New rearrangement of benzo[*d*]isoxazoles: recyclization of 4-R-6-nitrobenzo[*d*]isoxazole-3-carbaldehyde arylhydrazones into 2-aryl-4-(2-hydroxy-4-nitro-6-R-phenyl)-1,2,3-triazoles

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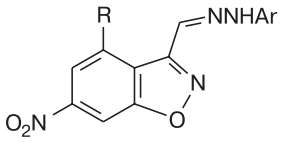
The previously unknown recyclization of nitrobenzo[*d*]isoxazoles into 1,2,3-triazoles was found. A general method for the synthesis of 2-aryl-4-(2-hydroxy-4-nitro-6-R-phenyl)-1,2,3-triazoles from 4-R-6-nitrobenzo[*d*]isoxazole-3-carbaldehyde arylhydrazones was developed.

Key words: nitro compounds, benzo[*d*]isoxazoles, 2-aryl-1,2,3-triazoles, recyclization.

We have previously[1] developed a method for the synthesis of 4,6-dinitrobenzo[*d*]isoxazole-3-carbaldehyde phenylhydrazone (**1a**) and some its derivatives **1b—d** from 2,4,6-trinitrophenylacetaldehyde. Compounds **1b—d** are the products of nucleophilic substitution of the nitro group at position 4 in benzoisoxazole **1a** by anionic nucleophiles. In this work we synthesized new 4,6-dinitrobenzo[*d*]isoxazole-3-carbaldehyde arylhydrazones **1e—g** and previously unknown 4-R-6-nitrobenzo[*d*]isoxazoles **1h—j**. The latter were prepared using regiospecific reactions (see Ref. 1) with S-nucleophiles.



1a—j

Compound	Ar	R
1a	Ph	NO_2
1b	Ph	N_3
1c	Ph	SPh
1d	Ph	SCH_2CO_2Me
1e	4-$NO_2C_6H_4$	NO_2
1f	4-ClC_6H_4	NO_2
1g	4-$MeOC_6H_4$	NO_2
1h	Ph	$PhCH_2S$
1i	Ph	*cyclo*-$C_6H_{11}S$
1j	4-$MeOC_6H_4$	4-ClC_6H_4S

The structures of the compounds were confirmed by a complex of physicochemical methods (^1H and ^{13}C NMR spectroscopy, IR spectroscopy) and elemental analysis data.

We found that heating (80 °C) of dinitro-substituted hydrazones **1a,e—g** with K_2CO_3 in *N*-methylpyrrolidone (NMP)* produces recyclization products, *viz.*, 2-aryl-4-(2-hydroxy-4,6-dinitrophenyl)-1,2,3-triazoles **2a—d** (Scheme 1), with the localized position of the hydroxy group (at the *ortho*-position of the 4-aryl substituent). Note that such a rearrangement in the benzo[*d*]isoxazole series was unknown. Published data concern similar reactions only in the series of nonbenzannelated isoxazoles,[2—4] whereas monocyclic isoxazoles produce the different derivatives, *viz.*, corresponding aldehydes or ketones of the 2-aryl-1,2,3-triazole series.

As follows from the proposed reaction scheme, recyclization is favored by a considerable lability of the N—O bond of the isoxazole cycle toward nucleophilic reagents. Apparently, two nitro groups in the benzene ring of the initial hydrazones facilitate intramolecular nucleophilic substitution (due to the readily leaving dinitrophenoxide fragment). Nevertheless, heating of mononitro derivatives **1c,h,i** in the presence of K_2CO_3 (as in the case of 4,6-dinitro derivatives) also produces the products of intramolecular recyclization, *viz.*, 2-aryl-4-(2-hydroxy-4-nitro-6-R-phenyl)-1,2,3-triazoles **2e—g** containing one nitro group and several functional substituents. The latter imparts greater synthetic valuables to these compounds. However, the reaction occurs at a higher temperature (100 °C) than in the case when dinitro derivatives **1a,e—g** are used because the initial hydrazones contain only one nitro group in the benzene ring.

The structure of 2-aryltriazoles **2** was determined from data of several chemical and physicochemical methods. For example, the ^{13}C NMR spectra exhibit signals at 156—157 ppm corresponding to the C atoms bound to the OH groups. At the same time, no signals are ob-

* The reactions can be carried out in DMF with a more difficult isolation of the target products.

