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Unexpected formation of 4-hydroxy-6-nitroindoles in the intramolecular cyclization of *O*-(3-amino-5-nitrophenyl)ketoximes

Sergei S. Vorob'ev,† Mikhail D. Dutov, Irina A. Vatsadze, Vadim V. Kachala,† Yuri A. Strelenko, Andrei V. Sedov and Svyatoslav A. Shevelev*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 495 135 5328; e-mail: shevelev@ioc.ac.ru

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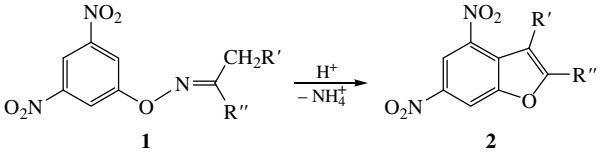
The acid-catalysed cyclization of *O*-(3-amino-5-nitrophenyl)ketoximes unexpectedly gives, along with 6-amino-4-nitrobenzofurans, 4-hydroxy-6-nitroindoles (in a 1:1 ratio).

This work was carried out within the scope of studies on the use of 1,3,5-trinitrobenzene (TNB) as a multipurpose synthone, including syntheses of polyfunctional benzo-annelated heterocycles on the basis of TNB.

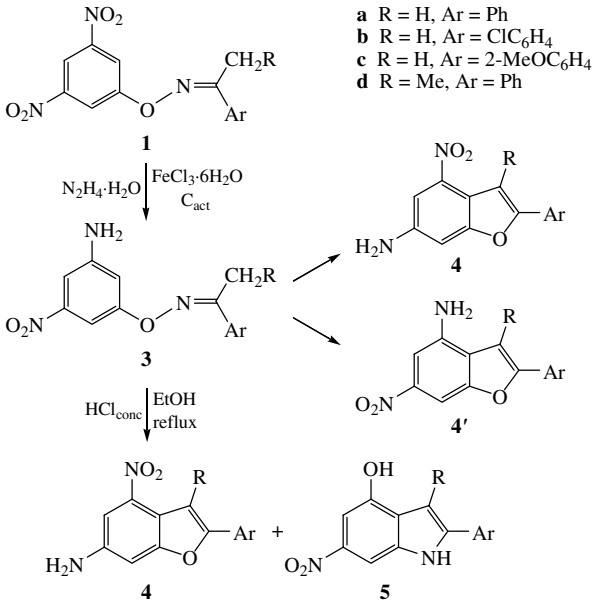
We have already reported the ability of *O*-(3,5-dinitrophenyl)-ketoximes **1**, which were obtained by the replacement of a nitro group in TNB by treatment with ketoximes in the presence of K_2CO_3, to undergo acid-catalysed cyclization to give 4,6-dinitrobenzo[*b*]furans **2**[1] (Scheme 1).



Scheme 1

In order to increase the functionalization index of nitro-substituted benzo[*b*]furans, we studied the cyclization of *O*-(3-amino-5-nitrophenyl)ketoximes **3**, which were in turn obtained by selective reduction of one nitro group in *O*-(3,5-dinitrophenyl)-ketoximes **1** (Scheme 2).‡ Note that the cyclization of ketoximes **1** could principally occur in different ways: either at the *ortho* carbon atom with respect to NO_2 or at the carbon atom adjacent to the NH_2 group, to give either 6-amino-4-nitrobenzo[*b*]furans **4** or 4-amino-6-nitrobenzo[*b*]furans **4′**, respectively (Scheme 2).

We have found that the heating of *O*-(3-amino-5-nitrophenyl)-ketoximes **3** in a mixture of concentrated hydrochloric acid (36%) and ethanol (1:1, v/v) always results in two products with the same composition (according to elemental analyses) in ~1:1 ratio (the overall yields are 55–70%). One of them was found to be substituted 6-amino-4-nitrobenzo[*b*]furan **4**, the structure of which was confirmed by ^{1}H NMR spectroscopy using an NOE experiment: NH_2 protons were found to interact with the H-5 and H-7 protons of the nitrobenzene ring. The second reaction product was unexpectedly identified as substituted 4-hydroxy-6-nitroindole **5** (Scheme 2): the ^{1}H NMR spectrum contained signals characteristic of the NH group (δ 12.15 ppm) of the indole ring and a signal of the OH group (δ 10.40 ppm) at the nitrobenzene ring; the NOE experiment shows interaction of OH group protons with the H-5 nitrobenzene fragment and interaction of the NH proton of the indole ring with the H-7 proton of the nitrobenzene fragment. The presence of an OH



Scheme 2

group was also confirmed chemically: the resulting indoles are readily soluble in a dilute aqueous alkali (we found indoles containing even two nitro groups at the benzene fragment[2] to be insoluble in an aqueous alkali at room temperature).

