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Route to Pyrrolo[1,2–a]quinoxalines *via* a Furan Ring Opening–Pyrrole Ring Closure Sequence

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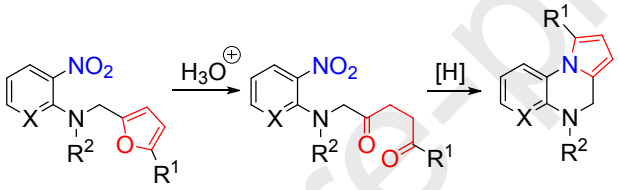

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Introduction

Pyrrolo[1,2-*a*]quinoxalines and their (partially) hydrogenated analogues belong to an important family of heterocycles found in various natural compounds, including those possessing a broad diversity of biological activities. For example, quinoxaline **I** was recently isolated from *Piper nigrum L.* and *Piper longum L.*;[1] compound **II** is an arginine vasopressin antagonist with selectivity for the V2 receptor;[2] carboxylic acid **III** and related compounds possess anti-allergic activity;[3] PPQ-102 is an inhibitor of the cystic fibrosis transmembrane conductance regulator;[4] CGS 12066B is a potent and selective agonist for the 5-HT1B receptor;[5] quinoxaline **IV** is an inhibitor of PARP-1.[6] The diverse biological activities of pyrrolo[1,2-*a*]quinoxalines

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ABSTRACT

A method was developed for the synthesis of pyrrolo[1,2-*a*]quinoxalines based on an acid-promoted furan ring opening of readily accessible *N*-(furan-2-ylmethyl)-2-nitroanilines or their heterocyclic analogues followed by a key reductive Paal-Knorr cyclization of the corresponding nitro-1,4-diketones.

oper of based on this heterocyclic motif.

Various synthetic protocols have been developed for the construction of pyrrolo[1,2-*a*]quinoxalines,[7] mostly based on the use of key 2-(1*H*-pyrrol-1-yl)anilines or their precursors.[8] Such an approach was firstly described almost 55 years ago by Cheeseman and Tuck (*a*, Scheme 1).[9] Subsequently, numerous synthetic protocols based on the related construction of a pyrazine core were reported using the Pictet–Spengler[10] and Bischler–Napieralski reactions[11] (*b*, Scheme 1). Despite the simplicity of such approaches, their application is restricted by

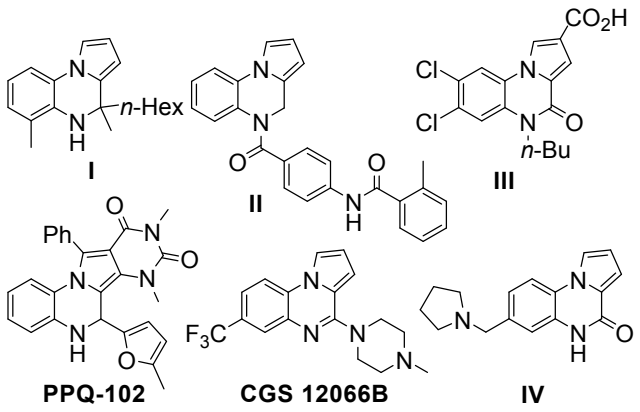
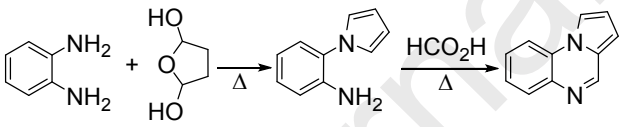


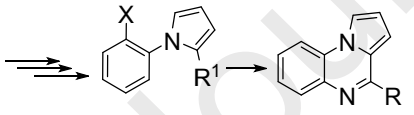
Figure. 1. Selected biologically important pyrrolo[1,2-*a*]quinoxalines.