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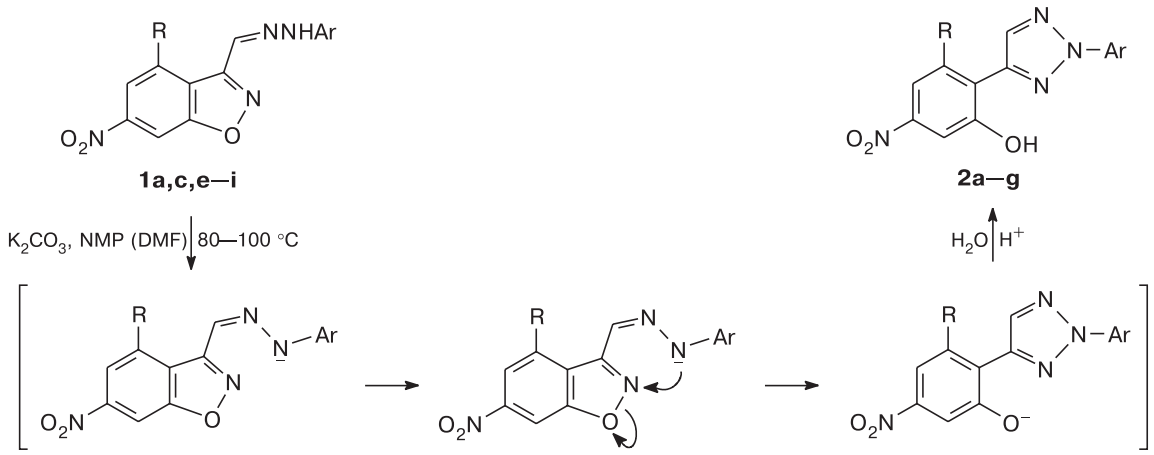
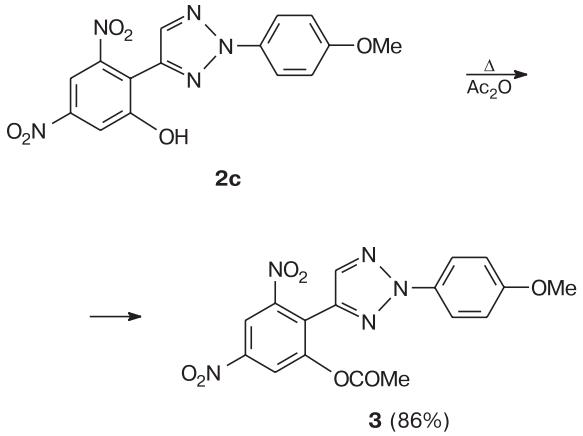
Scheme 1



Compound	Ar	R	Yield (%)	Compound	Ar	R	Yield (%)
2a	Ph	NO_2	60	**2e**	Ph	PhS	37
2b	4-$NO_2C_6H_4$	NO_2	73	**2f**	Ph	$PhCH_2S$	57
2c	4-$MeOC_6H_4$	NO_2	46	**2g**	Ph	*cyclo*-$C_6H_{11}S$	50
2d	4-ClC_6H_4	NO_2	30				

served at 162—163 ppm, which are characteristic of the C(7a) atom common for the isoxazole and benzene cycles and bound to the O atom in the initial dinitrobenzo[*d*]isoxazoles.[1] The position of signals from other C atoms remained virtually unchanged. The ^{14}N NMR spectra of compounds **2a—d** contain two signals corresponding to two nitro groups in the rearrangement products. In particular, for triazole **2a** they lie at −10.90 and −15.60 ppm. In addition, compounds **2** undergo *O*-acylation on boiling in Ac_2O, which is shown for triazole **2c** in Scheme 2.

Scheme 2



The ^{15}N NMR spectrum of *O*-acetyl derivative **3** exhibits signals characteristic of 2-substituted 1,2,3-triazoles.[5] The signal at −58.65 ppm corresponds to the N(2) atom of the triazole cycle, and the N(1) atom gives the signal at −120.37 ppm. At the same time, the signal corresponding to the N(3) atom of 2-substituted 1,2,3-triazole is absent in the spectrum. This takes place sometimes in the case of 4-substituted 1,2,3-triazoles (see, *i.e.*, Ref. 6). All above data along with results of other methods (IR spectroscopy, mass spectrometry, elemental analysis) allow the unambiguous determination of the structure of the recyclization products.

