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SIMPLIFIED METHOD FOR OBTAINING 3-BROMINDOL-5,6-DICARBONITRILS FROM 1-HYDROXINDOL-5,6-DICARBONITRILES

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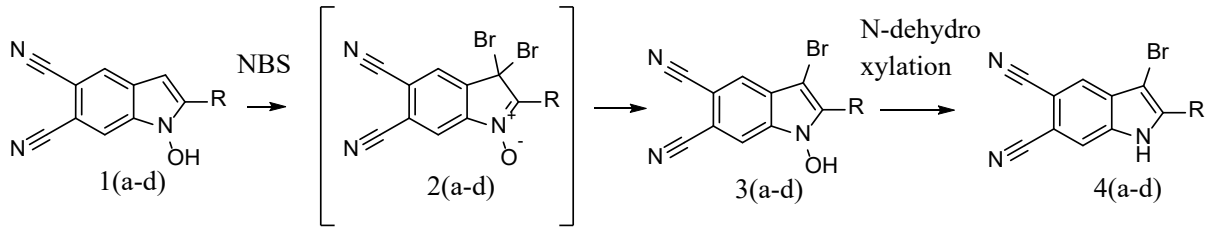
A simplified two-stage method was developed for the preparation of 2-aryl-3-bromoindole-5,6-dicarbonitriles from 2-aryl-1-hydroxyindole-5,6-dicarbonitriles, based on direct bromination with bromine and subsequent dehydroxylation of the resulting intermediates.

Introduction

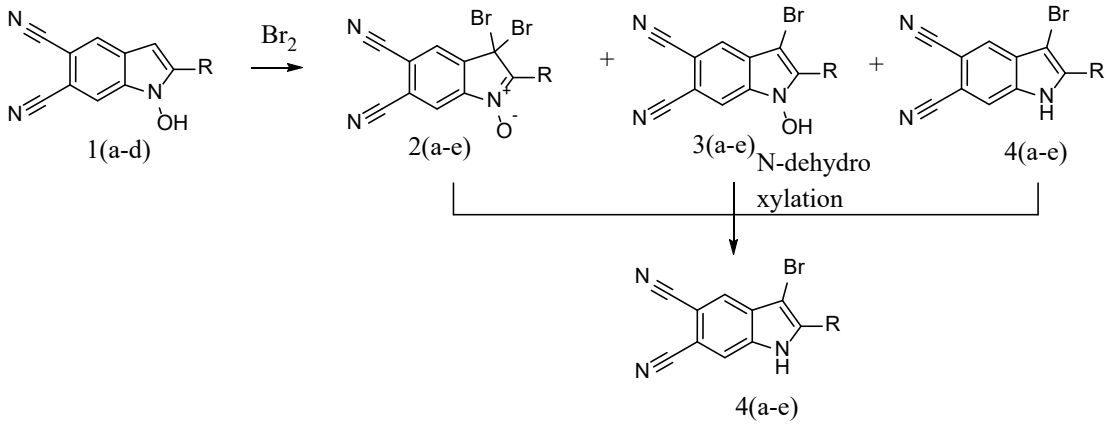
Brominated indoles are important organic synthesis products. They exhibit a number of biological properties, namely: they are inhibitors of monoamine oxidases A and B (MAO A and B) [1, 2], plant growth stimulators [3], and an integral part of some natural compounds [4]. In addition, heterocyclic bromine-containing compounds can be initial building blocks for further functionalization using metal catalysis [5, 6]. It should also be noted that aromatic compounds with two *ortho*-cyano groups are the main precursors for the preparation of macrocycles [7, 8] and branched polymers [9]. In this regard, the development of new methods for the synthesis of 3-bromoindole-5,6-dicarbonitriles is an urgent task.

There are various methods known of obtaining 3-bromoindoles [10-12]. The most frequently used method in preparative practice is the method of bromination of indoles at position 3 using *N*-bromosuccinimide [13, 14]. We previously used it to obtain 3-bromohydroxyindoles **3** [2, 15], and additionally used the dehydroxylation method to synthesize the corresponding 3-bromoindoles **4** [16]. It should be noted that hydroxyindoles **1** in the presence of *N*-bromosuccinimide are brominated selectively with the formation of mainly 3-bromo-1-hydroxyindole **3**. In this case, initially, as a rule, unstable 3,3-dibromoindole-*N*-oxides **2** are obtained, which are transformed into more stable 3-bromohydroxyindoles **3**, and they can already be converted to 3-bromoindoles **4** according to this scheme:



a – R=C_6H_5; b – R=4-MeC_6H_4; c – R=4-$MeOC_6H_4$; d – R=2-thienyl

We have found that direct bromination with liquid bromine in acetic acid or dioxane is not selective and, as a rule, leads to a mixture of bromination products **2-4**. However, the resulting mixtures of bromoindoles **2-4** without additional purification can be transformed into 3-bromoindoles **4** using the dehydroxylation method according to the following scheme. This makes it possible to simplify the method for obtaining the target 3-bromo indoles **4**, as well as to exclude the stages of purification and isolation of compounds **2**, thus reducing the overall cost of using reagents and solvents.