This unexpected result can be explained within the framework of the generally accepted cyclization mechanism of *O*-arylketoximes to benzo[*b*]furans[3] (Scheme 3), the key step of which consists in acid-catalysed [3,3]-sigmatropic rearrangement of the enehydroxylamine form of *O*-aryloxime (**B**→**C**) followed by aromatization of the six-membered ring (**C**→**D**), intramolecular addition of the OH group to the C=N bond (**D**→**E**) and subsequent elimination of the ammonium ion to give a benzo[*b*]-furan (**E**→**F**) (Scheme 3).

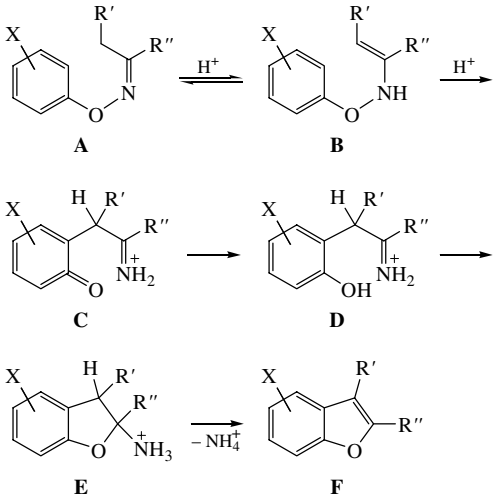
According to the data obtained, the [3,3]-sigmatropic rearrangement (**B**→**C**) in case of *O*-(3-amino-5-nitrophenyl)ketoximes **3** can occur at the *ortho* position to NO_2 and at the *ortho* position to NH_2 with equal probabilities (Scheme 4), giving corresponding intermediates **C′** and **C″** and further intermediates **D′** and **D″**. In the case of intermediates **D′**, cyclization occurs in the usual way to give 6-amino-4-nitrobenzo[*b*]furans **4** (**D′**→**E′**→**F′**, Scheme 4). In the case of intermediates **D″**, it is likely that intramolecular addition of an NH_2 group rather than an OH group to the C=NH_2^+ bond occurs (**D″**→**G**), which is followed

† S.S.V. is a former student of the Higher Chemical College (HCC) of the RAS (1997–2003).

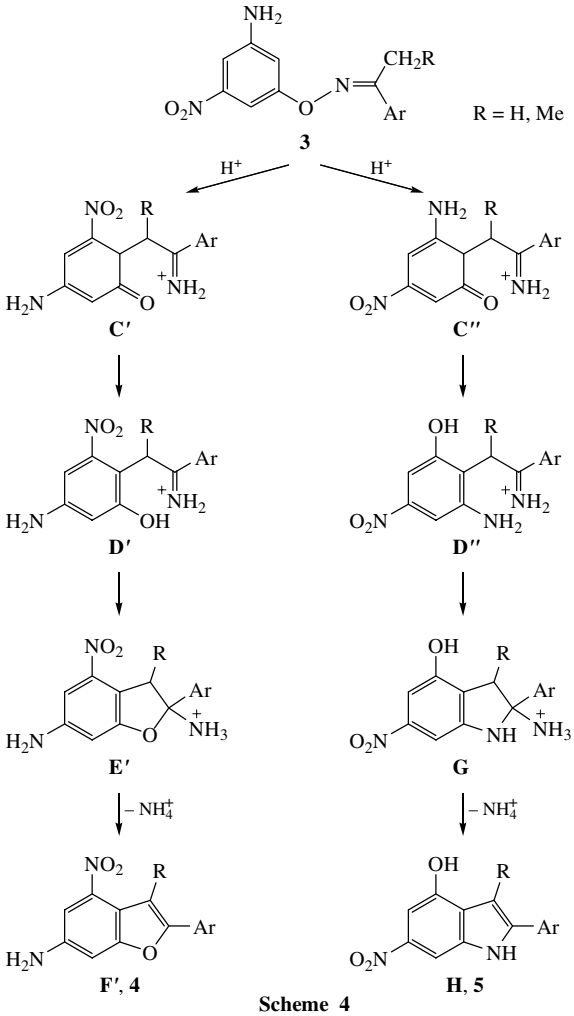
V.V.K. is a former student of the HCC RAS (1995–2000).

