-3-carbonitrile (2c). Yield 0.45 g (39%), light-yellow crystals, mp 213-215°C. R_f 0.65. IR spectrum, ν, cm^{-1}: 2224 (CN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.39-7.43 (2H, m, H Ar); 7.46-7.50 (1H, m, H-5 Py); 7.72-7.81 (5H, m, H Ar, H-6,7,8); 7.97 (1H, td, ^3J = 7.8, ^4J = 2.0, H-4 Py); 8.14 (1H, dd, ^3J = 7.8, ^4J = 0.8, H-3 Py); 8.82 (1H, dd, ^3J = 4.8, ^4J = 2.0, H-6 Py); 8.84-8.88 (1H, m, H-5). Mass spectrum, *m*/*z* (I_{rel}, %): 386 $[M+H]^+$ (100). Found, %: C 65.11; H 2.97; N 10.56. $C_{21}H_{12}BrN_3$. Calculated, %: C 65.30; H 3.13; N 10.88.

(1-Pyrido[1,2-*a*]indol-10-yl)-4-(4-tolyl)-1*H*-1,2,3-triazole-5-carbonitrile (3b). Yield 0.03 g (3%), colorless crystals, mp 196-198°C. R_f 0.8. IR spectrum, ν, cm^{-1}: 2232 (CN). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.46 (3H, s, CH_3); 6.77 (1H, td, ^3J = 7.0, ^4J = 1.0, H HetAr); 7.19-7.23 (1H, m, H HetAr); 7.35-7.39 (2H, m, H-3,5 Ar); 7.42-7.46 (1H, m, H HetAr); 7.48-7.56 (2H, m, H HetAr); 7.75 (1H, d, ^3J = 8.3, H HetAr); 8.00 (1H, d, ^3J = 8.3, H HetAr); 8.09-8.13 (2H, m, H-2,6 Ar); 8.48 (1H, d, ^3J = 7.0, H HetAr). ^{13}C NMR spectrum, δ, ppm: 21.5; 110.0; 110.3; 110.7; 115.9; 117.2; 117.4; 121.7; 123.7; 124.4; 125.1 (2C); 125.9; 126.6; 128.1; 130.0; 131.9; 140.6; 146.3; 151.8. Mass spectrum, *m*/*z* (I_{rel}, %): 350 $[M+H]^+$ (100). Found, %: C 75.48; H 4.22; N 19.83. $C_{22}H_{15}N_5$. Calculated, %: C 75.63; H 4.33; N 20.04.

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