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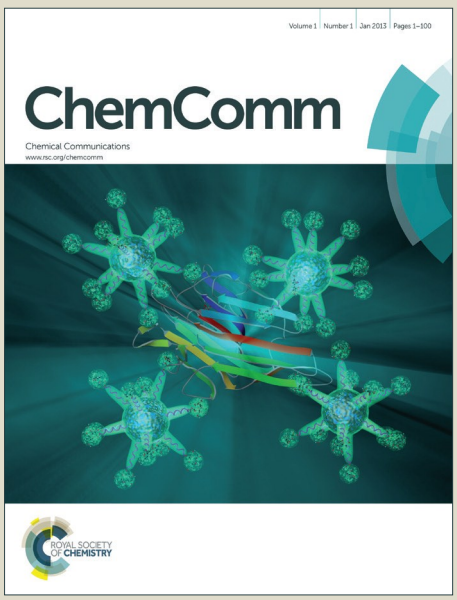

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Ugi-Derived Dehydroalanines as a Pivotal Template in the Diversity Oriented Synthesis of Aza-Polyheterocycles

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Various readily available, Ugi-derived dehydroalanines were used as pivotal templates to easily and efficiently assemble diverse pharmacologically important polyheterocyclic systems through cascade palladium-catalyzed C-C bond formation processes. Allyl, homoallyl and propargylamine led to the formation of benzopyrrolizidinones, benzoindolizidinones and pyrazinoisoquinolines, respectively, while the use of benzylamines and *o*-bromobenzylamines were precursors of tetracyclic-fused systems and pyrazionoisoquinolindiones.

In efforts to discover new compounds for the treatment of human diseases, the search for novel modulators of biological receptors has increased the demand for structurally diverse small molecules. A current challenge in synthetic organic chemistry is to devise short, inexpensive, and efficient syntheses of diversely substituted heterocyclic scaffolds through simple manipulation of the structures of the starting materials and/or the reaction conditions. Taking advantage of this Diversity-Oriented Synthesis (DOS),[1,2] a chemist should be able to use a single laboratory protocol and produce combinatorial collections of compounds with different molecular structures, tailored to their specific requirements. The programmed combination of a Ugi four-component reaction (Ugi 4-CR) with various chemical processes, has allowed the generation of libraries of structurally different compounds.[3] The Ugi 4-CR offers the unique opportunity to rapidly build-up structures with considerable molecular complexity because it couples four different substrates (an aldehyde, a carboxylic acid, an amine, and an isocyanide) resulting in the formation of a single adduct.[4] Previously, we have shown that the combination of a Ugi 4-CR with a free radical cyclization is a versatile entry to the construction of different heterocyclic scaffolds.[5] We next envisioned connecting the Ugi 4-CR technology with a reaction "cascade" involving a Pd-catalyzed C–C-bond forming process (a combination rarely described)[6] which might result in a powerful synthetic protocol for the rapid access of several natural product-like aza-polyheterocycles (Figure 1). In such a protocol, greater molecular complexity might be achieved since two reactions that involve the construction of more than one bond are combined. Along this line, the previously reported Ugi-derived dehydroalanines **A** attracted our attention because of their potential to function as pivotal templates in further transition metal catalyzed C–C-bond forming reactions (Figure 1).[7] Thus, upon the first Heck-type C-C bond forming process, the organopalladium intermediate **B** with no β-hydrogen might be inserted into another π-system to yield a new C-C bond. Thus, molecular diversity could be achieved simply by the variation of the nature of the unsaturated terminal palladium acceptor. On the basis of this idea, several polyheterocycles, related to, for example; pyrrolo[2,1-*a*]isoindolone **1**, a potent inhibitor of cyclins and cyclin-dependent kinases, the tetracyclic lennoxamine **2**, the cytotoxic isoindoloquinoline **3**, and the antitumor and antibacterial quinocarcin **4**, might be constructed.[8] Herein, we describe the implementation of a novel three-step synthetic sequence that gives access to several heterocyclic scaffolds using the Ugi-derived dehydroalanines **A** as pivotal templates.

