Synthesis and base-catalyzed cleavage of 1-aryl-4,9-dioxo-1*H*-naphtho[2,3-*d*][1,2,3]triazole 2-oxides

L. M. Gornostaev,[a] L. V. Dolgushina,[a] Yu. G. Khalyavina,[a] G. A. Stashina,[b] and S. I. Firgang[b]*

[a]V. P. Astafiev Krasnoyarsk State Pedagogical University,
89 ul. A. Lebedevoi, 660049 Krasnoyarsk, Russian Federation.
E-mail: gornostaev@kspu.ru
[b]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
E-mail: galina_stashina@chemical-block.com

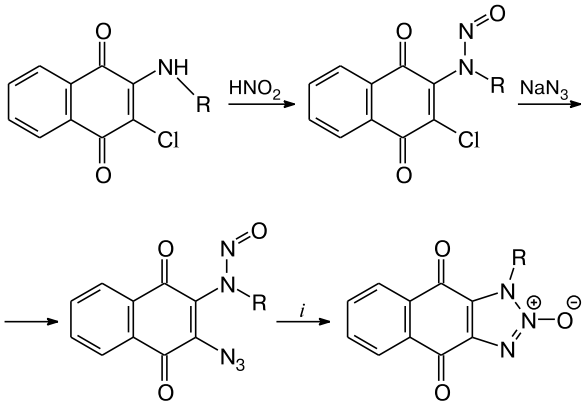
A method was developed for the synthesis of 1*H*-1-arylnaphtho[2,3-*d*][1,2,3]triazole-4,9-dione 2-oxides based on 2-arylamino-3-chloro-1,4-naphthoquinones. The reaction of 1*H*-1-arylnaphtho[2,3-*d*][1,2,3]triazole-4,9-dione 2-oxides with an ethanolic alkali solution affords 2-{[1-(aryl)-2-oxido-1*H*-1,2,3-triazol-4-yl]carbonyl}benzoic acids.

Key words: 1,2,3-triazole 2-oxides, quiones, cleavage, fused heterocycles.

Fused 1,2,3-triazole 2-oxides are rather difficult to prepare, and their chemical properties are poorly known.[1] Recently, it has been found[2] that 1*H*-1-alkylnaphtho[2,3-*d*]-[1,2,3]triazole-4,9-dione 2-oxides **1** exhibit antitumor activity, due to which these compounds are of additional interest.

Previously, we have developed[3] a simple but multistep approach to the synthesis of compounds **1** (*R* = Alk) described by Scheme 1.

Scheme 1

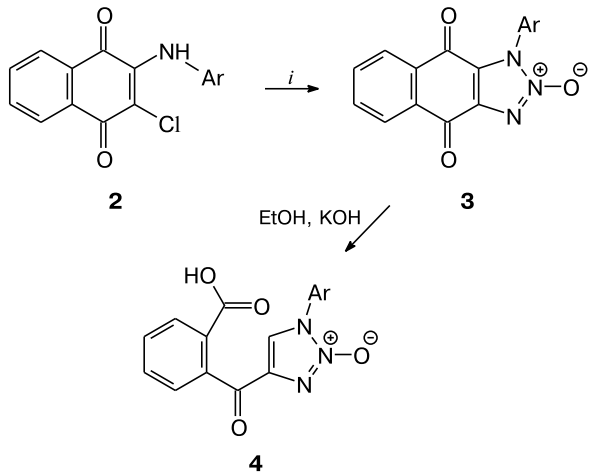


1

R = Alk
i. Heating.

In the present study, we simplified the method for the synthesis of *N*-aryl-substituted triazole oxides (**3a**—**c**) starting from available[4] 2-arylamino-3-chloro-1,4-naphthoquinones **2a**—**c** by excluding the isolation and purification of intermediate 2-(*N*-arylamino-*N*-nitroso)-3-chloro-1,4-naphthoquinones (Scheme 2).

Scheme 2



2 **3** **4**

Ar = Ph (**a**), 3-Me—C_6H_4 (**b**), 4-F—C_6H_4 (**c**)
i. HNO_2, NaN_3, heating.

We chose this method for the synthesis of triazole oxides **3a—c** because these compounds are relatively poorly soluble due to which they can easily be isolated in high total yield (50—60%).