Thus, the previously unknown recyclization of substituted benzo[*d*]isoxazoles into 1,2,3-triazoles was found. The method using this recyclization was developed for synthesis of 2-aryl-4-(2-hydroxy-4-nitro-6-R-phenyl)-1,2,3-triazoles from 4,6-dinitrobenzo[*d*]isoxazole-3-carbaldehyde arylhydrazones.

Experimental

^1H NMR spectra were recorded on a Bruker AC-200 instrument. ^{13}C, ^{14}N, and ^{15}N NMR spectra were obtained on a Bruker AM-300 instrument in DMSO-d_6. Chemical shifts are presented relatively to Me_4Si (^1H, ^{13}C) and $MeNO_2$ (^{14}N, ^{15}N). Upfield (relative to $MeNO_2$) chemical shifts of ^{15}N are presented with minus. IR spectra were recorded on a Specord M-80 instrument in KBr pellets. Mass spectra were obtained on a Kratos MS-30 instrument (EI, 70 eV). The reaction course and purity of substances were monitored by TLC on the Silufol UV-254 plates. Silica gel (0.035—0.070 mm (Acros), eluent $CHCl_3$) was used for column chromatography. Solvents were not specially dried. Compounds **1e—j** were prepared according to previously developed procedures.[1]

4,6-Dinitrobenzo[*d*]isoxazole-3-carbaldehyde *N*-(4-nitrophenyl)hydrazone (1e). Yield 67%, m.p. 248—250 °C (from EtOH). Found (%): C, 45.56; H, 2.22. $C_{14}H_8N_6O_7$. Calculated (%): C, 45.17; H, 2.17. ^1H NMR, δ: 7.24 (d, 2 H, H arom.,

J = 8.8 Hz); 8.16 (d, 2 H, H arom., *J* = 8.8 Hz); 8.41 (s, 1 H, CH=N); 8.83 (s, 1 H, H(5)); 9.15 (s, 1 H, H(7)); 11.85 (s, 1 H, NH). ^{13}C NMR, δ: 109.1, 113.5, 115.1, 119.0, 125.4, 138.8, 142.7, 146.4, 147.8, 149.9, 157.7, 173.4. IR, ν/cm^{-1}: 3280 (NH); 1610 (C=N); 1560, 1350 (NO_2).

4,6-Dinitrobenzo[*d*]isoxazole-3-carbaldehyde *N*-(4-chlorophenyl)hydrazone (1f). Yield 63%, m.p. 216—218 °C (from EtOH). Found (%): C, 46.22; H, 2.49. $C_{14}H_8ClN_5O_5$. Calculated (%): C, 46.49; H, 2.23. ^{1}H NMR, δ: 7.05 (d, 2 H, H arom., *J* = 8.2 Hz); 7.20 (d, 2 H, H arom., *J* = 8.2 Hz); 8.21 (s, 1 H, CH=N); 8.75 (s, 1 H, H(5)); 9.10 (s, 1 H, H(7)); 11.25 (br.s, 1 H, NH).

4,6-Dinitrobenzo[*d*]isoxazole-3-carbaldehyde *N*-(4-methoxyphenyl)hydrazone (1g). Yield 55%, m.p. 175—177 °C (from EtOH). Found (%): C, 50.12; H, 3.01. $C_{15}H_{11}N_5O_6$. Calculated (%): C, 50.43; H, 3.10. ^{1}H NMR, δ: 3.75 (s, 1 H, OMe); 6.80 (d, 2 H, H arom., *J* = 8.0 Hz); 7.03 (d, 2 H, H arom., *J* = 8.0 Hz); 8.14 (s, 1 H, CH=N); 8.76 (s, 1 H, H(5)); 9.05 (s, 1 H, H(7)); 11.02 (br.s, 1 H, NH). ^{13}C NMR, δ: 55.0, 110.5, 113.8, 114.2, 114.6, 119.8, 121.3, 137.3, 143.2, 147.9, 153.4, 153.8, 163.4.