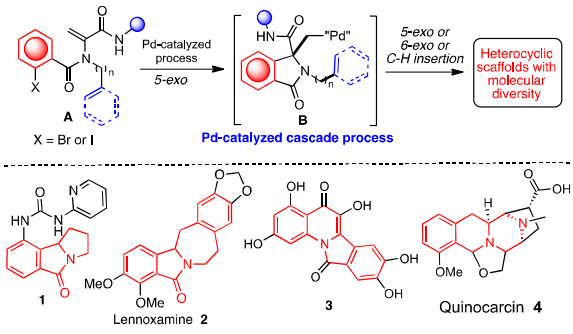
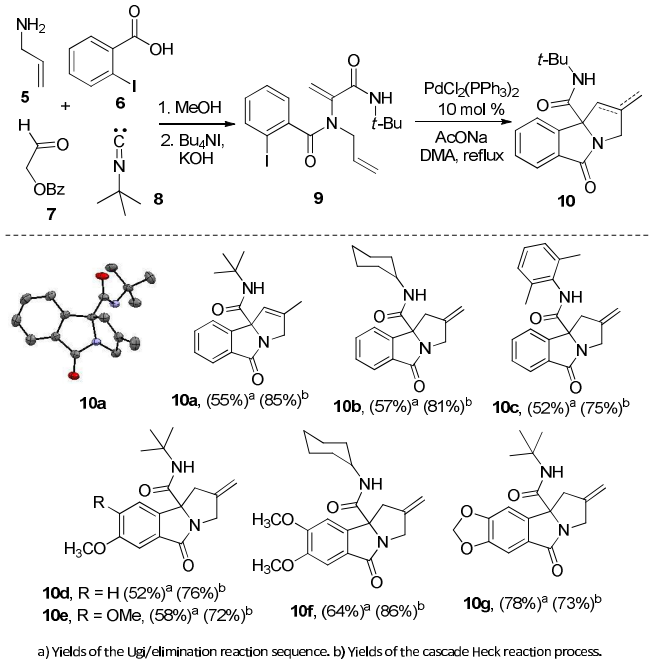


Figure 1. Some relevant aza-polyheterocycles

Our first plan was to use allyl amine and *o*-iodobenzoic acid as the amine and acid components in the Ugi 4-component coupling reaction, followed by a double *5-exo* Heck cascade process on **9** to possibly generate an isomeric mixture of the benzo-fused pyrrolizidinones **10** (Scheme 1).[9] Thus, the

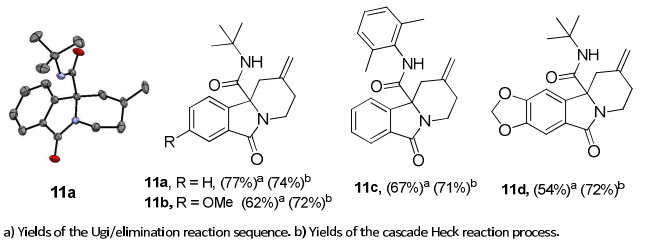
dehydroalanine **9** was obtained in 55% yield from allyl amine **5**, *o*-iodobenzoic acid **6**, *tert*-butyl isocyanide **8**, and benzoyloxyacetaldehyde **7**, using a two-step procedure under conditions described previously.[7] Heating a solution of **9** in refluxing dimethylacetamide, containing a catalytic amount of $PdCl_2(PPh_3)_2$ and NaOAc, provided a 1:9 exo/endo mixture (determined by ^1H NMR) of **10** in 85 % isolated yield. The *endo*-isomer **10a** crystallized from the mixture and its structure was confirmed by the X-ray crystallographic data (Scheme 1).[10]



Scheme 1. Tricyclic systems derived from the use of allyl amine .

We next evaluated the scope of the process using cyclohexyl isocyanide and 2,6-dimethylphenyl isocyanide and verified that changing the substituent on the amide nitrogen atom did not affect the outcome of the reaction. Thus, **10b** and **10c** were obtained in moderate yields after the three-step sequence as the *exo*-isomers. Furthermore, substituents in the aromatic moiety did not affect the outcome of the process, and the same methodology was utilized to prepare the benzopyrrolizidinones **10d–10g** from the corresponding substituted *o*-bromobenzoic acids. Notably, when the allyl amine was replaced by the homologous homoallyl amine, the usual three-step synthetic sequence resulted in the formation of the corresponding benzoindolizidinones[11] **11a-11d** *via* a 5-*exo*/6-*exo* Heck cascade reaction. In the case of product **11a**, a 1:1 *exo:endo* regioisomeric mixture of olefins was produced, the structure of the exo isomer **11a** being confirmed by X-ray crystallography (Scheme 2).[10]