The structures of compounds **3a—c** were confirmed by ^{1}H NMR spectroscopy and mass spectrometry. It should

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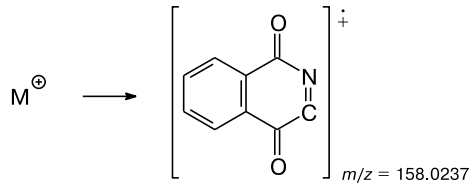
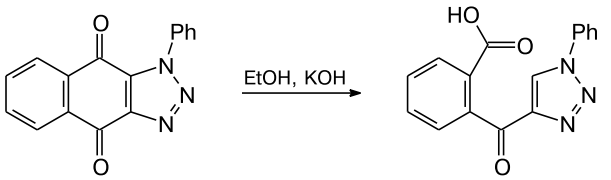
be noted that the molecular ions of triazole oxides **3a—c** and 1*H*-1-phenylnaphtho[2,3-*d*][1,2,3]triazole-4,9-dione (**5**) have different fragmentation patterns. The mass spectra of triazole oxides **3a—c** show the peak [M – 30] (NO) and the intense peak M – NO – ArNC at *m/z* 158, whereas the mass spectrum of triazole **5** exhibits a different fragmentation pattern. Taking into account the structure of triazole oxides **3a—c**, it could be suggested that the mass of the ion at *m/z* 158 corresponds to the mass of the fragmentation products of the composition $C_{10}H_6O_2$ or $C_9H_4NO_2$. For triazole oxide **3b**, the high-resolution mass spectrum was obtained. The exact mass of the ion at *m/z* 158 was evaluated at 158.0238, which corresponds to the composition $C_9H_4NO_2$ (*m/z* = 158.0237) and differs from the composition $C_{10}H_6O_2$ (*m/z* = 158.0362). Apparently, the fragmentation $[M]^+$ of compound **3b** affords the ion corresponding to the dehydrogenation of 2-aza-1,4-naphthoquinone (Scheme 3).

Scheme 3



Compounds **3a—c** appeared to be sensitive to an ethanolic alkali solution. These compounds were transformed into 2-{[1-(aryl)-2-oxido-1*H*-1,2,3-triazol-4-yl]carbonyl}benzoic acids **4a—c** already at 20—25 °C. These mild conditions of the cleavage of triazole oxides compared to, for example, 9,10-anthraquinone[4] are apparently associated with the electron-withdrawing effect of the triazole oxide ring on the quinoid moiety of the molecule. It should be noted that the activating effect of the triazole oxide moiety is substantially stronger than the effect of the triazole ring in the known cleavage reaction[5] of 1*H*-1-phenylnaphtho[2,3-*d*][1,2,3]triazole-4,9-dione **5** giving 2-[(1-phenyl-1*H*-1,2,3-triazol-4-yl)carbonyl]benzoic acid **6**. This fact was confirmed by kinetic data (see the Experimental section) (Scheme 4).

Scheme 4

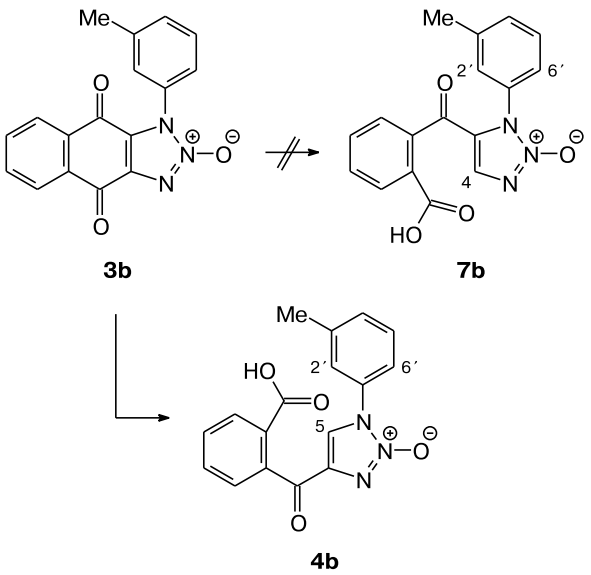


5 **6**

The stronger electron-withdrawing effect of the *N*-oxide moiety on the quinoid part is also indirectly evidenced by the proton chemical shifts of the heterocycles in compounds **4a** and **6**. The singlet for the proton of the triazole oxide moiety of compound **4a** is shifted downfield by approximately 0.6 ppm compared to the signal for the corresponding proton of product **6**.