4-Benzylthio-6-nitrobenzo[*d*]isoxazole-3-carbaldehyde *N*-phenylhydrazone (1h). Yield 55%, m.p. 183—185 °C (from EtOH). Found (%): C, 62.44; H, 3.73; S, 8.07. $C_{21}H_{16}N_4O_3S$. Calculated (%): C, 62.36; H, 3.99; S, 7.93. ^{1}H NMR, δ: 4.55 (s, 1 H, CH_2); 6.83 (m, 1 H, Ph); 7.12, 7.44, 7.57 (all m, 3 H each, Ph); 8.05 (s, 1 H, H(5)); 8.25 (s, 1 H, H(7)); 8.31 (s, 1 H, CH=N); 11.05 (s, 1 H, NH). ^{13}C NMR, δ: 36.7, 102.1, 112.8, 114.4, 120.0, 122.8, 127.5, 128.5, 128.7, 129.2, 134.7, 143.8, 148.8, 154.8, 162.5.

4-Cyclohexylthio-6-nitrobenzo[*d*]isoxazole-3-carbaldehyde *N*-phenylhydrazone (1i). Yield 25%, m.p. 167—169 °C (from EtOH). Found (%): C, 60.49; H, 4.98; S, 8.36. $C_{20}H_{20}N_4O_3S$. Calculated (%): C, 60.59; H, 5.08; S. 8.09. ^{1}H NMR, δ: 1.30—1.72 (m, 6 H, *cyclo*-C_6H_{11}); 1.85, 2.09 (both m, 2 H each, *cyclo*-C_6H_{11}); 3.57 (m, 1 H, CHS); 6.95 (m, 1 H, Ph); 7.34 (m, 4 H, Ph); 8.10 (s, 1 H, CH=N); 8.15 (s, 1 H, H(5)); 8.45 (s, 1 H, H(7)); 11.20 (s, 1 H, NH). ^{13}C NMR, δ: 25.1, 32.2, 46.1, 103.2, 113.7, 116.0, 118.9, 121.9, 128.9, 133.9, 142.9, 149.0.

4-(4-Chlorophenylthio)-6-nitrobenzo[*d*]isoxazole-3-carbaldehyde *N*-(4-methoxyphenyl)hydrazone (1j). Yield 80%, m.p. 142—144 °C (from EtOH). Found (%): C, 55.76; H, 3.11; S, 7.28. $C_{21}H_{15}ClN_4O_4S$. Calculated (%): C, 55.45; H, 3.32; S, 7.05. ^{1}H NMR, δ: 3.85 (s, 3 H, Me); 7.05 (d, 2 H, H arom., *J* = 8.8 Hz); 7.25 (s, 1 H, H(5)); 7.45 (s, 4 H); 7.61 (s, 1 H, H(7)); 8.03 (d, 2 H, H arom., *J* = 8.8 Hz); 8.25 (s, 1 H, CH=N); 10.98 (s, 1 H, NH). IR, ν/cm^{-1}: 3100 (NH); 1660, 1610 (C=N); 1510, 1350 (NO_2).

Preparation of 2-aryl-1,2,3-triazoles 2a—d (general procedure). Equimolar amounts (10 mmol) of hydrazone **1a** or **1e—g** and K_2CO_3 in NMP (50 mL) were stirred for 10 h at 80 °C until complete conversion of the initial hydrazone was monitored by TLC. The mixture was cooled to 20 °C, poured into water, and acidified with concentrated HCl to pH 2. The precipitate was filtered off, and the product was isolated by column chromatography. The eluate was concentrated, and the residue was dried in a vacuum desiccator. The yields of the products are presented in Scheme 1.

