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Arylglyoxal oximes as putative C-nucleophiles in eliminative nucleophilic substitution process

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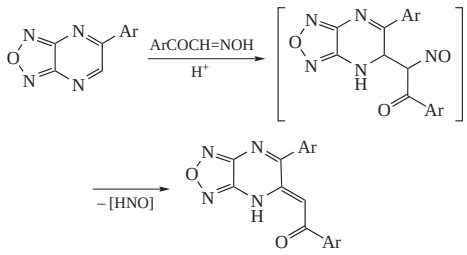
Reaction of arylglyoxal oximes ArCOCH=NOH (Ar = = 4-MeOC$_6$H$_4$, Ph) with 5-arylfurazanopyrazines proceeds as vicarious nucleophilic substitution of hydrogen in pyrazine ring with the elimination of hyponitrous acid, affording 5-(aroylmethylidene)-6-aryl-4*H*-furazano[3,4-*b*]pyrazines. Structure of the product was confirmed by X-ray diffraction.

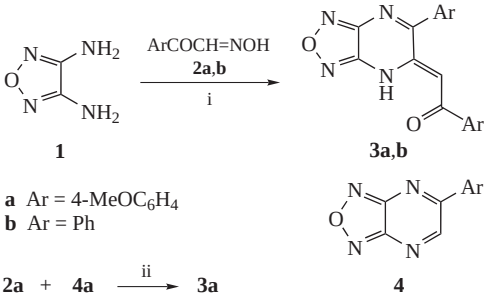


Biological activity of mono-substituted arylfurazanopyrazines has been poorly investigated, though the antibacterial, tranquilizing, herbicidal and other types of effects are known for furazanopyrazines.[1] There are a few patents on the bioactivity of the mono-substituted derivatives, probably due to a small number of compounds synthesized by now.[2] The mono-substituted arylfurazanopyrazines are typically prepared from arylglyoxals ArCOCHO, which are in turn obtained through oxidation of acetophenones by SeO_2.[3] To avoid the use of this toxic reagent, we searched for an alternative approach to the target compounds starting from readily accessible arylglyoxal oximes.

For this purpose, oximes ArCOCH=NOH (Ar = 4-MeOC$_6$H$_4$, Ph) had been prepared using nitrosation of acetophenones by isoamylnitrite,[4] and we anticipated that their condensation with 3,4-diaminofurazan **1** in acidic medium would result in the desired 5-arylfurazanopyrazines.

However, acid-catalyzed interaction of 3,4-diaminofurazan **1** and 4-methoxyphenylglyoxal oxime **2a** in equimolar amounts upon heating with AcOH–HCl for 1 h afforded previously unknown 5-[(4-methoxybenzoyl)methylidene]-6-(4-methoxyphenyl)-4*H*-furazano[3,4-*b*]pyrazine **3a** (Scheme 1) as a major product in moderate yield.† The expected 5-(4-methoxyphenyl)furazano[3,4-*b*]pyrazine **4a** was not observed under these reaction conditions.

Both longer reaction time and twofold molar excess of oxime **2a** led to slightly decreased yield of compound **3a** due to formation of by-products. The use of Pr^{i}OH or Bu^{t}OH instead of AcOH resulted in the mixture of products **3a** and **4a** in 2 : 1 or 1 : 2.5



Scheme 1 *Reagents and conditions*: i, AcOH, conc. HCl, reflux, 1 h; ii, AcOH, conc. HCl, reflux, 15 min.

† *5-[(4-Methoxybenzoyl)methylidene]-6-(4-methoxyphenyl)-4*H*-furazano[3,4-*b*]pyrazine* **3a**.

Method A. A solution of oxime **2a** (1.00 g, 5.58 mmol) and 3,4-diaminofurazan **1** (0.56 g, 5.60 mmol) in a mixture of AcOH (10 ml) and conc. HCl (10 ml) was refluxed for 1 h, then allowed to cool to room temperature. The resulting precipitate was filtered off, washed with hot AcOH (2 ml) and recrystallized from DMF. Yield 0.40 g (38%), bright-orange powder, mp 235–238 °C.

Method B. A suspension of oxime **2a** (0.55 g, 3.07 mmol) and 5-(4-methoxyphenyl)furazano[3,4-*b*]pyrazine **4a** (0.70 g, 3.07 mmol) in a mixture of AcOH (7 ml) and conc. HCl (7 ml) was refluxed for 15 min and then worked up according to the method A to give product **3a**. Yield 0.61 g (53%).