the low scope of substrates involved, since the synthesis and subsequent functionalization of the desired products proceed in a stepwise manner, and both steps impose demands on the functionalities that can be present in the starting materials. Thus, the development of straightforward and effective protocols for the synthesis of substituted pyrrolo[1,2-*a*]quinoxalines is an important task.

a) **Initial synthesis of pyrrolo[1,2-*a*]quinoxaline**

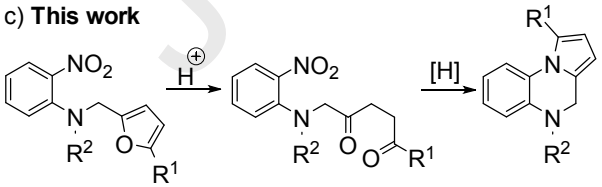


b) **Related approaches to pyrrolo[1,2-*a*]quinoxalines**



X=NO_2, NH_2, $NHCOR^2$; R^1=H, COR^2, CHO

c) **This work**



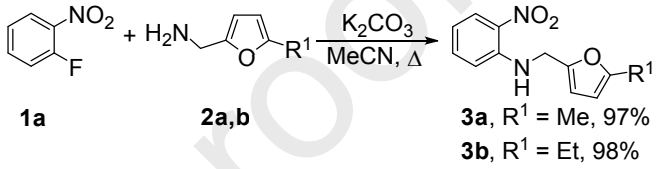
Scheme 1. Known approaches to pyrrolo[1,2-*a*]quinoxalines and the concept of this work.

Over the past decades, we have developed a general approach to the synthesis of functionalized heterocycles that can be referred to as "Furan Ring Opening − Heterocycle Ring Closure".[12] In particular, a series of protocols for the synthesis of various 1,2-annulated pyrroles has been proposed.[13] The starting furans, the simplicity of the synthetic procedures, and the high structural variability of the potential products.

Accounting for the significance of substituted pyrrolo[1,2-*a*]quinoxalines, we tried to apply the same strategy to the synthesis of these compounds. Herein, we report an original approach to substituted pyrrolo[1,2-*a*]quinoxalines based on a domino nitroarene reduction/intramolecular Paal-Knorr reaction (*c*, Scheme 1).

Results and Discussion

The starting point of our research was the synthesis of substituted *N*-(furan-2-ylmethyl)-2-nitroanilines **3** (Scheme 2). The desired products were synthesized in near quantitative yields by heating mixtures of 1-fluoro-2-nitrobenzene (**1a**), furfurylamines **2a,b** and freshly calcined K_2CO_3 at reflux in MeCN.

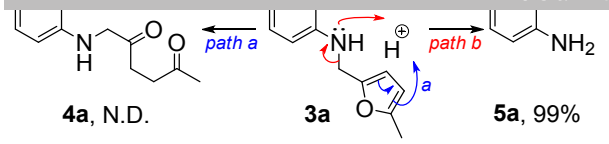


Scheme 2. Synthesis of the starting *N*-(furan-2-ylmethyl)-2-nitroanilines **3a,b**. Reagents and conditions: **1a** (6.5 mmol), K_2CO_3 (10 mmol), MeCN (10 mL), **2a,b** (7.5 mmol), reflux, 4−10 h.

The transformation of compounds **3** to the target pyrrolo[1,2-*a*]quinoxalines include three principal steps: reduction of the nitro group to an amine, hydrolysis of the furan to the corresponding 1,4-diketone, and the key intramolecular Paal-Knorr reaction. In general, these reactions can be performed either stepwise in the appropriate order or simultaneously accounting for the fact that the reduction step can be performed under the acidic conditions required for both the furan ring hydrolysis and the Paal-Knorr reaction.

