Furan ring transformation as a key stage in pyrrolopyrazine framework synthesis

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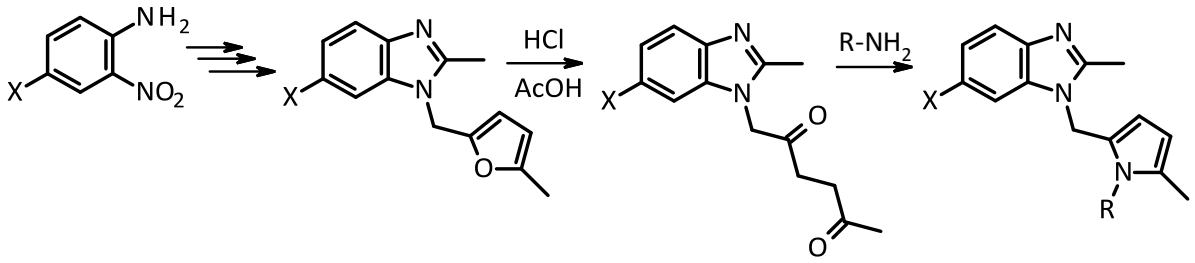
Introduction

For many years benzimidazoles are of interest for medicinal chemistry. Among them compounds having antihistamine [1] and antibacterial [1,2] activity are found. Benzimidazole derivatives exhibit cytostatic [1], anesthetic, hypotensive and antipyretic activities [3]. So synthesis of novel benzimidazole derivatives, including annelated polycyclic systems, is very important.

Results and discussion

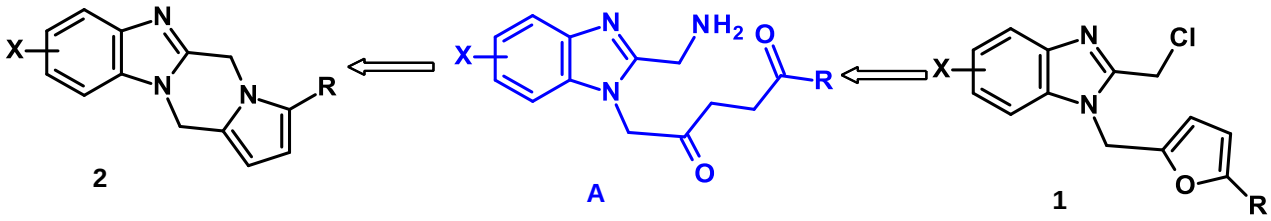
In continuation of our previous investigations on usage of furan compounds for various fused heterocyclic systems synthesis we studied a furan ring recyclization in 1-(5-alkylfuryl-2)benzimidazoles. Earlier we have used similar compounds bearing methyl group at position 2 of benzimidazole ring for 1-(pyrrol-2-ylmethyl)benzimidazole synthesis [4] (Scheme 1). The method included two stages: furan ring opening to obtain 1,4-diketone unit and N-substituted pyrrole ring formation via an interaction of the diketone with primary amines. We showed that an application of various primary amines (aliphatic or aromatic) allowed preparing a wide range of pyrrolylmethylbenzimidazoles which were hard-to-reach by another ways.

Scheme 1



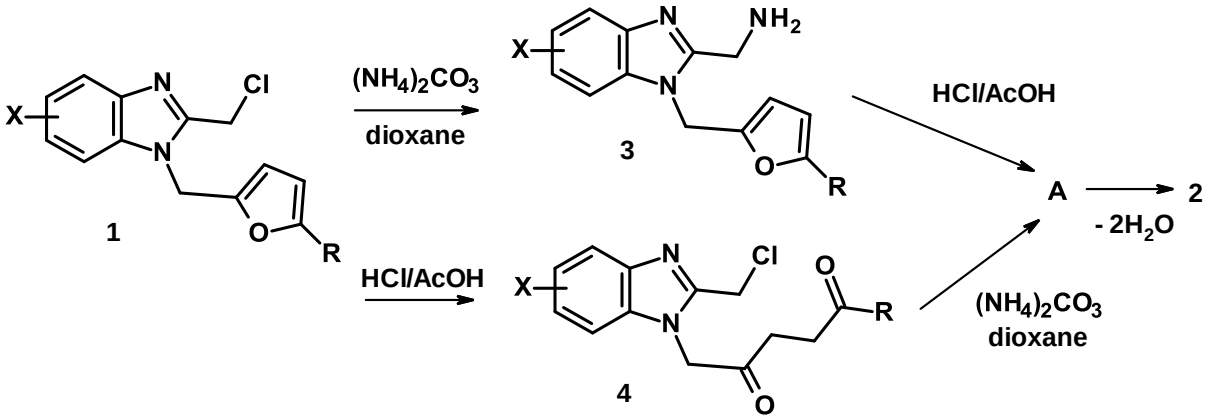
Now we present an original approach to pyrrolo[1',2':4,5]pyrazino[1,2-a]benzimidazole derivatives based on a recyclization of furan ring. Earlier we have utilized similar strategy for fused pyrrolo[1,2-a][1,4]diazepines [5] and pyrrolo[1,2-a][1,4]diazocines syntheses [6]. The unique feature of both transformations was a simultaneous formation of pyrrole and diazepine (or diazocine) ring. As described earlier for pyrrolodiazepines [5], the key stage of pyrrolopyrazinobenzimidazole framework synthesis is an intermediate A formation (Scheme 2).