^{1}H NMR (DMSO-d_6) δ: 3.83 (s, 3H, OMe), 3.89 (s, 3H, OMe), 6.60 (s, 1H, =CH), 7.07 (d, 2H, Ar, *J* 8.9 Hz), 7.17 (d, 2H, Ar, *J* 8.8 Hz), 7.78 (m, 4H, Ar), 13.52 (br. s., 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 55.8, 55.9, 100.9, 114.4 (2C), 114.7 (2C), 128.2, 130.1 (2C), 130.8, 131.5 (2C), 142.2, 143.4, 151.7, 162.2, 163.7, 169.2, 189.9. MS, *m*/*z* (%): 376 (M$^+$, 100), 346 (33), 268 (57), 241 (30), 135 (87). Found (%): C, 64.08; H, 4.44; N, 14.61. Calc. for $C_{20}H_{16}N_4O_4$ (%): C, 63.82; H, 4.28; N, 14.89.

*5-(Benzoylmethylidene)-6-phenyl-4*H*-furazano[3,4-*b*]pyrazine* **3b**. Compound **3b** was prepared according to the above method A from 3,4-diaminofurazan **1** (0.67 g, 6.70 mmol) and phenylglyoxal oxime **2b** (1.00 g, 6.71 mmol). Yield 0.45 g (42%), purity *ca.* 80%. Attempts to purify product **3b** by recrystallization from DMF or EtOH or by chromatography failed. ^{1}H NMR (DMSO-d_6, signals of the major product indicated) δ: 6.48 (s, 1H, =CH), 7.52 (t, 2H, Ar, *J* 7.7 Hz), 7.60–7.70 (m, 4H, Ar), 7.74 (d, 2H, Ar, *J* 7.6 Hz), 7.78 (d, 2H, Ar, *J* 7.1 Hz), 13.45 (br. s., 1H, NH).

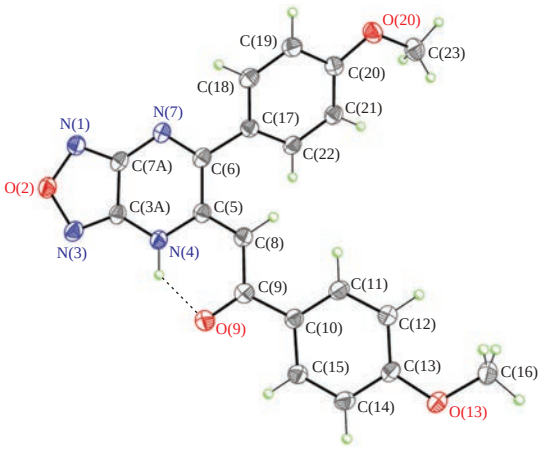


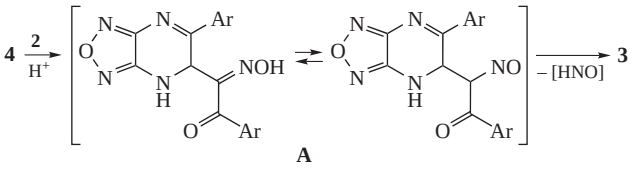
Figure 1 Molecular structure of compound **3a**. The intramolecular N–H···O hydrogen bond is shown by dashed line. Selected bond lengths (Å): N(1)–O(2) 1.397(3), O(2)–N(3) 1.426(2), N(3)–C(3A) 1.313(3), C(3A)–N(4) 1.358(3), N(4)–C(5) 1.391(3), C(5)–C(6) 1.499(3), C(6)–N(7) 1.315(3), N(7)–C(7A) 1.386(3), N(1)–C(7A) 1.317(3), C(3A)–C(7A) 1.430(3), C(5)–C(8) 1.370(3), C(8)–C(9) 1.472(3), O(9)–C(9) 1.262(3). Selected angles (°): O(2)–N(1)–C(7A) 104.7(2), N(1)–O(2)–N(3) 111.7(2), O(2)–N(3)–C(3A) 103.3(2), C(3A)–N(4)–C(5) 119.1(2), C(6)–N(7)–C(7A) 114.9(2).

ratio, respectively, *i.e.* the reaction outcome depended on acidity of the medium.

