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Two-Step Synthesis of 2,3-Dihydropyrroles via a Formal 5-*endo* Cycloisomerization of Ugi 4-CR/Propargyl Adducts

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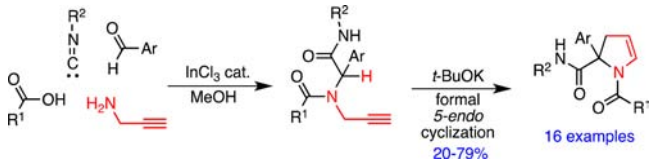
ABSTRACT



A practical two-step synthesis of 2,3-dihydropyrroles from Ugi 4-CR/propargyl adducts is presented. The protocol includes a base-mediated formation of an allenamide functional group and an in situ metal-free formal 5-*endo* cycloisomerization that occurs in a highly regioselective manner at the allenamide C-γ.

The 2,3-dihydropyrrole (2-pyrroline) core is an important motif present in numerous natural products with important biological activities. Two examples are sibiromycin (**1**) and anthramycin (**2**), two compounds isolated from actinomycetes which show significant antitumor properties, e.g., sequence-selective DNA alkylation (Figure 1).[1] The main synthetic approaches to this heterocyclic system have been based on metal-catalyzed reactions,[2] cycloadditions,[3] and tandem Michael/cyclization sequences.[4] Additionally, 2,3-dihydropyrroles derivatives have been used as a key building block in various total syntheses[5] as well as in the construction of other complex molecules.[6]

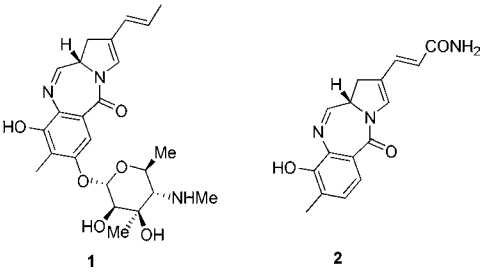


Figure 1. Natural products bearing the 2,3-dihydropyrrole core.

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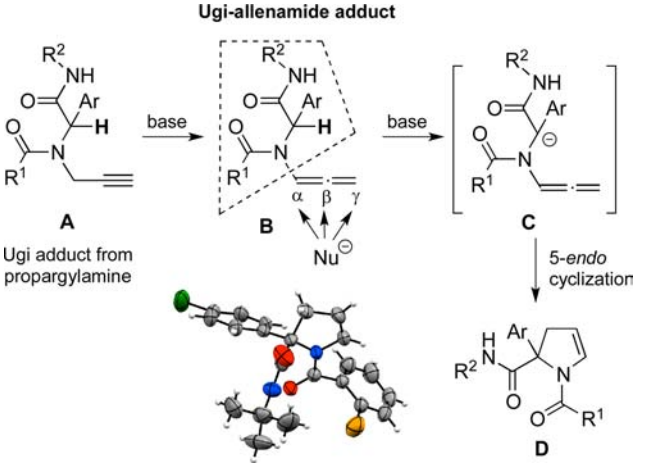
Heteroannulation of allenes and allenamides has attracted considerable attention for the elegant construction of miscellaneous heterocyclic scaffolds in recent years.[7] Among the most frequently used protocols are those which involve metal-catalyzed methods.[8] The unique contiguous nitrogen/two π-bonds array of allenamides makes their rich chemistry noteworthy. The interesting electronic arrangement provides them with the ability to participate in either electrophilic or nucleophilic processes, generally in a highly regioselective fashion.[9] Indeed, it has been reported that suitably substituted allenamides undergo nucleophilic addition (most of them in a metal-catalyzed protocol) at all three of their carbon atoms, α,[10] β,[11] and γ[12] (see Scheme 1, **B**). Several other allenamide transformations, including radical additions,[13] cycloadditions,[14] and oxidations,[15] are now well documented in the literature. On the other hand, the Ugi four-component reaction (Ugi 4-CR) is undoubtedly one of the most powerful methodologies to easily build up molecular complexity, generally from simple raw materials. Furthermore, when this reaction is sequentially combined with one or more meticulously selected process, the resultant synthetic sequence provides products with amplified molecular complexity and, in several cases, also with augmented molecular diversity.[16] Recently as part of our ongoing interest in the development of practical protocols to construct heterocyclic scaffolds using a programmed combination of a Ugi-4CR,[17] we envisaged that a Ugi-allenamide adduct such as **B** (Scheme 1) might be a useful template to easily construct heterocyclic scaffolds via a consecutive heteroannulation process. Preliminary observations on this endeavor are described in the present communication.

