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Intramolecular cyclization of *O*-(3,5-diaminophenyl)-substituted ketoximes as a route to 6-amino-4-hydroxyindoles

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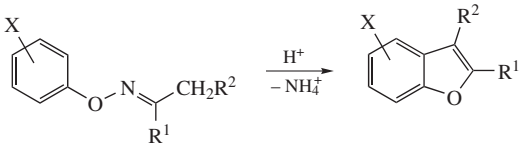
O-(3,5-Diaminophenyl)-substituted ketoximes undergo acid-catalysed cyclization to afford 6-amino-4-hydroxyindoles.

O-Arylated ketoximes **1** are known to undergo acid-catalysed intramolecular cyclization to give 2-R^1-3-R^2-benzo[*b*]furans **2** (Scheme 1).[1–4]

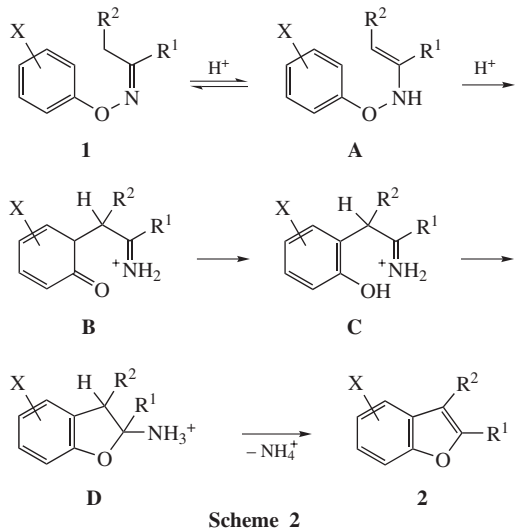


1 **2**

R^1 = Alk, Ar
R^2 = H, Alk

Scheme 1

Formation of benzofurans **2** is supposed to proceed through acid-catalysed [3,3]-sigmatropic rearrangement of the enamino tautomeric form of the ketoxime (**A** → **B**) followed by aromatization of the six-membered ring (**B** → **C**), intramolecular addition of the OH group to the C=NH_2^+ bond (**C** → **D**) and final elimination of ammonium ion (**D** → **2**) (Scheme 2).[3]

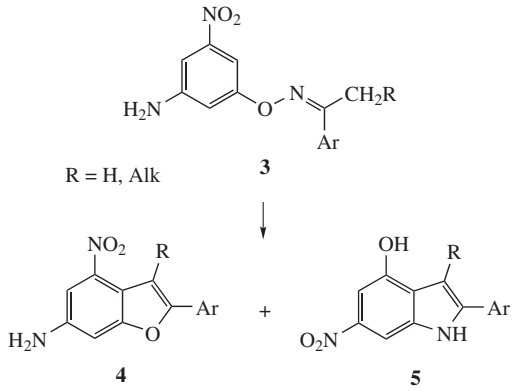


1 **A** **B** **C** **D** **2**

Scheme 2

We have recently shown[5] that intramolecular cyclization of ketoximes **3** bearing 3-amino-5-nitrophenyl substituent proceeds differently: two isomeric products, namely, 6-amino-4-nitrobenzofurans **4** and unexpected 4-hydroxy-6-nitroindoles **5** are formed in equal amounts (Scheme 3).

It can be assumed that cyclization occurs both at the *ortho* position to the nitro group and at the *ortho* position to the amino group. In the former case, 6-amino-4-nitrobenzofuran **4** is formed

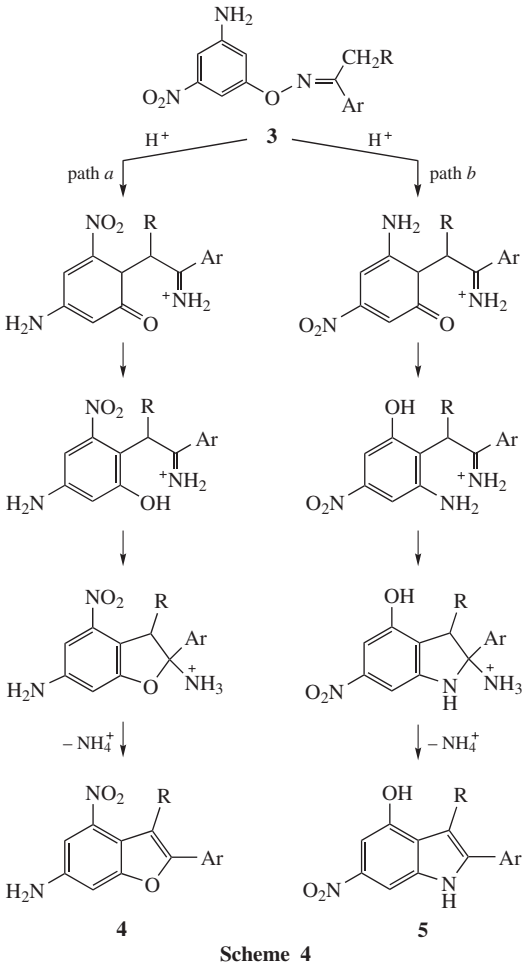


R = H, Alk

3

4 **5**

Scheme 3



3

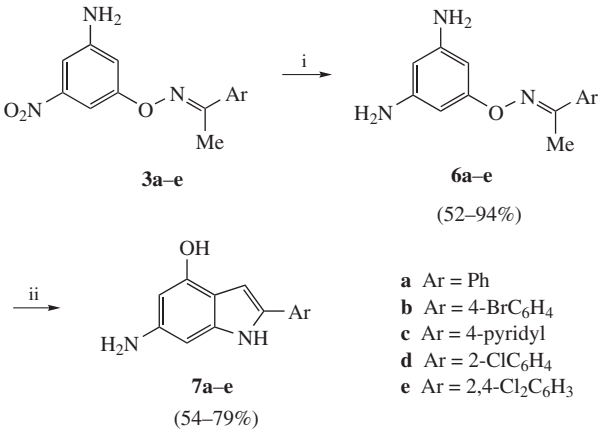
path *a* path *b*

4 **5**

Scheme 4

in the usual way (Scheme 4, pathway *a*), while in the latter case, not OH group but more nucleophilic NH_2 group adds to the $C{=}NH_2^+$ bond to furnish 4-hydroxy-6-nitroindole **5** (Scheme 4, pathway *b*).