The structure of product **3a** was determined by X-ray diffraction (Figure 1).‡

In a similar manner, reaction between 3,4-diaminofurazan **1** and phenylglyoxal oxime **2b** afforded compound **3b** as a major product (see Scheme 1). ^{1}H NMR spectra of compounds **3a**,**b** exhibit signals of CH= proton at *ca.* 6.5 ppm and NH proton in the low field at *ca.* 13.5 ppm.

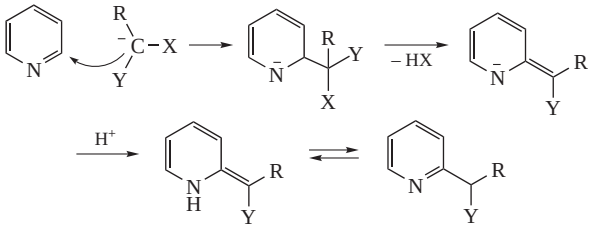
We assume that oxime **2** as a C-nucleophile attacks the 6-position of a highly electrophilic N-protonated form of the



Scheme 2

‡ *Crystal data for* **3a**. Single crystal (orange plate), $C_{20}H_{16}N_4O_4$, M = 376.37, monoclinic, space group $P2_1/c$, at T = 100 K, a = 19.679(4), b = 6.7608(14) and c = 13.572(3) Å, β = 102.68(3)°, V = 1761.7(7) Å^3, Z = 4, d_{calc} = 1.419 g cm^{-3}, $F(000)$ = 784, μ = 0.216 mm^{-1}. X-ray diffraction measurements were carried out using the 'Belok' beamline (λ = 0.96990 Å) of the Kurchatov Synchrotron Radiation Source.[5] Total 30968 reflections (3569 unique reflections, R_{int} = 0.096) were collected with an oscillation range of 1.0° in the φ scanning mode using two different orientations for the crystal. The semi-empirical correction for absorption was applied using the SCALA program.[6] The data were indexed and integrated using the iMOSFLM utility from the CCP4 software suite.[7,8] The structure was solved by direct methods and refined by a full-matrix least squares technique on F^2 with anisotropic displacement parameters for non-hydrogen atoms. The hydrogen atom of the NH-group was localized in the difference-Fourier maps and included into the refinement within the riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.2 U_{eq}(N)]. The other hydrogen atoms were placed in calculated positions and refined within the riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.5U_{eq}(C) for the Me group and U_{iso}(H) = 1.2 U_{eq}(C) for the other groups]. The final divergence factors were R_1 = 0.068 for 2705 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.160 for all independent reflections, S = 1.028. All calculations were carried out using the SHELXL program.[9]

CCDC 1881077 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



Scheme 3 General mechanism of vicarious substitution for electron-deficient azines. Y is an electron-withdrawing group.

intermediate 5-arylfurazano[3,4-*b*]pyrazine **4** to yield a key intermediate **A**, which then eliminates hyponitrous acid producing compound **3** (Scheme 2).

This suggested mechanism is supported by the following data. First, the reaction of 4-methoxyphenylglyoxal oxime **2a** with 5-(4-methoxyphenyl)furazano[3,4-*b*]pyrazine **4a** prepared beforehand by the known procedure[10] also gave product **3a** under similar conditions, *i.e.*, heating in AcOH–HCl (see Scheme 1). Second, oximes RCH=NOH, though being weak C-nucleophiles, can nevertheless react with electrophiles, as is known for halogenation[11] and Mannich reaction.[12] Third, 5-arylfurazano-[3,4-*b*]pyrazines **4** as highly electrophilic heterocycles can undergo the oxidative nucleophilic substitution of hydrogen (S_N^H) even with weak C-nucleophiles.[13]

Worthy of particular attention is a similarity of the proposed mechanism to a known mechanism of vicarious, or eliminative, nucleophilic substitution of hydrogen in electron-deficient aromatic carbo- and heterocycles by the action of C-nucleophiles,[14] where the hydrogen atom is eliminated together with a leaving group X, usually Cl^-, attached to the nucleophilic centre (Scheme 3). Vicarious nucleophilic substitution is known for 5-arylfurazano-[3,4-*b*]pyrazines **4** as well.[15]

The mechanism discussed seems to be a special version of the vicarious nucleophilic substitution, with the N=O moiety serving as the leaving group, that differs from the known cases due to the following features: (1) C-nucleophile is a neutral molecule rather than carbanion and (2) the reaction proceeds in acidic medium rather than basic one. The scope of this reaction, its synthetic value and optimal conditions yet need to be carefully investigated.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.018.

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