Nevertheless, we previously found that the acid-induced recyclization of the related *N*-furfurylanthranilamides have significant restrictions due to competitive side-processes.[13f] These side reactions can be significantly suppressed by using a hydrolysis/Paal-Knorr reaction sequence starting from *N*-furfuryl-2-nitrobenzamides as substrates. The successful synthesis of (hetero)arene-annulated pyrrolo[1,2-*d*][1,4]diazepines from the appropriate 5-(2-nitroaroyl)amino-1,4-diketones[13a] supports the idea that the preferable method for the transformation of **3** to pyrrolo[1,2-*a*]quinoxalines is the initial hydrolysis of the furan ring followed by reductive cyclization of the formed nitroanilino-1,4-diketones.

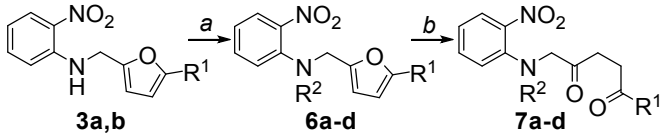
Therefore, we investigated the acid-catalyzed furan ring opening using *N*-[(5-methylfuran-2-yl)methyl]-2-nitroaniline (**3a**) as a model compound (Scheme 3). We found that the treatment of furan **3a** with various Brønsted acids unexpectedly led to the formation of only 2-nitroaniline (**5a**) in quantitative yield. The formation of 2-nitroaniline (**5a**) presumably resulted from the presence of two sites for protonation in **3**: the furan core and the amino group. The protonation of the furan core leads to hydrolysis affording the desired 1,4-diketones (path *a*); on the other hand, protonation of the amino group causes *C–N* bond cleavage furnishing a furfuryl cation, which undergoes various transformations, and 2-nitroaniline (path *b*).[14]



Scheme 3. Acid-catalyzed hydrolysis of *N*-[(5-methylfuran-2-yl)methyl]-2-nitroaniline (**3a**).

To suppress the undesirable *C*-*N* bond cleavage leading to the formation of 2-nitroaniline (**5a**), we protected the nitrogen atom by reacting the starting amines **3a**,**b** with various acyl chlorides under typical reaction conditions (Table 1). Indeed, we found that acid-catalyzed hydrolysis of *N*-protected furfurylamines **6** produced the desired 1,4-diketones **7** in high yields. The exception was furfurylamine **6c**, which gave rise to 1,4-diketone **7c** in only 43% yield; 4-methoxy-*N*-(2-nitrophenyl)benzamide **5b** was formed as a side product in this process. This result was presumably associated with the easier protonation of the amide moiety in **6c** due to the electron-releasing effect of a donor *para*-methoxy group providing efficient stabilization of the *O*-protonated amide moiety. In other cases, we observed the formation of side benzamides only in 5–10% yield.

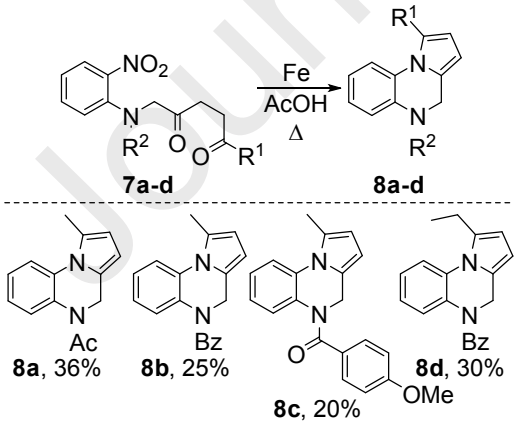
Table 1. Synthesis of 1,4-diketones **7**.