Due to the results, we were interested in the use of benzylamine in the same protocol. This relatively slight change in the 4-CR input set might result in a different Pd-catalyzed 5-*exo*/C-H oxidative insertion cascade reaction,[12] upon the required adjustment in the reactions conditions. Thus, after a small optimization process we observed that the use of the same palladium source ($PdCl_2(PPh_3)_2$) in DMA in the presence of 20 mol% of $Cu(OAc)_2$ as additive, afforded the tetracycle **14a** in 61% yield from the Ugi-derived dehydroalanine **12** (Scheme 3, Scheme 3). Increasing the amount of $Cu(OAc)_2$ or using $CuBr_2$ did not improve the yield. We also observed that the *tert*-butyl substituent on the amidic nitrogen was a determining factor in the yield of the Pd-catalyzed cascade reaction.

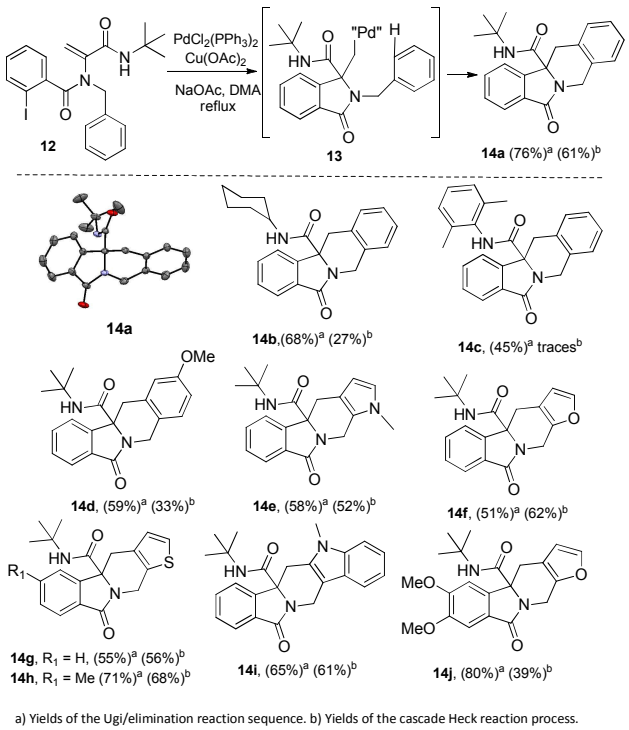


Scheme 2. Tricyclic systems derived from the use of homoallyl amine.

The presence of a cyclohexyl substituent resulted in decrement in the yield of the tricycle **14b**, while **14c**, having a 2,6-dimethylphenyl group, was obtained only in traces. Likewise, the *p*-OMe-substituted derivative **14d** was only obtained in 33% yield. Considering the requirement of bearing a *tert*-butyl in the amidic nitrogen, other aromatic systems in the amine 4-CR input were explored. Thus, the Pd-catalyzed 5-*exo*/C-H oxidative insertion cascade reaction proceeded in good yield when the benzene system was replaced by a *N*-methylpyrrole (**14e**). Similarly, furan, thiophene and *N*-methyl indole heterocyclic fused-systems **14f–14h**, were obtained in good yields. Electron-rich methyl and dimethoxy substituted derivatives **14h** and **14j** were also obtained from the corresponding substituted *o*-bromobenzoic acids as the 4-CR input-set.

Interestingly, the incorporation of propargylamine as the amine input in the Ugi reaction gave a remarkable variation in the course of the three-step synthetic sequence. When the Ugi propargyl-adduct **15a** was submitted to the basic elimination-conditions used before to obtain the dehydroalanine, the piperazinone **17a** was obtained in moderate yield. It is important to mention that this novel reaction was only effective when the 2,6-dimethylphenyl isocyanide was used, otherwise the reaction resulted only in the decomposition of the Ugi adducts. A close inspection of the literature revealed that allenamides such as **16** might be obtained from the corresponding propargylamide under basic conditions.[13] The scope of the process was examined using selected *o*-bromobenzoic acids bearing electron-withdrawing and electron-donating constituents (Scheme 4). The use of the 1-chloro-6-methylphenyl isocyanide in the Ugi reaction also gave good yield of the expected piperazinone after the two-step protocol. The presence of a nitro group as the unique substituent also efficiently yielded **17g**. We recently took advantage of this last process to transform propargyl-Ugi adducts into several dihydropyrrole scaffolds.[14] In accordance to that, a mechanism via the allenamide **16** is proposed as the key pathway in the construction of the piperazinone framework. Remarkably, both