4-(2-Hydroxy-4,6-dinitrophenyl)-2-phenyl-1,2,3-triazole (2a). M.p. 193—195 °C. Found (%): C, 51.01; H, 2.99. $C_{14}H_9N_5O_5$. Calculated (%): C, 51.38; H, 2.77. ^{1}H NMR, δ: 7.45 (t, 1 H, Ph, *J* = 7.2 Hz); 7.60 (t, 2 H, Ph, *J* = 7.8 Hz); 7.95 (d, 2 H, Ph, *J* = 7.8 Hz); 8.05 (s, 1 H, H(5′)); 8.23 (s, 1 H, H(3′)); 8.56 (s, 1 H, H(5)); 12.01 (s, 1 H, OH). ^{13}C NMR, δ: 109.4, 113.4, 115.4, 118.5, 128.5, 130.0, 137.7, 138.7, 139.24, 147.7, 149.9, 157.3. ^{14}N NMR (Me_2CO), δ: −10.90, −15.59. MS, *m/z*: 327 $[M]^+$. IR, ν/cm^{-1}: 3120 (OH); 1600 (C=N); 1550, 1360 (NO_2).

4-(2-Hydroxy-4,6-dinitrophenyl)-2-(4-nitrophenyl)-1,2,3-triazole (2b). M.p. 124—125 °C. Found (%): C, 45.36; H, 2.30. $C_{14}H_8N_6O_7$. Calculated (%): C, 45.17; H, 2.17. ^{1}H NMR, δ: 7.71 (s, 1 H, H(5′)); 7.85 (s, 1 H, H(3′)); 8.20, 8.44 (both d, 2 H each, *J* = 8.8 Hz); 8.62 (s, 1 H, H(5)). ^{13}C NMR, δ: 109.1, 113.5, 119.0, 119.6, 125.4, 138.8, 141.0, 142.8, 146.4, 150.0, 157.7. MS, *m/z*: 372 $[M]^+$.

4-(2-Hydroxy-4,6-dinitrophenyl)-2-(4-methoxyphenyl)-1,2,3-triazole (2c). M.p. 210—212 °C. Found (%): C, 50.30; H, 3.12; N, 19.99. $C_{15}H_{11}N_5O_6$. Calculated (%): C, 50.43; H, 3.10; N, 19.60. ^{1}H NMR, δ: 3.95 (s, 3 H, OMe); 4.53 (br.s, 1 H, OH); 7.11, 7.87 (both d, 2 H each, *J* = 8.2 Hz); 7.95 (s, 1 H, H(5′)); 8.02 (s, 1 H, H(3′)); 8.47 (s, 1 H, H(5)). ^{13}C NMR, δ: 55.4, 107.9, 113.3, 114.5, 115.7, 119.9, 132.6, 136.9, 138.8, 147.2, 149.8, 158.6, 159.0. MS, *m/z*: 357 $[M]^+$.

2-(4-Chlorophenyl)-4-(2-hydroxy-4,6-dinitrophenyl)-1,2,3-triazole (2d). M.p. 215—216 °C. Found (%): C, 46.46; H, 2.36; Cl, 10.38. $C_{14}H_8ClN_5O_5$. Calculated (%): C, 46.49; H, 2.23; Cl, 9.80. ^{1}H NMR, δ: 7.60, 8.01 (both d, 2 H each, H arom., *J* = 8.8 Hz); 8.07 (s, 1 H, H(5′)); 8.12 (s, 1 H, H(3′)); 8.39 (s, 1 H, H(5)); 12.02 (br.s, 1 H, OH). ^{13}C NMR, δ: 105.5, 109.1, 113.3, 115.4, 120.0, 129.5, 132.8, 135.9, 137.6, 147.4, 149.8, 157.4, 159.1. MS, *m/z*: 361 $[M]^+$.

Preparation of compounds 2e—g (general procedure). Equimolar amounts (10 mmol) of hydrazone **1c,h,i** and K_2CO_3 in NMP (50 mL) were stirred for 12 h at 100 °C until complete conversion of the initial hydrazone was monitored by TLC. The mixture was cooled to ~20 °C, poured into water, and acidified with concentrated HCl to pH 2. The precipitate was filtered off, and the product was isolated by column chromatography. The eluate was concentrated, and the residue was dried in a vacuum desiccator. The yields of the products are presented in Scheme 1.

