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Synthesis of Substituted Indazole-5,6-dicarbonitriles

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Abstract—Methods have been developed for the synthesis of previously unknown N-substituted 1*H*-indazole-5,6-dicarbonitriles from 4-methyl-5-nitrophthalonitrile.

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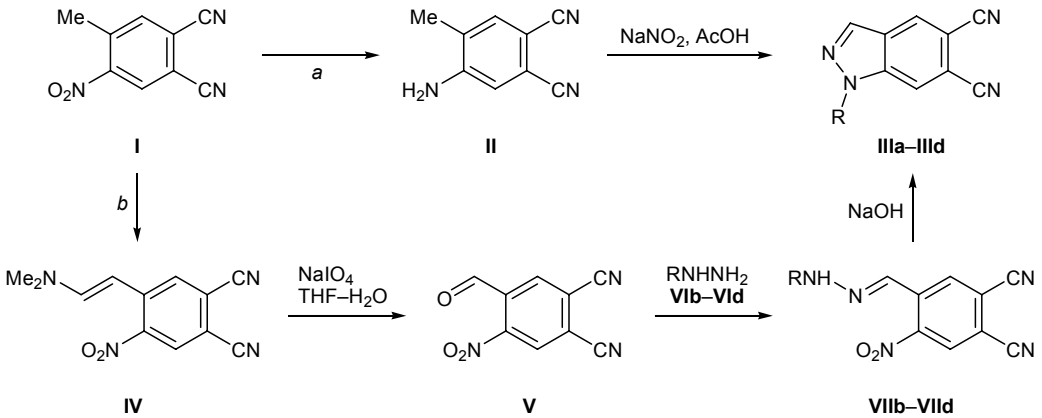
Heterocyclic systems containing an indazole fragment are efficient bioisosters of indole and benzimidazole derivatives possessing diverse biological activity, in particular antitumor [1], antimicrobial [2], and anti-inflammatory [3]. The presence of two cyano groups in the *ortho* position with respect to each other makes indazole-5,6-dicarbonitriles convenient building blocks for the synthesis of various phthalocyanines that are chromophoric compounds promising for use in optics [4], nonlinear optics [5], electronic power transmission systems [6], light-emitting diodes [7], and supramolecular chemistry [8]. Different synthetic approaches to indazoles have been reported, including those based on nucleophilic substitution reactions [9, 10]; however, we have found no published data on the synthesis of 1*H*-indazole-5,6-dicarbonitriles.

In the present article we describe two methods of synthesis of new *N*-substituted 1*H*-indazole-5,6-dicarbonitriles starting from 4-methyl-5-nitrophthalonitrile (**I**) [11] (Scheme 1). The first method (*a*) implies reduction of **I** with $SnCl_2$ to the corresponding amine **II** according to [12], followed by treatment of **II** with sodium nitrite in glacial acetic acid. Intramolecular azo coupling involving the activated methyl group of the substrate led to the formation of indazole **IIIa** in 65% yield.

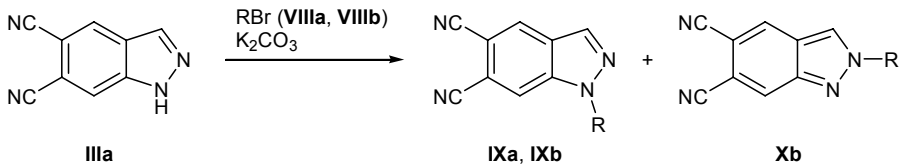
Following the second procedure (*b*), initial compound **I** was heated for 3 h in excess dimethylformamide dimethyl acetal. Dimethylaminoethenyl derivative **IV** thus obtained was oxidized with sodium periodate under stirring in 50% aqueous THF for 4 h at 55–65°C [13]. The product was 4-formyl-5-nitro-

Scheme 1.



R = H (**a**), Ph (**b**), 4-$MeOC_6H_4$ (**c**), 4-MeC_6H_4 (**d**).

Scheme 2.



R = 3,4-$Me_2C_6H_3C(O)CH_2$ (**a**), $PhCH_2$ (**b**).

phthalonitrile **V** (63%). Its condensation with substituted hydrazines **VIb**–**VId** in alcohol at 70–80°C gave the corresponding hydrazones **VIIb**–**VIId** which underwent intramolecular heterocyclization on heating in 4% alcoholic sodium hydroxide. As a result, *N*-substituted indazole-5,6-dicarbonitriles **IIIb**–**IIId** were isolated in 72–76% yield.