Scheme 2



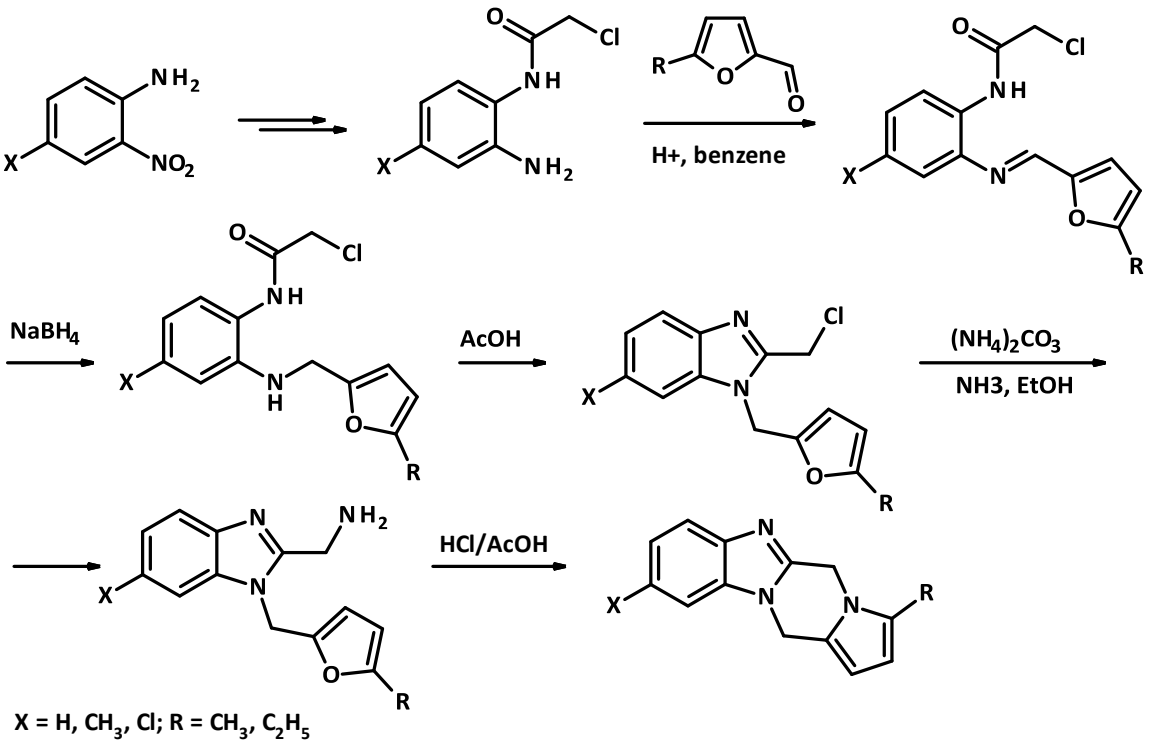
The intermediate A can be prepared from benzimidazoles 1 via two stages: an amino group introduction and formation of 1,4-diketone unit from furan ring (Scheme 3).

Scheme 3



The first path includes an acid-catalyzed transformation of furan ring in 2-aminomethyl-1-(5-alkylfuryl-2)methylbenzimidazoles. The reaction proceeds as a domino-process and lead to new heterocyclic system - pyrrolo[1',2':4,5]pyrazino[1,2-a]benzimidazole - via simultaneous pyrrole and pyrazine ring closure. The key stage of the reaction is an intramolecular furan ring recyclization (Scheme 4).

Scheme 4



According the second path firstly a diketone fragment was prepared from furan ring under the action of HCl/AcOH mixture. Treating the obtained compounds with NH_4HCO_3 in NH_4OH resulted in desired pyrrolo[1',2':4,5]pyrazino[1,2-a]benzimidazoles as main products.

Structures of all prepared compounds are determined using ^{1}H and ^{13}C NMR spectroscopy, mass-spectrometry and elemental analysis data.

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References

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