4-[2-Hydroxy-4-nitro-6-(phenylthio)phenyl]-2-phenyl-1,2,3-triazole (2e). M.p. 180—181 °C. Found (%): C, 61.52; H, 3.84; S, 8.20. $C_{20}H_{14}N_4O_3S$. Calculated (%): C, 61.53; H, 3.61; S, 8.21. ^{1}H NMR, δ: 7.22 (s, 1 H, Ph); 7.35—7.65 (m, 9 H, Ph); 8.10, 8.25 (both s, 1 H each, H(5) and H(7)); 11.03 (s, 1 H, NH). ^{13}C NMR, δ: 106.8, 112.8, 118.2, 121.2, 127.3, 129.1, 129.2, 129.7, 132.1, 134.1, 137.1, 139.1, 141.9, 142.0, 147.6, 156.8. MS, *m/z*: 390 $[M]^+$. IR, ν/cm^{-1}: 3080 (OH); 1590 (C=N); 1520, 1340 (NO_2).

4-(2-Benzylthio-6-hydroxy-4-nitrophenyl)-2-phenyl-1,2,3-triazole (2f). M.p. 154—155 °C. Found (%): C, 62.20; H, 4.17; S, 7.90. $C_{21}H_{16}N_4O_3S$. Calculated (%): C, 62.36; H, 3.99; S, 7.93. ^{1}H NMR, δ: 4.25 (s, 2 H, CH_2); 7.11—7.39 (m, 6 H, Ph); 7.49—7.62 (m, 4 H, Ph); 7.74 (s, 1 H, H(5′)); 8.05 (s, 1 H, H(3′)); 8.13 (s, 1 H, H(5)); 10.85 (s, 1 H, OH). ^{13}C NMR, δ: 37.3, 106.8, 111.4, 118.1, 121.6, 127.1, 127.3, 128.2, 128.8, 129.2, 135.7, 136.9, 139.1, 141.1, 142.0, 147.8, 156.6.

4-[6-(Cyclohexylthio)-2-hydroxy-4-nitrophenyl]-2-phenyl-1,2,3-triazole (2g). M.p. 130—132 °C. Found (%): C, 60.64; H, 5.14; S, 8.05. $C_{20}H_{20}N_4O_3S$. Calculated (%): C, 60.59;

H, 5.08; S, 8.09. ^{1}H NMR, δ: 1.18—1.40 (m, 5 H, *cyclo*-C_6H_{11}); 1.62 (m, 1 H, *cyclo*-C_6H_{11}); 1.69, 2.03 (both m, 2 H each, *cyclo*-C_6H_{11}); 3.31 (m, 1 H, CHS); 7.44 (t, 1 H, Ph, J = 7.3 Hz); 7.55 (t, 2 H, Ph, J = 7.4 Hz); 7.64, 7.70 (both s, 1 H each, Ph); 8.03 (s, 1 H, H(5′)); 8.06 (s, 1 H, H(3′)); 8.11 (s, 1 H, H(5)); 10.75 (s, 1 H, OH). ^{13}C NMR, δ: 25.6, 25.7, 32.7, 45.6, 107.4, 113.3, 118.5, 123.7, 127.6, 129.6, 137.2, 139.6, 140.2, 142.7, 148.3, 157.3.

4-(2-Acetyloxy-4,6-dinitrophenyl)-2-(4-methoxyphenyl)-1,2,3-triazole (3). A mixture of compound **2c** (0.25 g, 0.7 mmol) and Ac_2O (10 mL) was boiled for 3 h and cooled to ~20 °C. The solvent was evaporated, and the residue was recrystallized from CCl_4. Acetyl derivative **3** was obtained in 86% yield (0.24 g) with m.p. 162—163 °C (from CCl_4). Found (%): C, 51.08; H, 2.84; N, 17.33. $C_{17}H_{13}N_5O_7$. Calculated (%): C, 51.13; H, 3.28; N, 17.54. ^{1}H NMR, δ: 2.28 (s, 3 H, COMe); 3.90 (s, 3 H, OMe); 7.13, 7.88 (both d, 2 H each, J = 9.2 Hz); 8.31, 8.65, 8.75 (all s, 1 H each, H(5), H(3′), H(5′)). ^{13}C NMR, δ: 20.7, 55.3, 114.5, 116.7, 119.8, 119.9, 122.4, 122.9, 132.3, 135.8, 137.2, 147.1, 149.2, 149.4, 159.2, 167.7. ^{15}N NMR, δ: −58.65 (N(2)); −120.37 (N(1)). IR, ν/cm^{-1}: 1780 (C=O); 1600 (C=N); 1550, 1350 (NO_2).

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