The regioselectivity of the cleavage of triazole oxides **3a—c** was confirmed by 2D ^{1}H NOESY spectroscopy of compound **4b** (Scheme 5).

Scheme 5



3b **7b** **4b**

The above-described data provide evidence that there is the through-space interaction between the protons H(2′) and H(6′) of the tolyl moiety and the proton H(5) of the heterocycle in molecule **4b**. This interaction would not be observed in the case of the cleavage reaction of triazole oxide **3b** giving alternative 2-{[1-(3-methylphenyl)-2-oxido-1*H*-1,2,3-triazol-5-yl]carbonyl}benzoic acid **7b**.

To sum up, we developed an approach to the synthesis of non-fused diaryl-1,2,3-triazole 2-oxides **4**. The presence of the reactive groups in these compounds opens a route to their further modifications.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker DRX instrument (500 MHz) in DMSO-d_6 with Me_4Si as the internal standard. The progress of the reactions was monitored and the purity of the reaction products was checked by TLC on Silufol UV-254 plates. The melting points were measured on a Boetius hot-stage apparatus. The molecular weights of the reaction products were confirmed by mass spectrometry on a Finnigan MAT 8200 instrument. The high-resolution mass spectrum was obtained on a DFS high-resolution mass spectrometer.

The kinetics of the base-catalyzed cleavage was studied by spectrophotometry on an Evolution 300 instrument equipped with a temperature-controlled cell holder at 25 °C in a 10%

ethanolic solution of KOH in 1 cm quartz cells at the initial concentration of the starting compounds of $0.5 \cdot 10^{-4}$ mol L^{-1}. The changes in the concentration of triazole oxide **3a** and triazole **5** were detected at long-wavelength absorption maxima of 284 and 318 nm, respectively. The first-order rate constants were calculated according to the standard procedure based on the results of two experiments for each sample and then averaged. For compound **3a**, $k_{eff} = 40 \cdot 10^{-4}$ s^{-1}; for compound **5**, $k_{eff} = 1.9 \cdot 10^{-4}$ s^{-1}.

1-Aryl-4,9-dioxo-1*H*-naphtho[2,3-*d*][1,2,3]triazole 2-oxides (3a—c). Sodium nitrite (0.5—0.8 g) was added portionwise with stirring to a solution of 2-arylamino-3-chloro-1,4-naphthoquinone **2a—c** (4 mmol) in acetic acid (100 mL) at 15—20 °C for 60 min. Then the reaction mixture was stirred for 20—40 min (TLC, the absence of the starting chloroquinone) and poured into ice water (400—500 mL). The yellow precipitate of the corresponding *N*-nitrosoamine that formed was filtered off and washed with water. The reaction product was dissolved without drying in a mixture of ethanol (30 mL) and DMF (30 mL) and treated with a solution of NaN_3 (6 mmol) in water (3 mL) for 20—30 min. The reaction mixture was diluted with cold water (200 mL), and the precipitate of 2-azido-3-*N*-nitroso-1,4-naphthoquinone was extracted with benzene (50 mL). The benzene solution was dried with calcium chloride, brought to reflux during 30 min, and refluxed for 30 min. Then the solution was concentrated to 20—25 mL and cooled. 1-Aryl-4,9-dioxo-1*H*-naphtho[2,3-*d*][1,2,3]triazole 2-oxide (**3a—c**) that precipitated was washed with ethanol, dried, and crystallized from ethyl cellosolve.