Entry	R^1	R^2	Yield (%) **6**	Yield (%) **7**
a	Me	Ac	83	81[a]
b	Me	Bz	92	81[a]
c	Me	4-$MeOC_6H_4CO$	88	43[b]
d	Et	Bz	98	74[a]

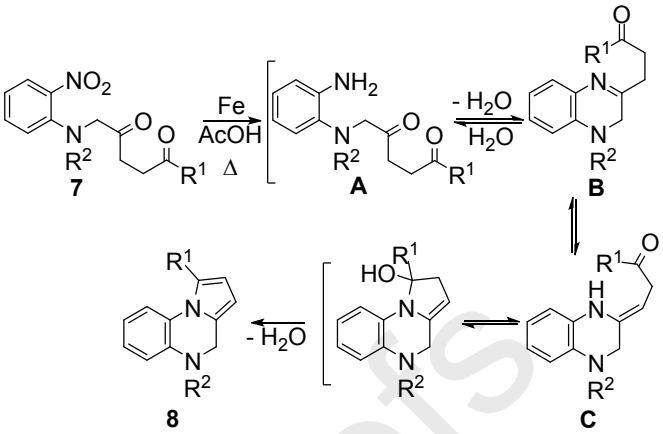
Reagents and conditions: (a) **3** (5 mmol), TEA (10 mmol), MeCN (10 mL), R^2Cl (10 mmol), reflux, 2–11 h; (b) **6** (3 mmol), AcOH (16 mL), HCl (12 M, 3.2 mL), rt, 7−24 h. [a]5–10% of the corresponding benzamide was also isolated. [b]20% of 4-methoxy-*N*-(2-nitrophenyl)benzamide was also isolated.

Finally, we studied the reductive Paal-Knorr cyclization of 1,4-diketones **7** aiming to synthesize pyrrolo[1,2-*a*]quinoxalines **8** (Scheme 4).



Scheme 4. Synthesis of pyrrolo[1,2-*a*]quinoxalines **8a-d**. Reagents and conditions: **7a-d** (1.5 mmol), AcOH (6 mL), Fe (22.5 mmol), reflux, 3−5 min.

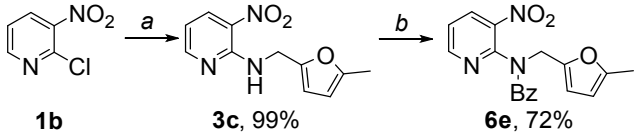
We found that the treatment of 5-(2-nitroanilino)-1,4-diketones **7** with iron in acetic acid induced the domino reaction including reduction of the nitro group to aniline **A**, its condensation with the nearest carbonyl group affording the second amine–carbonyl condensation accomplishing construction of the target pyrrolo[1,2-*a*]quinoxalines **8** (Scheme 5).



Scheme 5. Plausible reaction pathway to pyrrolo[1,2-*a*]quinoxalines **8**.

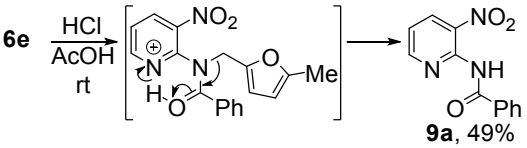
The moderate yields of products **8** presumably resulted from the competitive enolization/cyclodehydration of intermediate amino-1,4-diketone **A** providing the corresponding furans, which under acidic conditions undergo decomposition. In order to increase the yields of the desired pyrrolo[1,2-*a*]quinoxalines, we studied other commonly used reduction conditions. In particular, we tested sodium dithionite, tin(II) chloride, Zn, and catalytic hydrogenation in the presence of Pd/C or Ni Raney. However, in all cases we did not observe significantly increased yields.

Next, we applied the developed approach to the synthesis of heterocyclic analogues of pyrrolo[1,2-*a*]quinoxalines (Scheme 6). As the starting material, we chose commercially available 2-chloro-3-nitropyridine (**1b**), which was transformed into *N*-[(5-methylfuran-2-yl)methyl]-3-nitropyridin-2-amine (**3c**) and then to the corresponding *N*-protected amine **6e**.



Scheme 6. Synthesis of substituted furfurylamine **6e**. Reagents and conditions: (a) **1b** (6.5 mmol), K_2CO_3 (10 mmol), MeCN (10 mL), **2a** (7.5 mmol), reflux, 3 h; (b) **3c** (5 mmol), TEA (10 mmol), MeCN (10 mL), BzCl (10 mmol), reflux, 11 h.

