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# Novel synthesis of 4-aminofurazan-3-acetic acid

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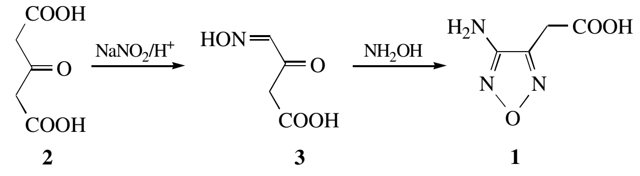
**The title compound 1 has been synthesized by a one-pot procedure starting from pyrrole; nitrosation and hydroxylamine treatment under basic conditions afford the target product in high yield.**

A number of substituted furazanic acids have been synthesized as potential pharmaceuticals. Thus, derivatives of the cephalosporin and penicillin class have been shown to be effective antibacterial agents,[1] and the set of amides are vasodilators[2] and anticonvulsants.[3] Hydroxyfurazancarboxylic acid has been investigated as a drug active on bones.[4]

As part of our program on the synthesis and investigation of compounds containing the furazan ring, we are interested in 4-aminofurazan-3-acetic acid **1**, which contains a carboxyl group at one end and an amino group at the other. These versatile groups allow us to perform selective linking reactions at either end of the furazan.

Only one preparative method exists for **1**, starting from 1,3-acetonedicarboxylic acid **2** and sodium nitrite to form 4-hydroxyimino-3-oxobutanoic acid **3** and subsequent treatment with hydroxylamine to give the target furazan (Scheme 1).[5] The maximum overall yield in this synthesis is about 50%, being limited by a destructive mono-nitrosation step in which the yield is quite variable.

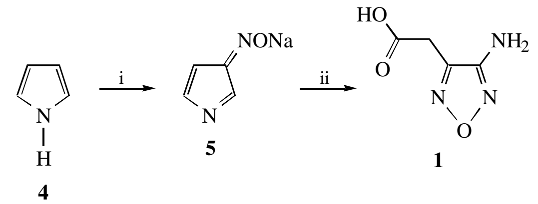


**Scheme 1**

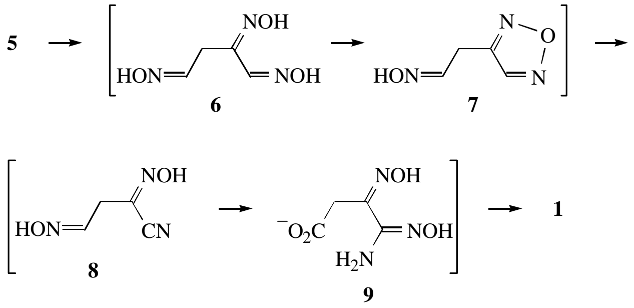
Because of the interesting properties of the amino acid **1** a search for an efficient preparation of the compound was undertaken.

A perusal of the literature had indicated few reasonable routes to furazan acetic acids.[6] From our viewpoint, however, the most attractive approach seemed to involve a recently-developed strategy,[7] as well as related studies,[8] which are based on the reactions of carbonyl compounds or their equivalents with hydroxylamine (being an oximating, aminating and redox reagent) and the capability of intermediate organic derivatives of hydroxylamine to undergo rearrangements.

We have successfully adapted this strategy to the synthesis of the amino acid **1**. As outlined in Scheme 2, pyrrole **4** was converted into the sodium salt of oxime **5** (quantitative yield) by nitrosation with alkyl nitrite in the presence of sodium alcoholate by a modified literature procedure.[9] Subsequent treatment with excess hydroxylamine and KOH under reflux and with vigorous stirring gave the target amino acid **1** in 78% yield. Both stages are carried out as one-pot procedures.



**Scheme 2** *Reagents and conditions*: i, AlkONO, AlkONa; ii, $NH_2OH{\cdot}HCl$, KOH, $H_2O$, reflux, 4 h.



**Scheme 3**

Based on (i), this result and our earlier observations and (ii), the knowledge that the reaction of 2,5-disubstituted 3-nitrosopyrroles and hydroxylamine is a method of synthesizing oximes of 3-acetonyl-4-alkyl(aryl)furazans,[10] we suggested a plausible mechanism for the above transformation (Scheme 3). Thus, initial cleavage of the pyrrole ring by oximation could produce an open-chain trioxime **6**, which then dehydrates to give an intermediate furazan **7**. Subsequent base promoted furazan ring cleavage could generate cyanooxime **8**.[†] This would react with hydroxylamine to yield compound **9** by addition to the C≡N bond and hydrolysis with oxidation of the terminal oxime function. The dioxime **9** dehydrated to the target aminofurazan **1**.

To conclude, the first synthesis of aminofurazans has been achieved using a methodology based on the transformation of a pyrrole precursor. The novel experimental procedure is straightforward. Current efforts in this laboratory are focused on further applications of this methodology for the formation of aminofurazans from pyrrole derivatives.

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[†] As shown earlier,[11] reaction of the salt **5** with hydroxylamine without heating yields a product with the empirical formula $C_4H_5N_3O_2$, which corresponds to compound **8**.

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