Synthesis of unsubstituted 4*H*,8*H*-bisfurazano[3,4-*b*:3′,4′-*e*]pyrazine

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The title compound **2a** was synthesized by a four-step sequence starting from 4,5-dichlorofurazano[3,4-*b*]pyrazine **3**; the key step being a one-pot transformation of tetrazolo sulfilimine **6** to **2a** *via* an oxidation/tetrazole ring cleavage/nitrogen loss/ring-closure/ proton trapping procedure.

Phenazines, phenodithiines and related polycyclic systems are well known for their pharmacological activity. Diverse structural modifications have been carried out in the search for new analogues with higher potency and a broad spectrum of activity. It was found that replacement of one or/and two the aromatic subunits by a heteroaromatic moiety interestingly alters their properties.

As part of our ongoing research into the chemistry of related tricyclic systems we synthesized the first example of the bisfurazano[3,4-*b*:3′,4′-*e*]ditiine ring system **1**.[1,2]
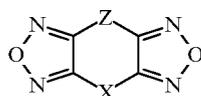

1 X = Z = S
2a X = Z = NH
2b X = Z = NCH₂Ph

Here we report the synthesis of the parent 4*H*,8*H*-bisfurazano[3,4-*b*:3′,4′-*e*]pyrazine **2a**. It may be noted that earlier attempts by Fischer and co-workers[3] to make **2a** by the deprotection of 4,8-dibenzyl derivative **2b** failed. However,

they found that treatment of di-*N*,*N*′-lithio salt of 3,4-di(R-amino)furazan with the *in situ* generated cyanogen di-*N*,*N*′-oxide followed by ring closure of the intermediate glyoxime using sodium hydroxide in ethylene glycol at 150 °C was the first pathway to 4,8-disubstituted tricyclic system. Since compound **2a** is not accessible by this latter pathway, we were interested in exploring new synthetic methodologies.

Whereas the central drawback of the previous strategy for **2a** synthesis is the deprotection of the *N*-substituted derivatives, our approach, as illustrated in Scheme 1, is based upon a complementary strategy in which *N*-unsubstituted pyrazine, heteroaromatic furazano[3,4-*b*]pyrazine such as **3**,[4–6] is employed as starting material.

Amination of **3** with ammonia in anhydrous chloroform was followed by azidation with NaN₃ to yield the desired amino-tetrazole **5** in 54% yield. The next step, shown in Scheme 1, was a modification of a published procedure[7] in which an amino group of **5** was readily transformed into a sulfilimino moiety by treatment with dimethyl sulfide ditrifluoroacetate to give **6** in 41% yield. Oxidation of the sulfilimine **6** with peroxy acid in dichloromethane was found to give a moderate yield of the equilibrium mixture of nitroso azide **8** with nitroso tetrazole **7**. An earlier publication by Boulton and co-workers[8] described a concise preparation of benzofurazans from *o*-nitrosophenyl azides *via* loss of nitrogen
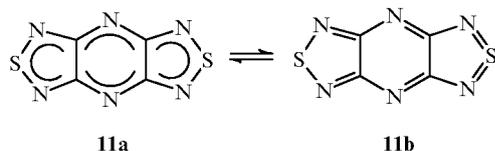
Scheme 1 (reaction figures with structures 3, 4, 5, 6, 7, 8, 9, 10, 2)
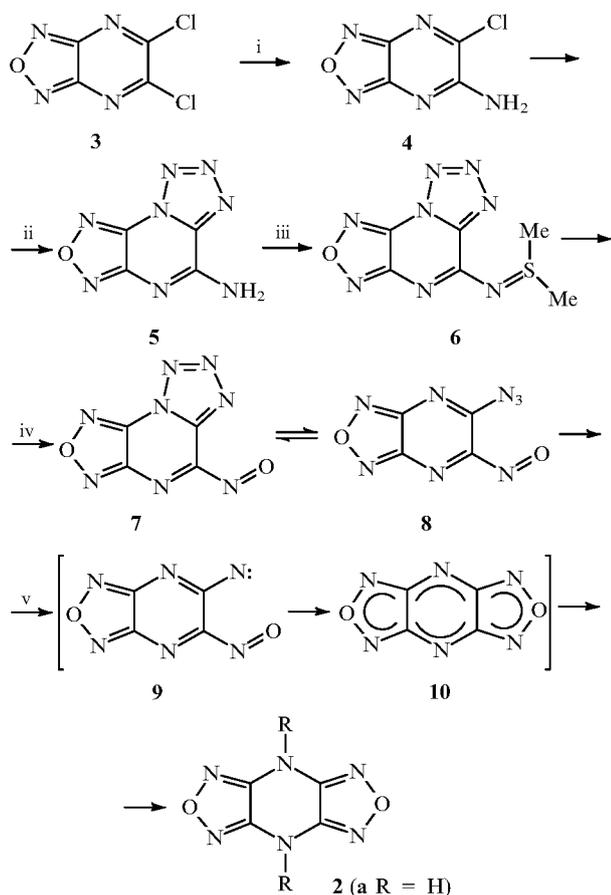
Scheme 1 *Reagents and conditions*: i, NH₃, CHCl₃; ii, NaN₃, DMF; iii, DMSO, (CF₃CO)₂O; iv, CF₃COOOH, CH₂Cl₂; v, MeOH/AcOH, heat.

