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One-step assembly of novel carbamoyl substituted 6-oxo-4,5,6,11-tetrahydropyrrolo[1,2-*b*][2,5]benzodiazocine

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ABSTRACT

In this work we have synthesized novel pharmaceutically relevant pyrrolo[1,2-*b*][2,5]benzodiazocines based entirely on the use of MCR between heterocyclic aldehyde-acid, amines, and isonitriles. The developed synthetic strategy provides an efficient one-step route to rare heterocyclic scaffold of paramount interest.

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Among physiologically active aryl- and heteroaryl-fused six- and seven-membered heterocyclic systems, including piperazines[1] and diazepines[2], eight- and nine-membered diaryl and heteroaryl-fused rings represent a relatively little-explored group with immense therapeutic potential. Indeed, in many cases their structures strongly resemble the whole composition of low-membered analogs in accordance to the fundamental bioisosteric rules. Therefore, the biological activity of such agents should be described jointly to reflect principal structural and topological features accurately.

The family of 6-oxo-4,5,6,11-tetrahydropyrrolo[1,2-*b*][2,5]benzodiazocines represents promising synthetic targets. Development of synthetic approaches to this scaffold may provide a valuable source of novel physiologically active agents. In this Letter, we communicate our success in developing a novel Ugi-type MCR for the synthesis of rare heterocyclic compounds from this series. The Ugi reaction[3] was shown to be an effective approach to the assembly of diverse compound libraries, which can be readily applied in combinatorial chemistry format.

In the present work we have focused specifically on broadening the scope and synthetic potential of the modified Ugi four-center three-component reaction (U-4C-3CR) based on the use of bifunctional components,[4] which we have recently developed and comprehensively evaluated.[5–10] Following our approach, we have synthesized heterocyclic compounds **5a–d** based on 2-(2-formyl-pyrrol-1-ylmethyl)-benzoic acid **1**, which were not described before in the thematic literature (Scheme 1).

Thus, key heterocyclic aldehyde-acid **4** for the synthesis of the target heterocyclic structure was obtained from acid **1** and corresponding 1*H*-pyrrole-2-carbaldehyde **2**, which are readily available from commercial sources. We have further found that the reaction of aldehyde-acid **4** with amines and isonitriles in methanol at 50 °C led to novel 6-oxo-4,5,6,11-tetrahydropyrrolo[1,2-*b*][2,5]benzodiazocines **5a–d** (Scheme 1). Typically, the full conversion of initial reactants was achieved within 5–10 h, depending on the structure of the initial amines and isonitriles. The process presumably follows the same initial course as the classical Ugi condensation with an intermediate imine being attacked by the isonitrile to give a nitrilium intermediate, which then undergoes intramolecular cyclization. In this work we have used two different amines and isonitriles, their structures can be identified in Scheme 1.

In the performed condensation variant, the desired cyclic products usually precipitated from the reaction mixtures after the reaction was cooled to room temperature. These reactions afforded the desired products in relatively low yields, depending on the nature of coupling components. However, it should be particularly noted that the yields of reactions leading to such heterocyclic systems depend directly on the size of the cycle assembled.[11]

All compounds were obtained as racemic mixtures of enantiomers. The assignment of all synthesized structures was made on the basis of ^{1}H NMR and high-resolution mass-spectroscopy data (see Supplementary data). The obtained spectral data gave satisfactory results consistent with the suggested molecular structures.