The molecule of 1*H*-indazole-5,6-dicarbonitrile (**IIIa**) possesses a fairly reactive NH group which could give rise to prototropic tautomerism [14], it is also capable of acting as nucleophile in nucleophilic substitution reactions. This was confirmed by successful alkylation of indazole **IIIa** with 3,4-dimethylphenacyl bromide (**VIIIa**) and benzyl bromide (**VIIIb**). The reactions were carried out in DMF in the presence of K_2CO_3 at 40–60°C (reaction time 1–2 h). In the reaction with more active bromide **VIIIa** we isolated 1-substituted isomer **IXa** as the major product, whereas the reaction with benzyl bromide gave a mixture of 1- and 2-substituted isomers **IXb** and **Xb** at a ratio of 5:3 (Scheme 2).

The structure of the newly synthesized compounds was determined on the basis of their IR, ^{1}H NMR, and mass spectra. The key signals in the ^{1}H NMR spectra of **IIIa**–**IIId** were singlets belonging to 4-H and 7-H, as well as to 3-H, in the region δ 8.0–8.8 ppm, which indicated formation of five-membered nitrogen-containing heterocycle. Compound **V** characteristically displayed a signal from the aldehyde proton at δ 10.22 ppm. The structure of indazoles **IXa**, **IXb**, and **Xb** was determined using NOESY spectroscopy. Substitution at the N^1 atom in compounds **IXa** and **IXb** followed from the presence of cross peaks between protons in the CH_2 group of the R substituent and 7-H and between 3-H and 4-H. The NOESY spectrum of 2-substituted isomer **Xb** showed cross peaks between the NCH_2 protons and 3-H and between 3-H and 4-H.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 30°C on a Bruker DRX-500 instrument from solutions in DMSO-d_6 using the residual proton signal of the solvent as reference (δ 2.50 ppm). The elemental compositions were determined on a CHN-1 analyzer. The IR spectra were measured on a Perkin Elmer RX-1 spectrometer from samples dispersed in mineral oil and placed between KBr plates. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT INCOS-50 GC–MS system (ion source temperature 100–220°C).

1*H*-Indazole-5,6-dicarbonitrile (IIIa). A solution of 0.3 g (4.4 mmol) of sodium nitrite in 0.6 ml of water was added in one portion under vigorous stirring to a suspension of 0.3 g (1.9 mmol) of 4-amino-5-methylphthalonitrile (**II**) in 5 ml of glacial acetic acid. The mixture was stirred for 40 min at room temperature and diluted with an equal volume of water, and the precipitate was filtered off, washed with water on a filter, and dried. Yield 0.207 g (65%), mp 185–187°C. IR spectrum, ν, cm^{-1}: 3270 (NH), 2231 (C≡N), 1611 ($C=C_{arom}$). ^{1}H NMR spectrum, δ, ppm: 8.38 s (1H, 4-H), 8.41 s (1H, 7-H), 8.64 s (1H, 3-H), 14.15 s (1H, NH). Found, %: C 64.09; H 2.35; N 33.10. $C_9H_4N_4$. Calculated, %: C 64.28; H 2.40; N 33.32.

4-Formyl-5-nitrophthalonitrile (V). Sodium periodate, 1.278 g (6 mmol), was dissolved in 10 ml of water, a solution of 0.484 g (2 mmol) of 4-[(*E*)-2-(dimethylamino)vinyl]-5-nitrophthalonitrile (**IV**) [13] in THF was added, and the mixture was stirred for 3–4 h at 50–60°C and extracted with methylene chloride. The extract was washed with water and subjected to chromatography on silica gel using methylene chloride–hexane (1:2) as eluent. The eluate was evaporated, and the precipitate was filtered off, washed with alcohol, and dried. Yield 0.253 g (63%), mp 155–157°C. IR spectrum, ν, cm^{-1}: 2233 (C≡N); 1670 (C=O); 1616 ($C=C_{arom}$); 1557, 1351 (NO_2). ^{1}H NMR spectrum, δ, ppm: 8.63 s (1H, 3-H), 9.02 s (1H, 6-H), 10.22 s (1H, CHO). Found, %: C 53.60; H 1.43; N 20.78. $C_9H_3N_3O_3$. Calculated, %: C 53.74; H 1.50; N 20.89.