and ring closure. We utilized a modification of this route for the synthesis of the second furazan subunit. Thus, we have found that heating the crude mixture of **8** and **7** (without purification) in the presence of a mixture of acetic acid and methanol behaves similarly, producing furazan **2a** (36%). The transformation from **6** to **2a** occured in one-pot.

Specificity of the transformation implies that in contrast to benzofurazans,[8] with immediate generation of the final product, the first labile intermediate **10**† was likely obtained, which was stabilized by proton trapping from the reaction media (Scheme 1).

After separation and purification, the new dihydro tricycle **2a** was characterized initially by spectroscopy.‡ The assignment was then chemically confirmed by converting **2a** into its *N*-derivative. Finally, the present assignments were unequivocally verified by X-ray crystallographic study of the tricycle **2a** that will be published elsewhere.

The tricycle **2a** is a strong diacid and can produce both mono- and di-salts. These salts are easily subjected to alkylation and acylation. Thus, treatment of di-Na-salt of **2a** with PhCH₂Cl or MeI gave di-*N*,*N'*-alkylated compounds, **2b** (R = PhCH₂, identical to an authentic sample³) and **2c** (R = Me), in 91 and 87% yields, respectively. Acylation with acetyl chloride afforded the corresponding derivative **2d** (R = Ac; 78%).

In conclusion, this strategy represents the first example of the preparation of furazans fused to nitrogen heterocycles by a one-pot oxidation/tetrazole ring cleavage/nitrogen loss/ring-closure/proton trapping procedure. Current efforts in this laboratory are focused on further applications of this methodology to the formation of related polycyclic systems. In addition, the tricycle **2a** may be an important candidate for further chemical investigation and potential pharmacological studies.

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† It should be noted that the thio analogue of **10**, such as the resonance-stabilized tricycle **11a**, is a stable compound.⁹ Apparently, the polyvalence state of the sulfur atom, as in **11b**, favours the high stability of this molecule having no-hydrogen atoms.

(structures **11a** ⇌ **11b**)

‡ All new compounds gave satisfactory combustion analyses and accurate mass measurements. *Selected data for* **4**: mp 219–222 °C, MS, *m/z*: 170, 172 (M⁺), ¹³C NMR ([²H₆]DMSO) 145.0, 149.9, 153.0 and 155.4. For **5**: mp 190–195 °C (decomp.); MS, *m/z*: 178 (M⁺), ¹³C NMR (CDCl₃) 140.8, 142.8, 151.3 and 154.5. For **6**: mp >330 °C; MS, *m/z*: 238 (M⁺), ¹³C NMR ([²H₆]DMSO) 30.7, 140.4, 144.8, 153.8 and 155.8. For **2a**:¹⁰ mp 294–296 °C (decomp.); MS, *m/z*: 166 (M⁺), ¹H NMR ([²H₆]DMSO) 11.8; ¹³C NMR ([²H₆]DMSO) 146.4. For **2c**: mp 215–216 °C. For **2d**¹⁰: mp 230 °C.