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Multicomponent access to novel dihydroimidazo[1′,5′:1,2]pyrido[3,4-*b*]indol-2-ium salts and indoles by means of Ugi/Bischler–Napieralski/heterocyclization two step strategy

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ABSTRACT

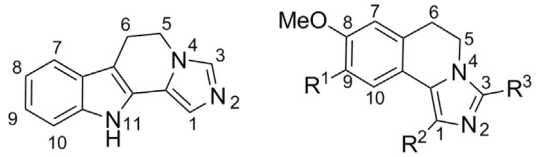
A simple, efficient and general two step procedure, through a sequential Ugi reaction followed by a Bischler–Napieralski/heterocyclization tandem closure, to give novel 6,11-dihydro-5*H*-imidazo[1′,5′:1,2]pyrido[3,4-*b*]indol-2-ium salt derivatives, is described. By changing the amine and the acid components with ammonium formate, the same procedure affords 6,11-dihydro-5*H*-imidazo[1′,5′:1,2]pyrido[3,4-*b*]indole derivatives.

1. Introduction

Multicomponent reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features to maximize structural complexity and convergence, while saving synthetic operations.[1] Since these highly step-economic reactions are particularly appealing in the context of diversity as well as target-oriented syntheses, they play an important role in drug discovery and biological probe chemistry. When coupled with post-MCR cyclizations, these reactions can lead to interesting heterocyclic scaffolds, becoming particularly useful for the construction of diverse arrays of drug-like molecules in medicinal chemistry. Among the several multicomponent protocols, the Ugi four-component reaction (Ugi-4CR)[2] has been, without any doubt, one of the most investigated in pharmaceutical industry and in academic research over the past two decades.[3]

In this context, we recently focused on tetrahydro-β-carboline (THBC)-based compounds[4] as privileged molecular targets, and on the Ugi reaction, as a powerful tool for the synthesis of related polycyclic structures.[5] Natural and synthetic products containing tryptophan-based pharmacophores exhibit a wide range of important bioactivities, particularly concerning the central nervous system. In particular, due to their unique rigid heterocyclic skeleton, THBC-based compounds are known to bind with high affinity to various receptor sites, such as the benzodiazepine (BzR), serotonin, and dopamine sites[6] and to inhibit monoamine oxidase A.[7] Moreover, some tetracyclic β-carbolines have been reported to act as selective inhibitors in the anticancer field,[8] or to be endowed with antimalarial properties.[9]

Recently, dihydroimidazo-fused THBC derivatives, in which the 6,11-dihydro-5*H*-imidazo [1′,5′:1,2]pyrido-[3,4-*b*]indole framework **1** has been incorporated (Fig. 1), have shown particular interest because of their potential therapeutic properties,[10] mainly as agonists of 5HT-2 serotonin receptors,[10a,b] and as inhibitors of Mitogen-activated protein-kinase-2.[11] Generally, available methods for the synthesis of type **1** compounds capitalized upon a conventional amidation/Bischler–Napieralski sequence, which, however, do not



1 **2**

Fig. 1. The 6,11-dihydro-5*H*-imidazo[1′,5′:1,2]pyrido[3,4-*b*]indole and 5,6-dihydroimidazo[5,1-*a*]isoquinoline frameworks.

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allow for the rapid introduction of different functional groups onto the core structure. Yet, considerable recent progress has been represented by Seganish's synthesis[12] of the related 5,6-dihydroimidazo [5,1-*a*]isoquinolines **2**,[13] via an efficient Ugi/Bischler–Napieralski reaction sequence.

Imidazolium salts, which are made up of a discrete cation and anion pair, have found widespread utility as ionic liquids.[14] Several areas of bio-applications, including antitumor, antibacterials, antimicrobial, antioxidant activities and bioengineering applications, have also been reported.[15] Both imidazoles and imidazolium salts are ubiquitous in nature and play a critical role in many structures and functions due to their ability to interact electrostatically with biological systems.[16]