4,9-Dioxo-1-phenyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole 2-oxide (3a). The yield was 60%, m.p. 249—252 °C. ^{1}H NMR ($CDCl_3$), δ: 7.48—7.70 (m, 5 H, Ph); 7.78 (dt, 1 H, H(7), J = 7.4 Hz, J = 1.6 Hz); 7.81 (dt, 1 H, H(6), J = 7.4 Hz, J = 1.6 Hz); 8.08 (dd, 1 H, H(8), J = 7.4 Hz, J = 1.6 Hz); 8.28 (dd, 1 H, H(5), J = 7.4 Hz, J = 1.6 Hz). Found (%): C, 66.07; H, 2.99; N, 14.10. $C_{16}H_9N_3O_3$. Calculated (%): C, 65.98; H, 3.09; N, 14.43. MS (EI, 70 eV), m/z (I_{rel} (%)): 261 $[M - NO]^+$ (8.21), 158 $[M - NO - C_7H_5N$ or $PhNC]^+$ (56.16), 102 $[C_7H_4N]^+$ (42.64).

1-(3-Methylphenyl)-4,9-dioxo-1*H*-naphtho[2,3-*d*][1,2,3]triazole 2-oxide (3b). The yield was 70%, m.p. 277—279 °C. ^{1}H NMR (DMSO-d_6), δ: 2.43 (s, 3 H, MePh); 7.48 (d, 1 H, H(4′), J = 7.6 Hz); 7.51 (s, 1 H, H(2′)); 7.53 (d, 1 H, H(6′), J = 7.6 Hz); 7.57 (d, 1 H, H(5′), J = 7.6 Hz); 7.91 (dt, 1 H, H(7), J = 7.4 Hz, J = 1.6 Hz); 7.94 (dt, 1 H, H(6) J = 7.4 Hz, J = 1.6 Hz); 8.02 (dd, 1 H, H(8), J = 7.4 Hz, J = 1.6 Hz); 8.18 (dd, 1 H, H(5), J = 7.4 Hz, J = 1.6 Hz). Found (%): C, 66.91; H, 3.64; N, 13.76. $C_{17}H_{11}N_3O_3$. Calculated (%): C, 66.89; H, 3.61; N, 13.77. MS (EI, 70 eV), m/z (I_{rel} (%)): 305 $[M]^+$ (3.70), 275 $[M - NO]^+$ (53.65), 158 $[M - NO - C_8H_7N$ or $MePhNC]^+$ (100), 102 $[C_7H_4N]^+$ (48.85), 91 $[C_7H_7]^+$ (16.42).

1-(4-Fluorophenyl)-4,9-dioxo-1*H*-naphtho[2,3-*d*][1,2,3]triazole 2-oxide (3c). The yield was 73%, m.p. 312—314 °C. ^{1}H NMR (DMSO-d_6), δ: 7.55 (t, 2 H, H(3′), H(5′), J = 8.8 Hz); 7.79 (dd, 2 H, H(2′), H(6′), J = 8.8 Hz, $J_{H,F}$ = 4.9 Hz); 7.92 (dt, 1 H, H(7), J = 7.4 Hz, J = 1.6 Hz); 7.95 (dt, 1 H, H(6), J = 7.4 Hz, J = 1.6 Hz); 8.03 (dd, 1 H, H(8), J = 7.4 Hz, J = 1.6 Hz); 8.19 (dd, 1 H, H(5), J = 7.4 Hz, J = 1.6 Hz). Found (%): C, 62.01; H, 2.48; N, 13.61. $C_{16}H_8FN_3O_3$. Calculated (%): C, 61.94; H, 2.58; N, 13.55. MS (EI, 70 eV), m/z (I_{rel} (%)): 309 $[M]^+$ (3.60), 279 $[M - NO]^+$ (10.11), 158 $[M - NO - C_7H_4FN]^+$ (100), 102 $[C_7H_4N]^+$ (51.65), 95 $[C_6H_4F]^+$ (50.85).

2-{[1-(Aryl)-2-oxido-1*H*-1,2,3-triazol-4-yl]carbonyl}benzoic acids (4a—c). 1-Aryl-4,9-dioxo-1*H*-naphtho[2,3-*d*][1,2,3]triazole 2-oxide **3a—c** (4 mmol) was added to a solution of KOH (1 g) in ethanol (12 mL). The reaction mixture was stirred at 20—25 °C for 5—10 h and then diluted with an equal volume of water. The undissolved residue (0.1—0.2 g) was filtered off, and the filtrate was acidified to pH = 2—3 with 10% hydrochloric acid. The precipitate was filtered off, washed with water, and recrystallized from ethanol.