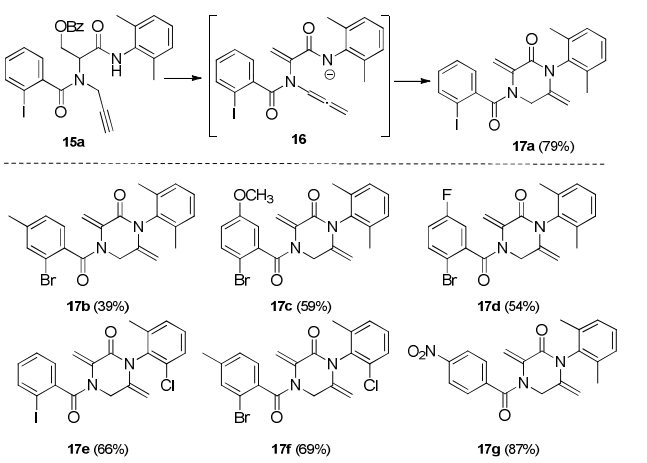
the isomerization of the propargyl amide and the elimination of the benzoyl group took place in a "parallel" fashion with the consecutive cyclization process occurring via the formation of a putative anion of the nitrogen on the benzamide. It is noteworthy that the augmented acidity of the hydrogen of the nitrogen atom conferred by the aromatic system, favored the complete transformation.



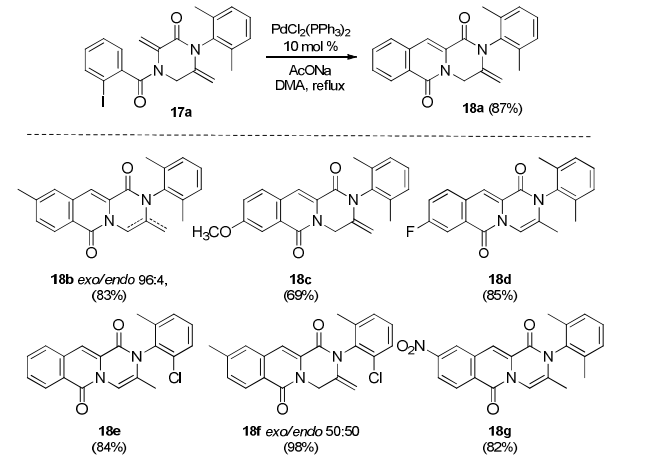
a) Yields of the Ugi/elimination reaction sequence. b) Yields of the cascade Heck reaction process.

Scheme 3. Tetracyclic systems derived from the use of benzyl amine.

It is well-documented the importance of the piperazinone system since this heterocyclic scaffold is frequently found as the main core of several pharmacologically important molecules, both synthetic compounds and natural products.[15] The later finding opened up the possibility to build on completely different heterocyclic fused-systems if the aforementioned consecutive Heck reaction could be further implemented. In order to enhance the molecular diversity produced by the designed protocol, selected piperazinones were subjected to the Heck reaction conditions. The molecular structure of piperazinone allowed the Heck cyclization to take place in a less common *6-endo* fashion to efficiently afford the fused isoquinolone **18a** from **17ab** (Scheme 5), under essentially the same conditions used in Scheme 1. The cross-coupling reaction proved to be efficient with different substituted benzene systems. In the presence of electron-withdrawing functional groups, the Heck reaction was fairly efficient, while the use of a methoxy electron-donating group the yield of the reaction dropped to a modest 69% (**18c**, Scheme 5). It is worth noting that pyrazinoisoquinolone fused system is present in important anti-carcinogen agents such as quinocarcin, ecteinascidin 743, saframycins and related natural products.[14]



