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

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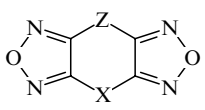
**The title compound 2a was synthesized by a four-step sequence starting from 4,5-dichlorofurazano[3,4-*b*]pyrazine 3; the key step being a one-pot transformation of tetrazolo sulfilimine 6 to 2a *via* an oxidation/tetrazole ring cleavage/nitrogen loss/ring-closure/proton trapping procedure.**

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]

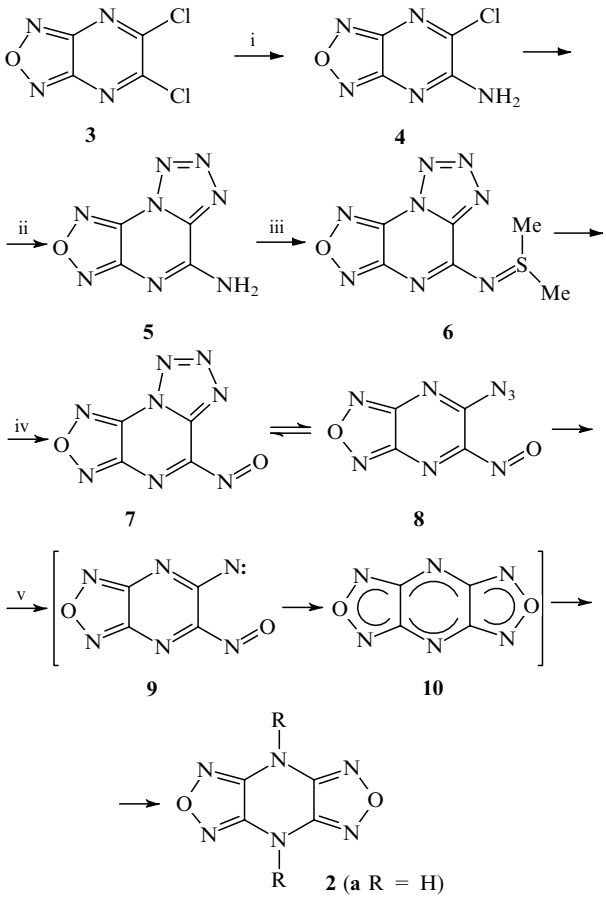


**1** X = Z = S
**2a** X = Z = NH
**2b** X = Z = $NCH_2Ph$

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 drowback 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 $NaN_3$ 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

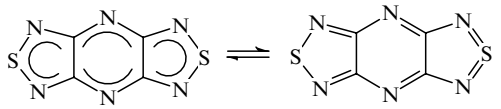


**Scheme 1** *Reagents and conditions*: i, $NH_3$, $CHCl_3$; ii, $NaN_3$, DMF; iii, DMSO, $(CF_3CO)_2O$; iv, $CF_3COOOH$, $CH_2Cl_2$; v, MeOH/AcOH, heat.

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).

† 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.



**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 ($M^+$), $^{13}C$ NMR ([$^2H_6$]DMSO) 145.0, 149.9, 153.0 and 155.4. For **5**: mp 190–195 °C (decomp.); MS, *m*/*z*: 178 ($M^+$), $^{13}C$ NMR ($CDCl_3$) 140.8, 142.8, 151.3 and 154.5. For **6**: mp >330 °C; MS, *m*/*z*: 238 ($M^+$), $^{13}C$ NMR ([$^2H_6$]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 ([$^2H_6$]DMSO) 11.8; $^{13}C$ NMR ([$^2H_6$]DMSO) 146.4. For **2c**: mp 215–216 °C. For **2d**[10]: mp 230 °C.

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 $PhCH_2Cl$ or MeI gave di-*N*,*N*′-alkylated compounds, **2b** (R = $PhCH_2$, identical to an authentic sample[3]) 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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