One-pot synthesis of 4,4′-diamino-3,3′-bifurazan

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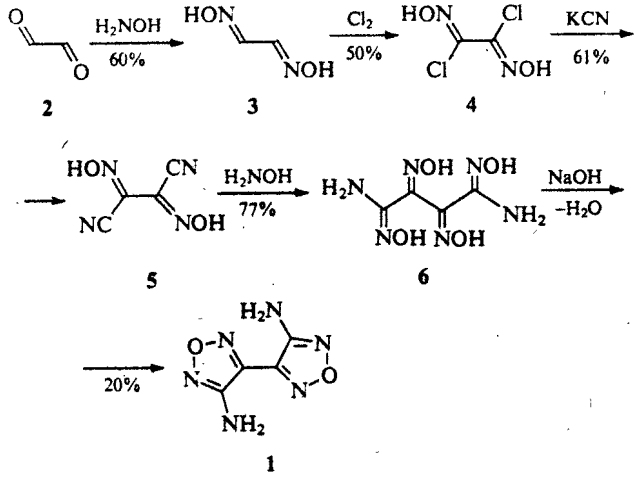
The title compound 1 has been synthesized by a one-pot procedure starting from 3,4-di(hydroximinomethyl)furoxan 7 and hydroxylamine, with pH increasing over the course of the reaction from 1 to 10.

Aminofurazans are well known for their usage as precursors to biologically active compounds and energetic materials. Some methods of synthesis and properties of these useful compounds have been reviewed by Andrianov and Eremeev.[1] The most common syntheses of aminofurazans involve the initial preparation of aminoglyoximes and their subsequent intramolecular base-catalysed condensation. A limited set of aminofurazans is available, largely because no satisfactory general route for the synthesis of aminoglyoximes appears to have been developed, as well as the extreme conditions required for their dehydration to aminofurazans.

In the course of our recent work[2] on the design, synthesis and investigation of functionalized furazans, we were interested in the synthesis of 4,4′-diamino-3,3′-bifurazan **1** which was a precursor for some of our target molecules. Earlier, Coburn reported a multistep, low-yield procedure for the synthesis of **1**[3] starting with dichloroglyoxime synthesized from glyoxal (Scheme 1). It should be noted that the overall yield starting from commercially available glyoxal **2** was only about 3%, and some intermediate products and reagents were extremely toxic. There are considerable difficulties that must be overcome for this method to be practical.

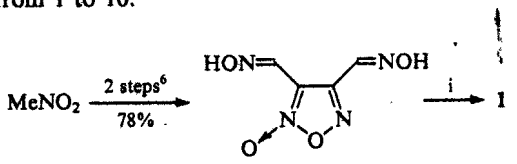


Scheme 1

We therefore sought a straightforward and simple method for the synthesis of **1**. One intriguing possibility is use of the Boulton–Katritzky rearrangement.[4]

In this communication we elaborate a new, one-pot method for the preparation of **1**. The strategy is based on the known ability of 1,2,5-oxadiazoles possessing an oxime group in the side chain to undergo this rearrangement[4] as well as the transformation of monosubstituted furazan into aminoglyoximes with hydroxylamine.[5] We utilized readily available 3,4-di(hydroximinomethyl)furoxan **7** as the key precursor in the investigation.[6,7] A proposed pathway to **1** is outlined in Scheme 2.

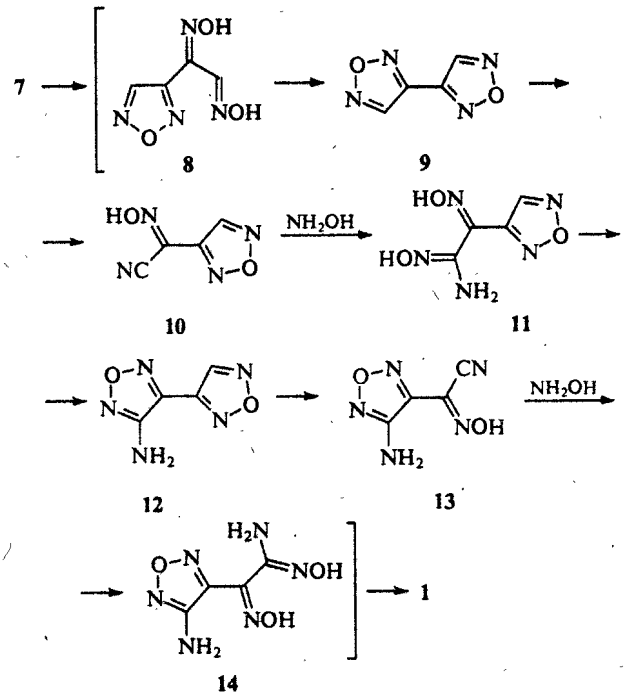
† The identity of product **1** was confirmed by NMR spectroscopy, mp, MS, IR, and comparison with the literature data.[3]



Scheme 2 *Reagents and conditions*: i, $NH_2OH·HCl$ (15 mol), pH 1→10, 45 °C→reflux, 4 h.

We have found that slow addition of an aqueous solution of KOH to a suspension of **7** and a hydroxylamine salt in aqueous DMSO, with stirring and heating, results in the formation of **1**. The product was separated by a simple filtration after cooling. The yield of **1**† was 18% (from **7**), and 14% reckoning up commercially available nitromethane. Two by-products, 3-aminofurazancarboxylic acid[8] (10%) and furazandicarboxylic acid[9] (7%), can be isolated if required from the filtrate by acidificaton.

This transformation is closely related to Wieland's finding[10] that **7** readily undergoes cleavage of the furoxan ring to produce, depending on the reaction conditions, a wide variety of rearrangement products.[11] A suggested sequence involves a series of reactions connected with the opening and closure of heterocycles. Our view of how **1** is formed is outlined in Scheme 3. Here it is proposed that the Boulton–Katritzky rearrangement produces glyoxime **8** in the normal manner which dehydrates to **9**. The bifurazan **9** can then undergo a proton shift[5,11,12] to produce **10**, which subsequently reacts with NH_2OH to give **11**. Dehydration of **11** generates a monoamine **12**. A repeat of the previous reaction three times to form the second aminofurazan moiety leads to the final



Scheme 3

product **1**.† It should be noted that an analogous treatment of an authentic sample of the bifurazan **9** with hydroxylamine affords **1**† in 39% yield, whereas at pH 10 only tetraoxime **6** (64%) was produced.

In conclusion, we have demonstrated that treatment of **7** with hydroxylamine provides a new and versatile approach to the one-pot synthesis of **1**. The starting compounds and reagents for this reaction are readily available and inexpensive. We believe that this is by far the simplest route to **1** currently available, and are now exploring the use of the products in various reactions.

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

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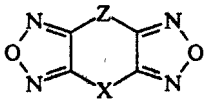
The title compound 2a was synthesized by a four-step sequence starting from 4,5-dichlorofurazano[3,4-*b*]pyrazine 3; the key step being a one-pot transformation of tetrazolo sulfilimine 6 to 2a *via* an oxidation/tetrazole ring cleavage/nitrogen loss/ring-closure/proton trapping procedure.

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
2h 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