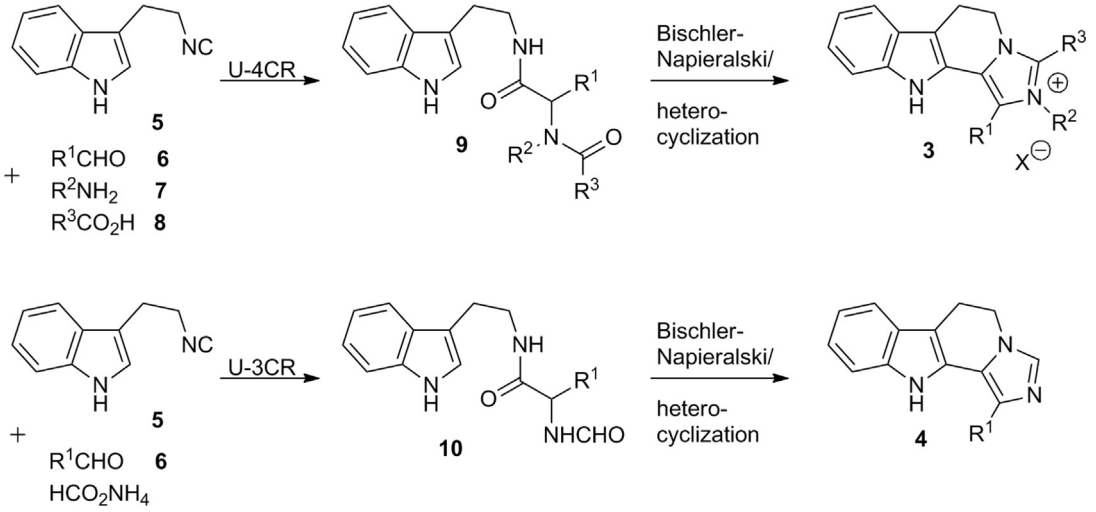
2. Results and discussion

As part of our ongoing interest in the development of MCRs-based heterocycles, we herein report the synthesis of diverse 1,2,3-trisubstituted 6,11-dihydro-5*H*-imidazo[1′,5′:1,2]pyrido[3,4-*b*]indol-2-ium salts **3** and 1-substituted 6,11-dihydro-5*H*-imidazo [1′,5′:1,2] pyrido[3,4-*b*]indoles **4**, via an Ugi/Bischler–Napieralski/heterocyclization two steps sequence (Scheme 1).

(1.0 equiv) in methanol. The mixture was stirred for 24–120 h at 40 °C to provide intermediates **9** in moderate to good yields (Table 1). An investigation on temperature and solvent revealed that the use of methanol at 40 °C gave the optimal results both in terms of yields and reaction rates. When other solvents, such as CH_2Cl_2, CF_3CH_2OH or toluene, or higher reaction temperatures were applied, yields decreased significantly. This first multicomponent step was tolerant with a variety of aromatic (entries 1, 4–6) and aliphatic (entries 2–3, 7–10) aldehydes, having different electronic properties. Acid sensible furfural afforded smoothly the Ugi adduct in 77%. Notably, the steric hindrance of amine (entries 7, 8 and 10) as well as of acid (entries 3, 9) components does not play a determinant role in terms of reactivity and product yields.

The subsequent Bischler–Napieralski/heterocyclization of Ugi-adducts **9** was carried out in toluene under nitrogen atmosphere at 80–110 °C, using a large excess of phosphoryl chloride (15 mol equiv) as dehydrating reagent for 60–360 min. Following this double dehydration protocol, we obtained the target products **3**, which could be easily isolated by standard aqueous work-up, followed by conventional flash chromatography as hydrochloride salts.

It should be noted that the reaction time and yields somewhat depend on the starting components of the Ugi step, which de-



Scheme 1. Multicomponent access to novel dihydroimidaszo[1′,5′:1,2]pyrido[3,4-*b*]indol-2-ium salts and indoles.

Notably, starting from a tryptamine-derived isocyanide, and aldehydes, carboxylic acids and amines as Ugi-components, a non-conventional degree of chemical diversity could be introduced at the N-2 nitrogen atom of **1**, to afford imidazolium salts structures.

Then, by a careful selection of starting materials, this two step strategy can, potentially, give access to a multitude of diversified molecules for testing of biological assays and catalytic ligand properties,[17] with improved synthetic efficiency. To the best of our knowledge, this represents the first protocol, which allows to achieve unique indole-imidazolium structures, by means of a multicomponent approach.

The 3-(2-isocyano-ethyl)-1*H*-indole precursor **5** was prepared in 82% overall yield, by formylation of tryptamine followed by dehydration using triphenylphosphine and carbon tetrachloride in dichloromethane at room temperature.[18] It must be noted that any attempt to dehydrate *N*-formyl tryptamine by means of phosphoryl chloride[19] at room temperature only led to a fast decomposition of the starting material.

The Ugi reaction was undertaken following a general procedure, consisting of the sequential addition of aldehyde **6** (1.1 equiv), amine **7** (1.1 equiv), carboxylic acid **8** (1.1 equiv) and, finally, isocyanide **5** termine the structure of the R^{1-3} residues. In general, as for the Ugi reaction step, also in this case both aliphatic and aromatic residues, having different electronic properties, as well as those bearing bulky substituents showed to be suitable for the reaction.

An exception is the Ugi adduct **9f** containing a furan moiety: due to the acidic reaction conditions, we observed only a rapid degradation of the starting material with the production of unidentified by-products. Importantly, the reaction proceeded smoothly in the presence of electron-donating groups on the benzene ring (entries 7, 8, 10), where competition of the electron-rich benzene ring to capture the transient Bischler–Napieralski iminium salt, can, in principle, occur. On the other hand, bulkiness seems to play a role in the rate of the tandem reaction, as highlighted by the higher temperature and longer reaction times required in the presence of an *ortho* substituent on the aniline-derived ring (entries 9, 10).

We envisioned that the transformation of **9** to **3** might occur affording firstly mono-cyclized products **11** (Scheme 2), which, subsequently, could further cyclize to provide final compounds **3**. To gain support for this mechanistic proposal, on selected Ugi-products **9** the reaction was performed using a minor excess of phosphoryl chloride (5 mol equiv) at 50 °C. No cyclic intermediates