Hydrazonomethylphthalonitriles VIIb–VIId (*general procedure*). Substituted hydrazine **VIb**–**VId**, 3 mmol, was added to a solution of 0.426 g (2 mmol) of compound **V** in 5 ml of alcohol. The mixture was

stirred for 1 h at 70–78°C, and the precipitate was filtered off, washed with alcohol, and dried.

4-Nitro-5-[(*E*)-phenylhydrazonomethyl]phthalonitrile (VIIb). Yield 0.43 g (74%), mp >300°C. IR spectrum, ν, cm^{-1}: 3276 (NH); 2230 (C≡N); 1605 (C=C_{arom}); 1541, 1330 (NO_2). ^1H NMR spectrum, δ, ppm: 6.94 t (1H, 4′-H, *J* = 7.2 Hz), 7.28 m (4H, Ph), 8.17 s (1H, CH), 8.73 s (1H, 3-H), 11.55 s (1H, NH). Found, %: C 61.70; H 3.05; N 23.95. $C_{15}H_9N_5O_2$. Calculated, %: C 61.86; H 3.11; N 24.04.

4-[(*E*)-(4-Methoxyphenyl)hydrazonomethyl]-5-nitrophthalonitrile (VIIc). Yield 0.514 g (80%), mp 259–260°C (decomp.). IR spectrum, ν, cm^{-1}: 3280 (NH); 2233 (C≡N); 1604, 1487 (C=C_{arom}); 1541, 1330 (NO_2); 1255, 1235, 1029 (OMe). ^1H NMR spectrum, δ, ppm: 3.73 s (3H, OMe), 6.91 d (2H, 3′-H, 5′-H, *J* = 9.0 Hz), 7.21 d (2H, 2′-H, 6′-H, *J* = 9.0 Hz), 8.12 s (1H, CH), 8.94 s (1H, 3-H), 9.17 s (1H, 6-H), 11.56 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 321 (69) $[M]^+$, 274 (66) $[M - HNO_3]^+$, 259 (39), 231 (40), 204 (11), 178 (14), 64 (15). Found, %: C 59.64; H 3.38; N 21.70. $C_{16}H_{11}N_5O_3$. Calculated, %: C 59.81; H 3.45; N 21.80. *M* 321.29.

4-[(*E*)-4-Methylphenylhydrazonomethyl]-5-nitrophthalonitrile (VIId). Yield 0.476 g (78%), mp 245–247°C (decommp.). IR spectrum, ν, cm^{-1}: 3279 (NH); 2231 (C≡N); 1605 (C=C_{arom}); 1541, 1329 (NO_2). ^1H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 7.08 d (2H, 3′-H, 5′-H, *J* = 8.5 Hz), 7.12 d (2H, 2′-H, 6′-H, *J* = 8.5 Hz), 8.14 s (1H, CH) , 8.65 s (1H, 3-H), 8.77 s (1H, 6-H), 11.47 s (1H, NH). Found, %: C 62.78; H 3.57; N 22.81. Mass spectrum: *m*/*z* 305 $[M]^+$. $C_{16}H_{11}N_5O_2$. Calculated, %: C 62.95; H 3.63; N 22.94. *M* 305.30.

Indazole-5,6-dicarbonitriles IIIb–IIId (*general procedure*). Sodium hydroxide, 0.168 g (3 mmol), was added to a solution of 2 mmol of compound **VIIb**–**VIId** in a mixture of 4 ml of alcohol and 1 ml of DMF. The mixture was stirred for 1 h at room temperature, and the precipitate was filtered off, washed with alcohol, and dried.

1-Phenyl-1*H*-indazole-5,6-dicarbonitrile (IIIb). Yield 0.342 g (70%), mp >300°C. IR spectrum, ν, cm^{-1}: 2238 (C≡N); 1609, 1520 (C=C_{arom}); 1258. ^1H NMR spectrum, δ, ppm: 7.70 m (5H, Ph), 8.75 m (3H, NH, 4-H, 7-H). Found, %: C 73.60; H 3.23; N 22.83. Mass spectrum: *m*/*z* 244 $[M]^+$. $C_{15}H_8N_4$. Calculated, %: C 73.76; H 3.30; N 22.94. *M* 244.26.