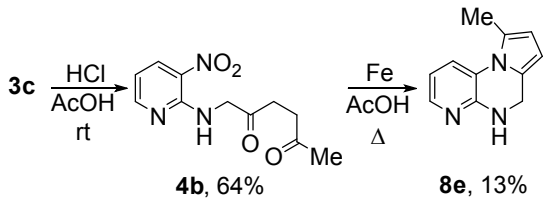
However, the acid-catalyzed hydrolysis of furan **6e** led to tarring of the reaction mixture, and only *N*-(3-nitropyridin-2-yl)benzamide **9a** was isolated (Scheme 7). The *C*–*N* bond cleavage in this case is facilitated by preferential protonation of the pyridine core yielding an amidinium-type cation.



Scheme 7. Acid-catalyzed hydrolysis of furfurylamine **6e**. Reagents and conditions: **6e** (3 mmol), AcOH (16 mL), HCl (12 M, 3.2 mL), rt, 6 h.

We suggested that in this case we could expect to promote an acid-catalyzed hydrolysis of the furan ring without using a protecting group on the amine moiety (Scheme 8). Indeed, we found that the furfurylamine **3c** was transformed into the corresponding 1,4-diketone **4b** in good yield; the 3-nitropyridin-

2-ar an, performed the intramolecular reductive Paal-Knorr cyclization of 1,4-diketone **4b**, and the desired pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **8e** was formed in 13% yield.



Scheme 8. Synthesis of pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **8e**. Reagents and conditions: **3c** (1.5 mmol), AcOH (6 mL), Fe (22.5 mmol), reflux, 3−5 min.

The cytotoxicity of **8c** and **8d** was investigated against MCF10A, VA13, MCF7, and A549 cell lines (Table 2). Both compounds contain a 2,5-dimethyl-1-phenyl-1*H*-pyrrole fragment, which is a commonly found substructure in toxic ligands. The cytotoxicity (CC50) of **8d** was in low micromolar concentrations, whereas, in contrast, the CC50 of **8c** was in nanomolar concentrations. These compounds may be compared with structurally related pyrrolo[1,2-*d*][1,4]diazepines[13a] that have a diazepine ring instead of a pyrazine ring, and the same predicted cytotoxic substructure. The cytotoxicity of **8d** was an order of magnitude higher than its nearest homologue; the cytotoxicity of **8c** was 2–3 orders of magnitude higher than that for the corresponding pyrrolodiazepine. This substrate can be used as a lead compound for the search of new anticancer drugs.

Table 2. The cytotoxicity (CC_{50}, μM) of quinoxalines **8c,d**.

Entry	MCF10A	MCF7	A549	VA13
8c	0.0044±0.0015	0.0033±0.0015	0.035±0.029	0.47±0.26
8d	2±0.3	2.4±0.5	2.29±0.12	5.21±1.34
doxoru-bicin	0.08±0.02	0.12±0.02	0.11±0.01	0.25±0.02

In conclusion, we have developed a simple route for the synthesis of functionalized pyrrolo[1,2-*a*]quinoxalines starting from furfurylamines and 1-fluoro-2-nitrobenzene (or their heterocyclic analogues). The key step of the developed method is based on reductive Paal-Knorr cyclization of the corresponding nitro-1,4-diketones. The commercially available and inexpensive starting materials and mild reaction conditions are attractive features of the developed method.

- Route for the synthesis of functionalized pyrrolo[1,2-*a*]quinoxalines was developed
- The hydrolysis of *N*-protected furfurylamines produced 1,4-diketones in high yields
- The reductive Paal-Knorr reaction afforded the target pyrrolo[1,2-a]quinoxalines
- The cytotoxicity of obtained pyrrolo[1,2-a]quinoxalines was investigated

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Appendix A. Supplementary data

Supplementary data to this article can be found online at

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