2-[(2-Oxido-1-phenyl-1*H*-1,2,3-triazol-4-yl)carbonyl]benzoic acid (4a). The yield was 89%, m.p. 165—166 °C. ^{1}H NMR (DMSO-d_6), δ: 7.15 (t, 1 H, *p*-Ph, J = 7.4 Hz); 7.38 (t, 2 H, *m*-Ph, J = 7.4 Hz); 7.66 (d, 2 H, *o*-Ph, J = 7.4 Hz); 7.70 (dt, 1 H, H(3), J = 7.5 Hz, J = 1.2 Hz); 7.71 (dd, 1 H, H(5), J = 7.5 Hz, J = 1.2 Hz); 7.77 (dd, 1 H, H(4), J = 7.5 Hz, J = 1.26 Hz); 8.01 (dd, 1 H, H(2), J = 7.5 Hz, J = 1.2 Hz); 10.18 (s, 1 H, H(5′)); 13.64 (br.s, 1 H, COOH). Found (%): C, 62.14; H, 3.64; N, 13.66. $C_{16}H_{11}N_3O_4$. Calculated (%): C, 62.14; H, 3.56; N, 13.59. MS (EI, 70 eV), m/z (I_{rel} (%)): 309 $[M]^+$ (77.38), 281 $[M - CO]^+$ (13.81), 264 $[M - COOH]^+$ (10.11), 263 $[M - CO_2H - H]$ (22.02), 219 (36.24), 161 (61.66), 149 (92.89), 133 (56.86), 105 (100), 77 (96.10).

2-{[1-(3-Methylphenyl)-2-oxido-1*H*-1,2,3-triazol-4-yl]-carbonyl}benzoic acid (4b). The yield was 92%, m.p. 147—148 °C. ^{1}H NMR (DMSO-d_{60}), δ: 2.32 (s, 3 H, MePh); 6.17 (d, 1 H, H(4″), J = 8.65 Hz); 7.35 (t, 1 H, H(5″), J = 8.65 Hz); 7.46 (s, 1 H, H(2″)); 7.46 (d, 1 H, H(6″), J = 8.65 Hz); 7.69 (t, 1 H, H(3), J = 7.75 Hz); 7.70 (d, 1 H, H(5), J = 7.75 Hz); 7.77 (t, 1 H, H(4), J = 7.75 Hz); 8.01 (d, 1 H, H(2), J = 7.75 Hz); 10.12 (s, 1 H, H(5′)); 13.10 (br.s, 1 H, COOH). Found (%): C, 61.90; H, 3.46; N, 13.49. $C_{17}H_{13}N_3O_4$. Calculated (%): C, 63.16; H, 4.02; N, 13.00. MS (EI, 70 eV), m/z (I_{rel} (%)): 323 $[M]^+$ (7.21), 295 $[M - CO]^+$ (2.0), 277 $[M - CO_2H - H]$ (1.30), 233 (1.31), 161 (13.01), 149 (13.91), 133 (11.61), 107 (77.78), 105 (28.93), 91 (100), 77 (36.34).

2-{[2-Oxido-1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl]carbonyl}benzoic acid (4c). The yield was 90%, m.p. 145—146 °C. ^{1}H NMR (DMSO-d_6), δ: 7.22 (t, 2 H, H(3″), H(5″), J = 8.8 Hz, $J_{H,F}$ = 8.8 Hz); 7.67—7.72 (m, 4 H, H(3), H(5), H(2″), H(6″)); 7.77 (t, 1 H, H(4), J = 7.5 Hz); 8.01 (d, 1 H, H(2), J = 7.5 Hz); 10.16 (s, 1 H, H(5′)); 13.60 (br.s, 1 H, COOH). Found (%): C, 58.45; H, 3.05; N, 12.91. $C_{16}H_{10}FN_3O_4$. Calculated (%): C, 58.72; H, 3.06; N, 12.84. MS (EI, 70 eV), m/z (I_{rel} (%)): 327 $[M]^+$ (4.30), 299 $[M - CO]^+$ (1.70), 281 $[M - CO_2H - H]$ (0.90), 161 (47.35), 133 (22.42), 122 (23,52), 111 (100), 105 (62.86), 95 (23.32), 77 (43.84).

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