1-(4-Methoxyphenyl)-1*H*-indazole-5,6-dicarbonitrile (IIIc). Yield 0.406 g (74%), mp 229°C. IR spectrum, ν, cm^{-1}: 2235 (C≡N); 1610, 1518 (C=C_{arom}); 1258, 1117, 1023 (C–O–C); 825 (δC_6H_4-1,4). ^1H NMR spectrum, δ, ppm: 3.86 s (3H, OMe), 7.18 d (2H, 3′-H, 5′-H, *J* = 8.9 Hz), 7.72 d (2H, 2′-H, 6′-H, *J* = 8.9 Hz), 8.58 s (1H, 3-H), 8.69 s (1H, 7-H), 8.81 s (1H, 4-H). Mass spectrum, *m*/*z* (I_{rel}, %): 274 (100) $[M]^+$, 259 (39), 231 (40), 204 (11), 178 (14), 64 (15). Found, %: C 69.04; H 2.83; N 15.03. $C_{16}H_{10}N_4O$. Calculated, %: C 70.07; H 3.67; N 20.43. *M* 274.28.

1-(4-Methylphenyl)-1*H*-indazole-5,6-dicarbonitrile (IIId). Yield 0.392 g (76%), mp 224–225°C. IR spectrum, ν, cm^{-1}: 2229 (C≡N); 1610, 1518 (C=C_{arom}); 831 (δC_6H_4-1,4). ^1H NMR spectrum, δ, ppm: 2.43 s (3H, Me), 7.24 d (2H, 3′-H, 5′-H, *J* = 7.7 Hz), 7.69 d (2H, 2′-H, 6′-H, *J* = 7.7 Hz), 8.61 s (1H, 3-H), 8.68 s (1H, 7-H), 8.78 s (1H, 4-H). Mass spectrum, *m*/*z* (I_{rel}, %): 258 (100) $[M]^+$, 230 (17), 91 (44), 77 (27), 65 (41). Found, %: C 74.23; H 3.83; N 21.58. $C_{16}H_{10}N_4$. Calculated, %: C 74.41; H 3.90; N 21.69. *M* 258.25.

1- and 2-Substituted indazole-5,6-dicarbonitriles IXa, IXb, and Xb (*general procedure*). Bromide **VIIIa** or **VIIIb**, 3 mmol, and potassium carbonate, 0.414 g (3 mmol), were added to a solution of 0.504 g (3 mmol) of compound **IIIa** in 5 ml of DMF. The mixture was stirred for 1–2 h at 40–60°C and diluted with water, and the precipitate was filtered off, washed with alcohol, and dried.

1-[2-(3,4-Dimethylphenyl)-2-oxoethyl)-1*H*-indazole-5,6-dicarbonitrile (IXa). Yield 0.593 g (65%), mp 234–235°C. ^1H NMR spectrum, δ, ppm: 2.34 s (6H, Me), 6.29 s (2H, CH_2), 7.38 d (1H, 5′-H, *J* = 7.9 Hz), 7.82 d.d (1H, 6′-H, *J* = 7.9, 1.8 Hz), 7.87 d (1H, 2′-H, *J* = 1.8 Hz), 8.52 s (1H, 3-H), 8.71 s (1H, 7-H), 8.73 s (1H, 4-H). Mass spectrum, *m*/*z* (I_{rel}, %): 314 (3) $[M]^+$, 134 (10), 133 (100), 105 (18), 77 (16).

1-Benzyl-1*H*-indazole-5,6-dicarbonitrile (IXb). Yield 0.488 g (63%) (in a mixture with **Xb**). ^1H NMR spectrum, δ, ppm: 5.67 s (2H, CH_2), 7.22 d (2H, 2′-H, 6′-H, *J* = 7.8 Hz), 7.35 t (2H, 3′-H, 5′-H, *J* = 7.8 Hz), 7.41 t (1H, 4′-H), 7.82 s (1H, 7-H), 8.26 s (2H, 3-H, 4-H). Mass spectrum, *m*/*z* (I_{rel}, %): 258 (41) $[M]^+$, 91 (100).

2-Benzyl-2*H*-indazole-5,6-dicarbonitrile (Xb). Yield 0.286 g (37%) (in a mixture with **IXb**). ^1H NMR spectrum, δ, ppm: 5.67 s (2H, CH_2), 7.33–7.36 m (4H, 2′-H, 3′-H, 5′-H, 6′-H, *J* = 7.8 Hz), 7.40 t (1H, 4′-H, *J* = 7.8 Hz), 8.16 s (1H, 3-H), 8.21 s (1H, 4-H), 8.24 s (1H, 7-H). Mass spectrum, *m*/*z* (I_{rel}, %): 258 (41) $[M]^+$, 91 (100).

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