by abstraction of the ammonium ion to give 4-hydroxy-6-nitroindoles **5** (**G→H**, Scheme 4); in this case, the OH group cannot compete with NH_2 (NH_2 is much more nucleophilic than non-ionised OH), otherwise 4-amino-6-nitrobenzofurans **4′** would have formed, which is not the case.

Similar results were obtained when the cyclization was carried out in other acidic mixtures (MeOH/$HCl_{conc.}$/reflux, MeOH/HCl_{dry}/reflux, CF_3COOH/80 °C, MeCOONa/MeCOOH/80 °C, MeCOOH/H_2SO_4/60 °C, H_2SO_4/60 °C, $POCl_3$/benzene/reflux) or in the presence of Lewis acids ($ZnCl_2$/*p*-cresol/180 °C); the **4/5** ratio was ~1:1 in all the cases.



Scheme 3



Scheme 4

‡ The compounds were characterised by ^{1}H NMR spectra, electron impact mass spectra and satisfactory elemental analyses. ^{1}H NMR spectra were recorded on a Bruker AC-250 spectrometer in [$^2H_6$]DMSO solutions. Mass spectra were obtained using a Kratos MS-30 instrument. The spectra of all the compounds contained a molecular ion peak (M^+). The course of the reactions was monitored by TLC on Silufol UV-254 (silica gel plates).

General procedure for the synthesis of O*-(3-amino-5-nitrophenyl)-ketoximes* **3**. Hydrazine hydrate (10 ml, 0.2 mol) was added to a mixture of a corresponding *O*-(3,5-dinitrophenyl)ketoxime (0.1 mol, 0.13 g), $FeCl_3 \cdot 6H_2O$ (0.5 mmol) and activated carbon (6 g) in methanol (700 ml). The reaction mixture was refluxed until the parent dinitro compound was converted (monitoring by TLC with $CHCl_3$ as an eluent). The hot reaction mixture was filtered, and the activated carbon was washed with hot methanol (2×50 ml) on filter. The filtrate was cooled to +4 °C. The precipitate was filtered off. The following compounds were obtained.

3a: reaction time, 3 h; yield 72%; mp 157–159 °C. ^{1}H NMR, δ: 2.45 (s, 3H), 5.92 (s, 2H), 6.92 (s, 1H), 7.10–7.22 (m, 2H), 7.45–7.55 (m, 3H), 7.76–7.90 (m, 2H).

3b: reaction time, 7 h; yield 60%; mp 155–157 °C. ^{1}H NMR, δ: 2.43 (s, 3H), 5.91 (s, 2H), 6.89 (s, 1H), 7.10–7.18 (m, 2H), 7.55 (d, 2H, ^3J 8 Hz), 7.65 (d, 2H, ^3J 8 Hz).

3c: reaction time, 7 h; yield 71%; mp 146–147 °C. ^{1}H NMR, δ: 2.32 (s, 3H), 3.83 (s, 3H), 5.88 (s, 2H), 6.82 (s, 1H), 6.95–7.18 (m, 4H), 7.30–7.55 (m, 2H).

3d: reaction time, 3 h; yield 68%; mp 188–192 °C. ^{1}H NMR, δ: 1.15 (t, 3H, ^3J 7 Hz), 2.92 (q, 2H, ^3J 7 Hz), 5.92 (s, 2H), 6.91 (s, 1H), 7.10–7.16 (m, 2H), 7.45–7.56 (m, 3H), 7.71–7.87 (m, 2H).