At the outset, we envisioned that the Ugi-allenamide adducts **B** might be obtained from the propargyl Ugi-adduct **A** under typical base-induced isomerization conditions (catalytic potassium *tert*-butoxide).[18] In principle, the propargyl Ugi adduct might be prepared in a straightforward manner by simply using propargylamine as the amine input in the component set of an Ugi 4-CR. We recognized that under certain basic conditions the anion **C** might be formed by deprotonation of the Ugi moiety[17b,19] and undergo cyclization into the allenamide moiety in a base-induced cycloisomerization (Scheme 1). However, our question was, "At which carbon atom would the cyclization take place, if it did indeed occur?"

Scheme 1. Synthetic Strategy toward 2,3-Dihydropyrroles from Ugi Adducts



This query was rapidly addressed in our first experiment. We observed that the 2,3-dihydropyrrole **4a** was directly formed when the Ugi adduct **3a** was treated with a catalytic amount (0.2 equiv) of *t*-BuOK in THF, although in rather low yield, after 12 h at room temperature (Table 1, entry 1). Nevertheless, this promising result demonstrated that under the basic conditions, both processes, i.e., formation of the allenamide, and formal 5-*endo*[20] cycloisomerization at C-γ did occur. The starting material **3a** for this process was easily prepared (77% yield) by the reaction of 4-chlorobenzaldehyde, propargylamine **5**, 2-bromobenzoic acid, and *tert*-butyl isocyanide [catalytic indium(III) chloride in methanol (0.3 M) under microwave heating conditions (50 °C, 100 W, 2 h)]. Encouraged by the highly regioselective, uncommon, metal-free cycloisomerization[18] of the Ugi-allenamide adduct, we performed a short survey of reaction conditions to optimize the yield of the 2,3-dihydropyrrole using the Ugi adduct **3a** as the model compound. The use 1.0 equiv of *t*-BuOK once again gave

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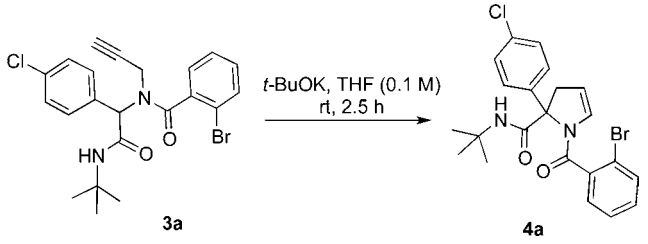
only traces of the product (entry 2); however, the use of 2.5 equiv of *t*-BuOK afforded **4a** in improved 51% yield after 30 min (entry 3). The optimal conditions were ultimately fixed when the reaction time was extended to 2.5 h using 2.5 equiv of the base, affording **4a** in 71% yield (entry 4). Neither longer reaction times (entries 5 and 6) nor the use of 3 equiv of *t*-BuOK (entry 7) improved the yields.