To prove this mechanism, it seemed reasonable to perform cyclization of *O*-(3,5-diaminophenyl)-substituted ketoximes **6** (Scheme 5). However, to access diamino compounds **6** by reduction of nitro group in precursors **3** was difficult. In fact, the previously used[5] method of selective reduction of dinitrophenyl ketoximes **1** with a considerable excess of hydrazine hydrate catalyzed by $FeCl_3$/activated carbon proved inefficient in case of compounds **3** and resulted in resinification only. The procedure involving hydrazine hydrate on Raney nickel under standard conditions (MeOH, reflux for 1 h) resulted in oxime cleavage to give 3,5-diaminophenol. Luckily, performing the reaction at room temperature and prolonging exposure led to diaminooximes **6** in acceptable yields. Cyclization of the latter in a mixture of ethanol and concentrated HCl afforded 6-amino-4-hydroxyindoles **7** as the only products, which unambiguously confirms our above mechanistic assumptions.



Scheme 5 *Reagents and conditions*: i, $N_2H_4{\cdot}H_2O$ (2 equiv.), Raney Ni, activated catalyst, 50% slurry in water, MeOH, room temperature, 1.5 h; ii, EtOH–HCl (1:1), reflux, 0.5–3 h.

The structures of the compounds synthesized were confirmed by the ^{1}H NMR spectroscopy, mass spectrometry (molecular ions were recorded in all cases) and microanalysis.[†]

In conclusion, we have pioneered in indole preparation by intramolecular cyclization of O-arylated ketoximes.

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[†] ^{1}H NMR spectra (in DMSO-d_6) were recorded on a Bruker AM-300 spectrometer.

6a: yield 73%, mp 91–92 °C. ^{1}H NMR, δ: 2.35 (s, 3H), 4.77 (s, 4H), 5.53 (s, 1H), 5.77 (s, 2H), 7.46 (s, 2H), 7.76 (s, 1H).

6b: yield 52%, mp 151–152 °C. ^{1}H NMR, δ: 2.33 (s, 3H), 4.77 (s, 4H), 5.53 (s, 1H), 5.75 (s, 2H), 7.64–7.73 (m, 4H).

6c: yield 94%, mp 132–133 °C. ^{1}H NMR, δ: 2.35 (s, 3H), 4.81 (s, 4H), 5.55 (s, 1H), 5.78 (s, 2H), 7.71 (d, 2H, *J* 5.8 Hz), 8.66 (d, 2H, *J* 5.8 Hz).

6d: yield 87%, oil. ^{1}H NMR, δ: 2.30 (s, 3H), 4.75 (s, 4H), 5.51 (s, 1H), 5.69 (s, 2H), 7.40–7.49 (m, 3H), 7.54–7.57 (m, 1H).

6e: yield 79%, oil. ^{1}H NMR, δ: 2.29 (s, 3H), 4.75 (s, 4H), 5.51 (s, 1H), 5.68 (s, 2H), 7.48–7.54 (m, 2H), 7.74 (m, 1H).

7a: yield 57%, mp > 300 °C. ^{1}H NMR, δ: 5.08 (s, 2H), 5.85 (s, 1H), 6.13 (s, 1H), 6.72 (s, 1H), 7.15–7.20 (m, 1H), 7.34–7.39 (m, 2H), 7.68–7.71 (m, 2H), 9.10 (s, 1H), 10.76 (s, 1H).

7b: yield 61%, mp > 300 °C. ^{1}H NMR, δ: 4.74 (s, 2H), 5.81 (s, 1H), 6.06 (s, 1H), 6.73 (s, 1H), 7.53 (d, 2H, *J* 8.3 Hz), 7.64 (d, 2H, *J* 8.4 Hz), 9.09 (s, 1H), 10.75 (s, 1H).

7c: yield 64%, mp > 300 °C. ^{1}H NMR, δ: 4.93 (s, 2H), 5.84 (s, 1H), 6.07 (s, 1H), 7.00 (s, 1H), 7.61 (d, 2H, *J* 4.6 Hz), 8.46 (d, 2H, *J* 4.4 Hz), 9.27 (s, 1H), 10.93 (s, 1H).

7d: yield 54%, mp 163–164 °C. ^{1}H NMR, δ: 4.98 (s, 2H), 5.85 (s, 1H), 6.11 (s, 1H), 6.88 (s, 1H), 7.21–7.26 (m, 1H), 7.36–7.41 (m, 1H), 7.51 (d, 1H, *J* 7.8 Hz), 7.66 (d, 1H, *J* 7.6 Hz), 9.13 (s, 1H), 10.66 (s, 1H).

7e: yield 79%, mp 171–172 °C. ^{1}H NMR, δ: 4.91 (s, 2H), 5.84 (s, 1H), 6.09 (s, 1H), 6.93 (s, 1H), 7.47 (d, 1H, *J* 8.1 Hz), 7.65–7.69 (m, 1H), 9.17 (s, 1H), 10.71 (s, 1H).