a – R=C_6H_5; b – R=4-MeC_6H_4; c – R=4-$MeOC_6H_4$; d – R=2-thienyl

The best results were achieved by heating the reaction mixture to 110 °C with a twofold excess of bromine in acetic acid for 3-4 hours. According to ^{1}H NMR data, it was found that the mixture of products consists mainly of compounds **3** and **4**, with the content of the target product up to 20-30%. In this case, the total yield reached 78%. Attempts to optimize the reaction conditions in order to obtain selectively 3-bromoindole **4** were unsuccessful and often led to a significant decrease in the overall yield of products, as well as partial hydrolysis of cyano groups due to the released hydrogen bromide. Therefore, it was proposed to use an additional stage of dehydroxylation to convert the mixture into a homogeneous product **4**. For this, the mixture, consisting mainly of products **3** and **4**, was heated in isopropyl alcohol in the presence of an equimolar amount of phenacyl bromide and triethylamine according to a previously developed method. As a result, the target product **4** was obtained with a yield of 89%, which is slightly higher than in the reaction with pure 3-bromo-1-hydroxyindole **3**, which is probably due to the presence of the target 3-bromoindole **4** in the mixture.

The physicochemical characteristics of the target compound **4**, obtained by the reaction with bromine, did not differ from the products synthesized using *N*-bromosuccinimide [2]. It should be noted that when compound **1c** was used, the thiophene ring was also brominated. As a result, 3-bromo-2-(5-bromothiophen-2-yl)-1H-indole-5,6-dicarbonitrile **4c** was formed in a yield of up to 30%. The dibromination product was isolated by fractional crystallization from alcohol, since it accumulated in the solvent.

Experimental part

IR spectra were recorded on a Fourier "RX-1 Perkin Elmer" instrument with a wavelength of 700–4000 cm^{-1}. The analyzed substances were in the form of a suspension in liquid paraffin.

NMR spectra were recorded on a "Bruker DRX-400" or "Bruker DRX-500" instrument for DMSO-d_6 solutions at 30 °C. The signals of residual protons of the solvent in ^{1}H NMR (δ_H 2,50 ppm) or in ^{13}C NMR (δ_C 39,5 ppm) were used as a reference for counting chemical shifts; the signal of tetramethylsilane was used as a marker. Mass spectra were recorded on a „FINNIGAN MAT.INCOS 50" gas chromatography-mass spectrometer at an ionization voltage of 70 eV and a temperature in the ionization chamber of 100–220 °C. Elemental analysis was performed on Perkin Elmer 2400. Melting points were determined on a Büchi M-560 melting point and boiling point apparatus.

General method for the synthesis of compounds **2 (a-c)** and **3 (a-d)** (General method). To a solution of 1 mmol of compound **1 (a-d)** in 10 ml of glacial acetic acid was added 2 mmol of bromine. The reaction mixture was heated at 80–100 °C for 4–8 h. Then it was cooled and diluted with a tenfold excess of cold water. The formed crystalline precipitate was filtered off, recrystallized from ethyl alcohol (to obtain compounds **4 (a-d)**, and dried in air.

Synthesis of compounds **4 (a-d)** (General method). To the mixture of compounds **2 (a-c)** and **3 (a-d)** obtained at the previous stage, 3 ml of alcohol, 1 mmol of phenacyl bromide, 2.5 mmol of TEA were added and the mixture was stirred at 40–65 °C for 2–8 h. Then the reaction mixture cooled and kept at room temperature for 24 h. After completion of the reaction (monitored by TLC), 3 ml of water was added, the formed precipitate was filtered off, thoroughly washed with water, and recrystallized from EtOH. Air dried.

3-bromo-2-phenyl-1*H*-indole-5,6-dicarbonitrile**(4a)**

Gray powder 228 mg (71%), temp. 273–275 °C. IR (υ_{max}, oil): 3278 (NH), 2238, (CN), 1608 (Ar), MS (EI, 70 eV): *m/z* (%): 323 $[M]^+$ (99), 321 $[M]^+$ (100), 215 (22). IR (υ_{max}, oil): 3267 (NH), 2238, (CN), 1605 (Ar),^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.54 (*t*, *J*=7.5 Hz, 1 H, 7-H), 7.60 (*t*, *J*=7.5 Hz, 2 H, 3',5'-H), 7.91 (d, *J*=7.5 Hz, 2 H, 2',6'-H), 8.17 (s, 1 H), 8.22 (s, 1 H, 4-H) 13.13 (br. s., 1 H, NH). Found, %:C, 59.43; H, 2.48; N, 13.01. $C_{16}H_8BrN_3$. Calculated, %: C, 59.65; H, 2.50; N, 13.04.