Table 1. Optimization of the Reaction Conditions

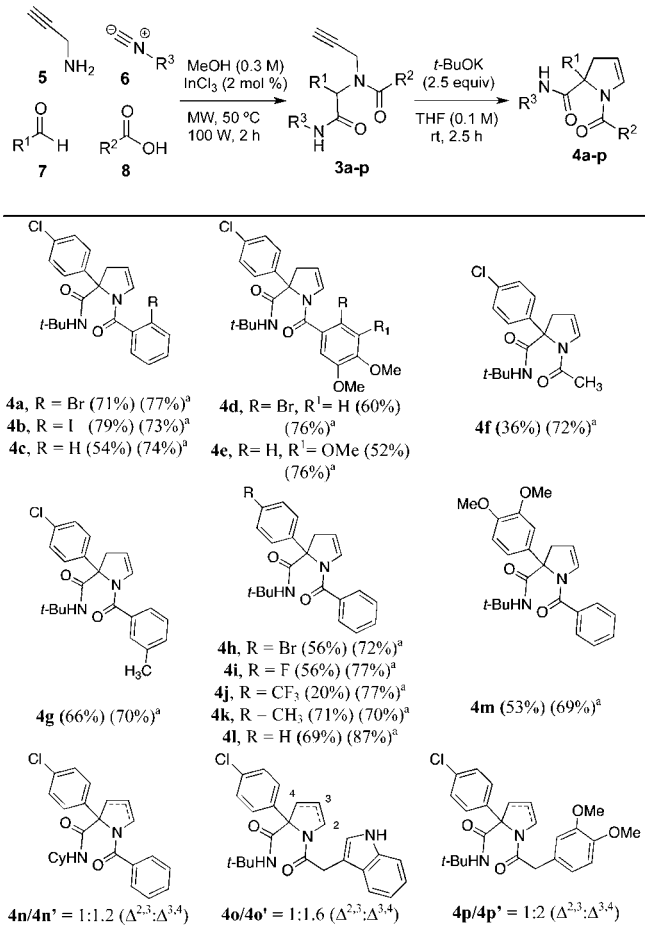


entry	*t*-BuOK (equiv)	time (h)	yield **4a**[a] (%)
1	0.2	12	trace
2	1.0	12	trace
3	2.5	0.5	51
4	**2.5**	**2.5**	**71**
5	2.5	3.5	57
6	2.5	6.5	39
7	3.0	2.5	53

[a] Yields given are those of the isolated pure products.

With the optimal conditions in hand, we evaluated the scope of the methodology on a wide variety of Ugi adducts obtained similarly to **3a** (See Supporting Information). The use of different substituted benzoic acids **8** (R_2) were surveyed (Scheme 2). *o*-Iodo and *o*-bromo substituents both gave good yields of the *N*-acylated 2,3-dihydropyrroles (**4a**,**b**). Polyoxygenated systems (**4d**,**e**), an unsubstituted variant **4c**, as well as a methyl group **4g** were well tolerated in the reaction. The use of an aliphatic acid, such as acetic acid, in the Ugi reaction resulted in a modest yield of the expected product **4f**. We then conducted a preliminary investigation of the scope of substituted benzaldehydes (R_1) and observed a strong influence of electron-withdrawing groups on the yield of the product. While *p*-bromo- **4h** and *p*-fluoro-substituted **4i** products were obtained in moderate yields, the presence of the trifluoromethyl group considerably reduced the yield (**4j**, 20%), and a *p*-nitro group completely hampered the reaction (**3q**, 0%). Apparently, the putative anion intermediate (Scheme 1) is rapidly generated as a result of the effect of the electron-withdrawing group, obstructing the allenamide formation.[21] The best results were observed when electron-donating groups were present on the aromatic ring (**2k**−**m**). The use of cyclohexyl isocyanide instead of *tert*-butyl isocyanide resulted in the formation of an separable isomeric mixture of 2,3 (**4n**) and 2,5-dihydropyrroles (**4n′**) in 71% yield (1:1.2). When Ugi adduct derivatives bearing 3-indoleacetic or 3,4-dimethoxyphenylacetic acids were submitted to the same cycloisomerization conditions, we observed similar results: a mixture of the isomeric dihydropyrroles **4o** and **4o′**, as well as **4p** and **4p′**, were obtained after purification by flash column chromatography.