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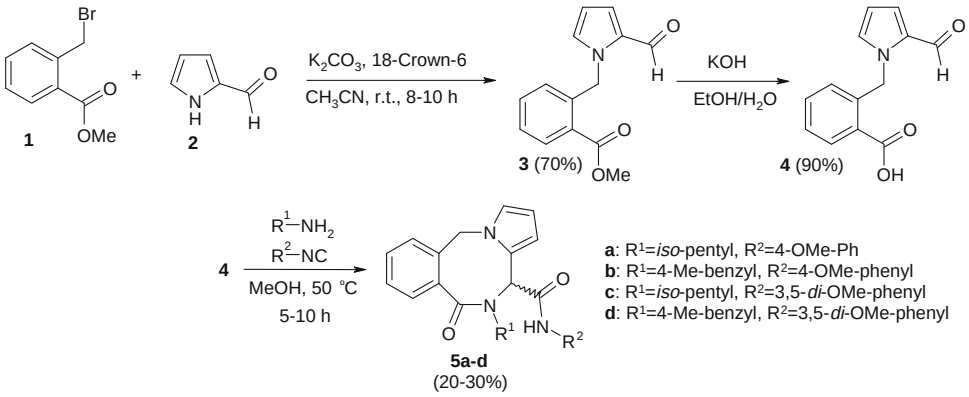

Scheme 1. Synthesis of N-substituted 6-oxo-4,5,6,11-tetrahydropyrrolo[1,2-*b*][2,5]benzodiazocine-4-carboxamides **5a–d**.

In some cases, pure crystalline substances could be obtained, thus allowing analysis of the individual compounds through X-ray crystallography. For instance, the structure of **5b** was unambiguously established as 5-(4-methoxyphenyl)-*N*-(4-methylbenzyl)-6-oxo-4,5,6,11-tetrahydropyrrolo[1,2-*b*][2,5]benzodiazocine-4-carboxamide (Fig. 1), by single-crystal X-ray analysis. Single crystals of compounds suitable for X-ray analysis were grown by slow evaporation from diethyl ether. The corresponding valence angles and bond lengths of these molecules in the asymmetric unit are the same within three standard deviations. As shown in Figure 1, the space orientation of two bulky substituents derived from amine and isonitrile components is completely different. The inner 1,4-diazocine space turn can also be clearly recognized. Presumably, the observed conformation corresponds to the global minima of the free kinetic energy.

In summary, we have shown that unique heterocyclic compounds can be efficiently prepared by a novel modification of Ugi MCR reaction of heterocyclic aldehyde-acid, amines, and isonitriles. Considering the ease of the preparation of initial reactants, convenient synthesis, and isolation of products, this synthetic route provides a new valuable entry to novel eight-membered heterocyclic systems which can be reasonably regarded as unique bioisosteric analogs of related biologically active six- and seven-membered heterocyclic compounds. As a synthetic tool for creating diverse compound libraries, the MCR developed in this work offers a large number of potential input reactants and resulting products. Therefore, the synthetic scope of the method described will be broadened in further paper. It is quite obvious that the obtained compounds represent valuable starting points for the development of compounds of biological interest. The use of compounds from series **V** in the search for novel bioactive agents is under investigation in ChemDiv. Inc company and will be reported in due course.

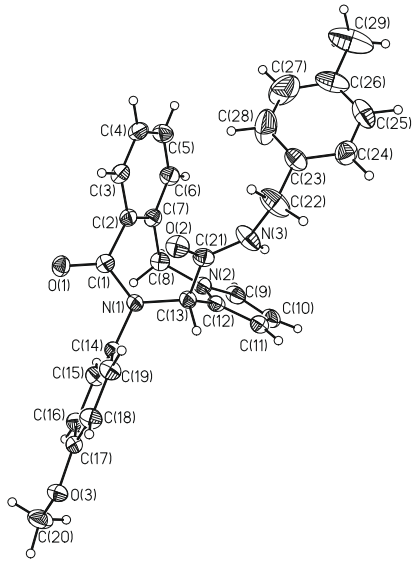

Figure 1. ORTEP plots (50% probability thermal ellipsoids) of compound **5b**. Hydrogen atoms are omitted.

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Supplementary data

Supplementary data (including synthetic procedures for compounds obtained in this work, corresponding NMR spectra and HRMS protocols as well as detailed X-ray data, is available online with the paper in ScienceDirect) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.160.

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