3-bromo-2-(p-tolyl)-1*H*-indole-5,6-dicarbonitrile**(4b)**

Gray powder 261 mg (78%), temp. 286–288 °C. IR (υ_{max}, oil): 3283 (NH), 2242, 2222 (CN), 1571 (Ar). MS (EI, 70 eV): *m/z* (%): 337 $[M]^+$ (98), 335 $[M]^+$ (100), 254 (14). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.40 (s, 3H, Me), 7.41 (d, 2H, *J*=8.0 Hz, 3',5'-H), 7.81 (d, 2H, *J*=8.0 Hz, 2',6'-H), 8.13 (s, 1H, 7-H), 8.20 (s, 1H, 4-H), 13.02 (s, 1H, NH).^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm): 20.9, 88.7, 104.7, 106.0, 117.1, 117.2, 118.6, 125.6, 126.3, 128.1 (2C), 129.4 (2C), 130.0, 135.5, 139.5, 140.7. Found, %: C 60.48; H 2.98; N 12.46. $C_{17}H_{10}BrN_3$. Calculated, %: C, 60.73; H, 3.00; N, 12.50.

3-bromo-2-(4-methoxyphenyl)-1*H*-indole-5,6-dicarbonitrile **(4c)**

Gray powder 267 mg (76%), temp. 300–302 °C. ИК (υ_{max}, oil): 3274 (NH), 2240, 2222 (CN), 1604 (Ar), 1247, 1182, 1081(OCH_3), MS (EI, 70 eV): *m/z* (%): 353 $[M]^+$ (100), 351 $[M]^+$ (99), 338 $[M\text{-}Me]^+$ (24), 336 $[M\text{-}Me]^+$ (25), 310 (11), 308 (11). ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 3.85 (s, 3H, OMe), 7.16 (d, 2H, *J*=8.8 Hz, 3',5'-H), 7.87 (d, 2H, *J*=8.8 Hz, 2',6'-H), 8.12 (s, 1H, 4-H), 8.18 (s, 1H, 7-H), 12.98 (s, 1H, NH). ^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm):

55.4, 88.1, 104.7, 105.8, 114.3 (2C), 117.2, 117.3, 118.3, 121.3, 125.3, 129.6 (2C), 130.0, 135.4, 140.6, 160.3. Found, %: C 57.76; H 2.84; N, 11.89. $C_{17}H_{10}BrN_3O$. Calculated, %: C 57.98; H 2.86; N 11.93.

3-bromo-2-(thiophen-2-yl)-1*H*-indole-5,6-dicarbonitrile **(4d)**

Gray powder 140 mg (43%), temp. 307–309 °C. IR (υ_{max}, oil): 3270 (NH), 2239, 2225 (CN), 1590 (Ar), MS (EI, 70 eV): *m/z* (%): 328 $[M]^+$ (100), 326 $[M]^+$ (99), 248 (11), 165(11),. 82(11). ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 7.37 (dd, *J*=4.9, 3.9 Hz, 1 H, 7.59 (d, *J*=3.9 Hz, 1 H), 8.01, (d, *J*=4.9 Hz, 1 H), 8.27 (s, 1 H), 8.61 (s, 1 H), 13.0 (s, 1 H, NH). Found, %: C, 51.07; H, 1.82; N, 12.77. $C_{14}H_6BrN_3S$ 328,19. Calculated, %: C 51.24; H 1.84; N 12.80.

3-bromo-2-(5-bromothiophen-2-yl)-1*H*-indole-5,6-dicarbonitrile (**4e**)

Gray powder 118 mg (29%), temp>300 °C with decomposition. IR (υ_{max}, oil): 3268 (NH), 2240, (CN), 1593 (Ar), MS (EI, 70 eV): *m/z* (%): 409(43), 406 $[M]^+$ (76),405 (37) 344 $[M]^+$ (19), 343 (100), 344(94), ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 7.51 (d, *J*=4.0 Hz, 1 H), 7.44 (d, *J*=4.0Hz, 1 H), 8.29 (s, 1 H), 8.63 (s, 1 H), 13.1 (s, 1H, NH). IR (υ_{max}, oil): 3268 (NH), 2237, 2227 (CN), 1596 (Ar). Found, %: C 41.23; H 1.22; N 10.29.$C_{14}H_5Br_2N_3S$. Calculated, %: C 41.31; H 1.24; N 10.32.

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