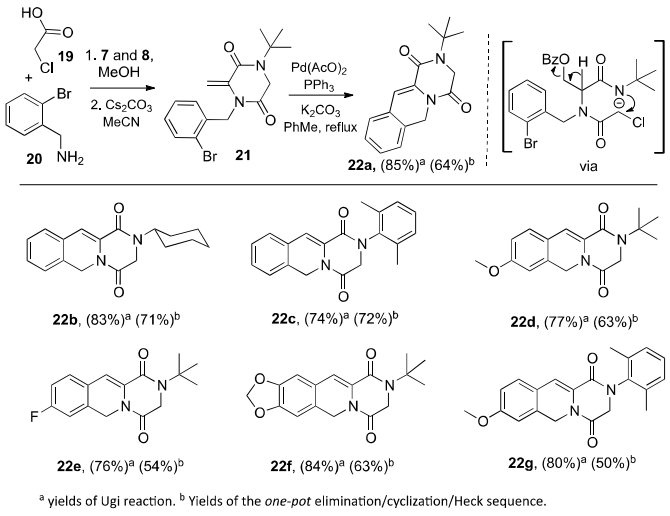
Scheme 4. Piperazinones derived from the use of propargylamine



Scheme 5. Pyrazinoisoquinolones from the use of propargylamine.

Considering the biological importance of diketopiperazines, specifically pyrazino[1,2-*b*]isoquinolindiones which possess cytotoxic and cytostatic activities,[16,17] we extended this methodology by using chloroacetic acid **15** and *o*-bromobenzylamine derivatives in the Ugi 4C-input set. We envisioned that an elimination/S_N2 cyclization parallel process of the Ugi adduct might be possible under basic conditions (Scheme 6). After a short optimization, the methylendiketopiperazine **21** was afforded in one step by using cesium carbonate in refluxing acetonitrile (Scheme 6). Interestingly, crude **21** was used without further purification, to perform the Pd-catalyzed C-C bond formation after replacement of the solvent. The use of $PdCl_2(PPh_3)_2$ as the catalyst produced the desired tricyclic compound **22a** but only in 15% yield. Afterwards it was found that the use of $Pd(AcO)_2$ as the palladium source (15 mol%) and PPh_3 as the ligand, afforded the 6-*endo* ring closing in good to moderate yields (**22a-g**). Then, the influence of the isocyanide in the cross coupling reaction was explored by using cyclohexyl and 2,6-dimethylphenyl isocyanides and these modifications accomplished the reaction with no significant variation in the yield (examples **22b** and **22c**). Similarly, the Ugi adducts bearing a substituent in the benzylamine moiety (both electron-

withdrawing **22e** and electron-donating groups **22d-g**) gave the expected *one-pot* sequence in moderate yields.



[a] yields of Ugi reaction. [b] Yields of the *one-pot* elimination/cyclization/Heck sequence.

Scheme 6. Pyrazinoisoquinolindiones derived from the use of chloroacetic acid.

Conclusions

We have demonstrated that Ugi-derived dehydroalanines are practical and pivotal templates for the facile, three step assembly of pharmacologically important fused polyheterocyclic systems with diverse molecular structures. This concept was realized merely by careful selection of the starting materials in the Ugi 4-CR set. Depending on the amine starting material, the Ugi-derived dehydroalanine permitted conceptually different Pd-catalyzed C-C bond formation protocols. When allyl or homoallyl amines were used, various substituted benzopyrrolizidinones and benzoindolizidinones were obtained, while the molecular platform of the dehydroalanine using benzylamines underwent a Pd-catalyzed 5-*exo*/C-H oxidative insertion cascade reaction to easily construct several structurally diverse tetracyclic-fused systems. Using propargylamine as the input in the same three-step protocol, various pyrazinoisoquinolones were obtained, in this case *via* an unconventional 6-*endo* Heck reaction. Finally, the use of dehydroalanines bearing a chloroacetoyl moiety and an *o*-bromobenzylamine derivative, led to the synthesis of pyrazinoisoquinolindiones in a *one-pot* protocol. We believe that the methodology described in this communication is likely to be extendable to the construction of many structurally different fused heterocyclic systems by exploiting the functionality of the isocyanides and/or by adjusting the chain length of the initial amines. Studies along these lines are currently underway in our laboratory.

Notes and references

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