Scheme 2. Synthesis of 2,3-Dihydropyrroles



[a] Yields of Ugi-4CR adducts.

Although we currently have no logic explanation for this putative isomerization, the data in Scheme 2 nevertheless demonstrates that a variety of diversely substituted 2,3-dihydropyrroles could be prepared using the two-step protocol described herein. The structures of compounds **4a**, **4h**, and **4l** were confirmed by an X-ray analysis.[22]

Interestingly, allenamide intermediate **B** was not observed in all of the experiments described under catalytic conditions or in the stoichiometric reactions. However, when the 6-bromopiperonal propargyl-Ugi adduct **3r** was

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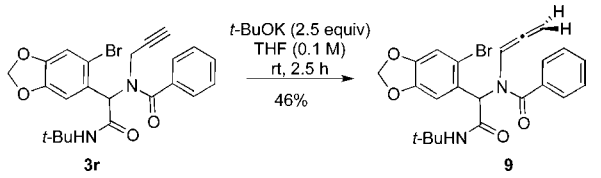
submitted to the same base-induced cycloisomerization, the major product observed was the corresponding allenamide **9**, supporting its intermediacy in the process. Apparently, the presence of the *o*-bromo substituent exerts a strong steric hindrance in the vicinity of the intermediate anion, preventing its cyclization onto the allenamide double bond (Scheme 3).

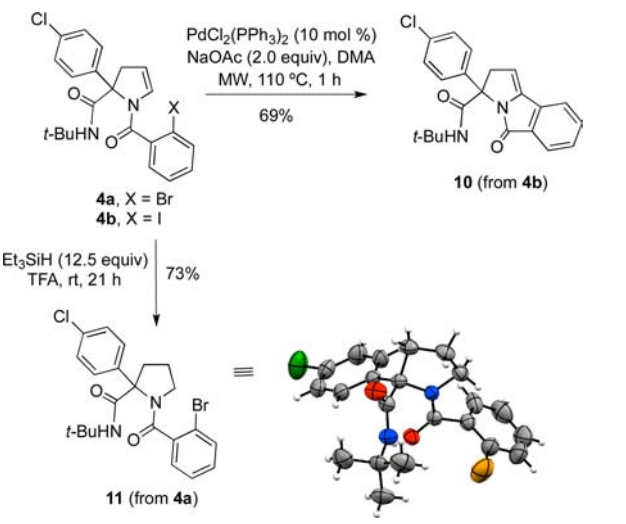
Scheme 3



The 2,3-dihydropyrroles obtained using this modular approach might be useful as building blocks for the construction of more complex molecules if the starting materials are suitably functionalized for further transformations prior to introduction into the Ugi process. For instance, the pyrrolo[2,1-*a*]isoindolone[23] **10** was obtained in good yield when **4b** was subjected to typical Heck conditions[24] (three-step synthetic sequence from a commercial Ugi four-component set). Furthermore, the dihydropyrrole **4a** was transformed into the *N*-acyl-2-aryl prolinamide **11**[19] by simply reducing the double bond using triethylsilane hydride as the reductant (Scheme 4). It is important to note that this three-step protocol constitutes an easy entry to the pharmacologically important 2-arylproline derivatives[25]

In conclusion, a two-step synthesis of 2,3-dihydropyrroles via a formal 5-*endo* cycloisomerization of Ugi 4-CR/propargyl adducts is described. The convergent character, atom economy, operational simplicity, and the structural

Scheme 4



diversity of the resulting dihydropyrroles make this protocol attractive for both the construction of libraries of molecules of this kind in the search for diverse biological properties, and also for their use as building blocks in the construction of more complex molecules. In this two-step sequential protocol, simple starting materials are transformed into not-easily anticipated, more complex molecules by creating several bonds. It is worth noting that the atom economy of this protocol is almost perfect; only one H_2O molecule (in the imine formation) is lost from the starting Ugi four-component set to the final dihydropyrrole.

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Supporting Information Available. Experimental procedures, NMR spectra, and characterization for all new materials. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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