General procedure for the synthesis of 4-amino-6-nitrobenzofurans **4** *and 4-hydroxy-6-nitroindoles* **5**. A corresponding *O*-(3-amino-5-nitrophenyl)oxime (0.01 mol) was placed in a mixture of ethanol (10 ml) and concentrated hydrochloric acid (36%, 10 ml). The reaction mixture was refluxed until complete conversion of the parent aminonitro compound occurred (TLC monitoring using $CHCl_3$ as the eluent). The mixture was cooled to room temperature; the resulting precipitate was filtered off and placed in water (50 ml), and aqueous ammonia was added until the mixture became weakly alkaline. The precipitate (6-amino-4-nitrobenzofuran **4**) was filtered off and dried *in vacuo*. The reaction mixture was filtered, and the filtrate was evaporated to dryness; the residue was placed in water (50 ml) and aqueous ammonia was added until the mixture became weakly alkaline; the precipitate (4-hydroxy-6-nitroindole **5**) was filtered off, crystallised from a minimum amount of ethanol, and dried *in vacuo*. The following compounds were obtained.

4a: reaction time, 2 h; yield 38%; mp 192–194 °C. ^{1}H NMR, δ: 5.88 (s, 2H), 7.18 (s, 1H), 7.32–7.61 (m, 4H), 7.68 (s, 1H), 7.75–8.11 (m, 2H).

4b: reaction time, 3 h; yield 31%; mp 278–280 °C. ^{1}H NMR, δ: 5.90 (s, 2H), 7.15 (s, 1H), 7.45–7.60 (m, 3H), 7.68 (s, 1H), 7.89 (d, 2H, ^3J 8 Hz).

4c: reaction time, 2 h; yield 36%; mp 212–214 °C. ^{1}H NMR, δ: 4.00 (s, 3H), 5.58 (s, 2H), 7.09 (t, 1H, ^3J 8 Hz), 7.15–7.27 (m, 2H), 7.41 (t, 1H, ^3J 8 Hz), 7.52 (s, 1H), 7.64 (s, 1H), 7.90 (d, 1H, ^3J 8 Hz).

4d: reaction time, 4 h; yield 29%; mp 149–150 °C. ^{1}H NMR, δ: 2.32 (s, 3H), 5.82 (s, 2H), 7.08 (s, 1H), 7.38 (s, 1H), 7.39–7.59 (m, 3H), 7.65–7.76 (m, 2H).

5a: reaction time, 2 h; yield 24%; mp 183–185 °C. ^{1}H NMR, δ: 7.10 (s, 1H), 7.22 (s, 1H), 7.31–7.42 (m, 1H), 7.45–7.58 (m, 2H), 7.75–8.00 (m, 3H), 10.4 (s, 1H), 12.15 (s, 1H).

5b: reaction time, 3 h; yield 36%; mp 232–234 °C. ^{1}H NMR, δ: 7.10 (s, 1H), 7.27 (s, 1H), 7.58 (d, 2H, ^3J 8 Hz), 7.86 (s, 1H), 7.92 (d, 2H, ^3J 8 Hz), 10.49 (s, 1H), 12.32 (s, 1H).

5c: reaction time, 2 h; yield 21%; mp 252–254 °C. ^{1}H NMR, δ: 3.97 (s, 3H), 7.02–7.25 (m, 4H), 7.30–7.47 (m, 1H), 7.78–7.88 (m, 1H), 7.98 (s, 1H), 10.32 (s, 1H), 11.79 (s, 1H).

5d: reaction time, 4 h; yield 37%; mp 139–140 °C. ^{1}H NMR, δ: 2.60 (s, 3H), 7.25 (s, 1H), 7.38–7.46 (m, 2H), 7.51–7.58 (m, 2H), 7.65–7.71 (m, 2H), 10.37 (s, 1H), 11.83 (s, 1H).

References

1 M. D. Dutov, I. A. Vatsadze, S. S. Vorob'ev and S. A. Shevelev, *Mendeleev Commun*., 2005, 202.

2 V. V. Rozhkov, A. M. Kuvshinov, V. I. Gulevskaya, I. I. Chervin and S. A. Shevelev, *Synthesis*, 1999, 2065.

3 P. R. Guzzo, R. N. Buckle and M. Chou, *J. Org. Chem*., 2003, **68**, 770.

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