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# Differentiating alkyne reactivity in the post-Ugi transformations: Access to polycyclic indole-fused frameworks

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ABSTRACT

The Ugi adducts prepared from propiolic acids, propargylamines, indole-2-carbaldehydes, and isocyanides were utilized to assemble polycyclic indole-fused frameworks *via* two consecutive carbocyclizations involving triple bonds. First, the peptidyl position of Ugi adduct underwent potassium carbonate-mediated cyclization onto the triple bond derived from propiolic acid. Then, the position 3 of indole core engaged into gold-catalyzed cyclization onto the propargylamine-originated alkyne, completing the construction of polycyclic core.



Many structurally interesting and biologically active natural products contain indole moiety imbedded into complex polycyclic framework.[1] In virtue of this, the development of practical strategies to synthesize libraries of alkaloid-mimicking indole-annulated heterocyclic systems has become a popular research direction.[2–10] Following this trend, a number of diversity-oriented approaches towards this class of compounds have been established relying on either intramolecular Ugi reaction[11] or various post-Ugi transformations.[12]

The possibility to bring together virtually any kind of functional groups into a linear peptide-like precursor, which can be readily transformed into heterocycle, placed a four-component Ugi reaction among the major diversification tools.[13] For example, the Ugi adducts bearing alkyne group and a suitable nucleophilic reactive site can undergo a large variety of hetero-[14] and carbocyclizations[15,16] with the aid of gold and silver catalysis. It was also demonstrated that the propiolic acid-derived Ugi adducts could be readily transformed into pyrrol-2-ones[17] and β-lactams,[18] exploiting the nucleophilicity of the peptidyl position *via* enolization-triggered 5-*endo*-*dig* and 4-*exo*-*dig* cycloisomerizations, respectively.

In 2016, Van der Eycken and coworkers disclosed an interesting study towards imidazole-fused polycyclic scaffolds **7** (Scheme 1a).[19] Subjecting propiolic acid **1**, propargylamine **2**, 1*H*-imidazole-2-carbaldehyde (**3**) and isocyanide **4** in the Ugi reaction led to the formation of adduct **5** that at the elevated temperature of 50 °C underwent spontaneous cyclization into pyrrol-2-one **6**, deploying peptidyl nucleophilic site and the propiolic acid-originated triple bond. Next, the remaining alkyne group underwent a nucleophilic attack by an imidazole moiety upon the activation by silver(I) hexafluoroantimonate catalyst, giving rise to the target structure **7** *via* 6-*exo*-*dig* heterocyclization. We envisaged that the analogous approach based on the strategic differentiation of the triple bond reactivity could be applied for the synthesis of polycyclic indole-fused frameworks. Herein, we present the resulting three-step sequence for the synthesis of indolizino[8,7-*b*]indoles **11** and pyrrolo[1′,2′:1,2]azepino[3,4-*b*]indoles **12** (Scheme 1b). The first step of the strategy involved the four-component Ugi reaction of propiolic acid **1**, propargylamine **2**, indole-2-carbaldehyde **8** and isocyanide **4** that worked best at the elevated temperature of 50 °C. In the next step, the resulting Ugi adduct **9** underwent cyclization into pyrrol-2-one **10** in the presence of potassium carbonate in DMF at room temperature. Finally, the treatment of **10** with catalytic amount of gold(I) triphenylphosphine chloride and silver(I) triflate in chloroform at room temperature produced desired polycyclic scaffold **11** or **12**. The results of the substrate scope investigation are summarized in Table 1.

At first, we have evaluated different propiolic acids **1** in combination with terminal propargylamine (**2a**), indole-2-carbaldehyde (**8a**) and *tert*-butyl isocyanide (**4a**). In all cases, the overall sequence worked well producing indolizino[8,7-*b*]indoles **11a–c** with moderate to good efficiency per step (Table 1, entries 1–3). The final alkyne hydroarylation step involved a cationic gold-catalyzed cyclization of propargylamine-originated terminal triple

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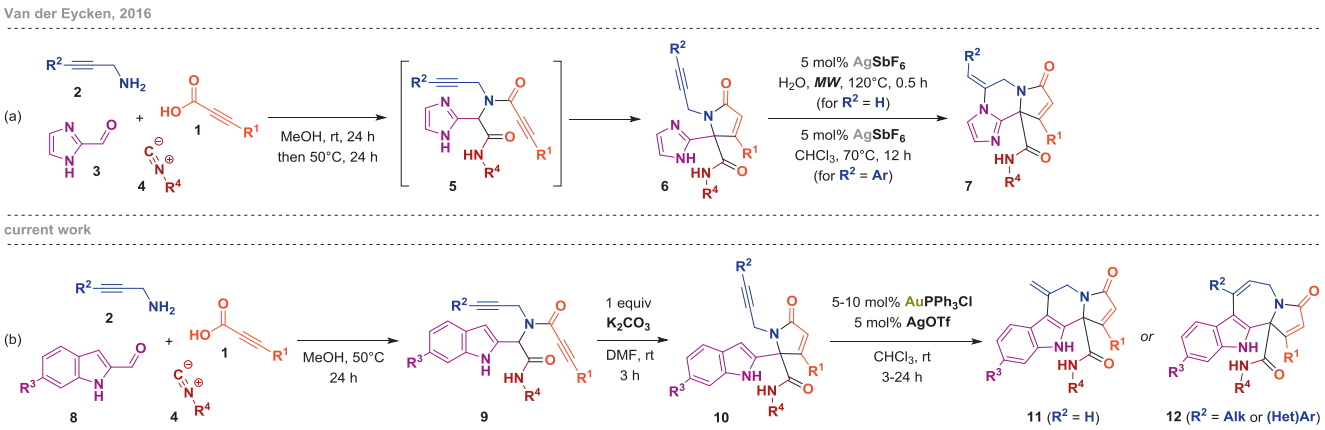
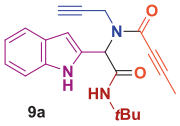
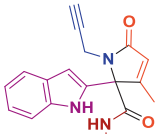
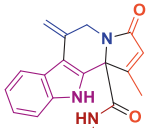
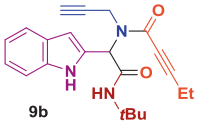
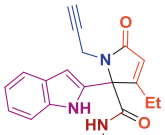
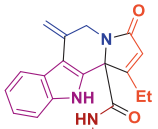
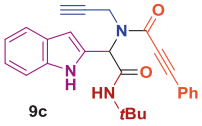
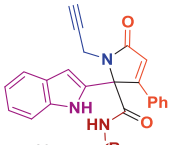
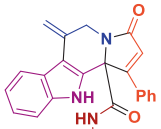
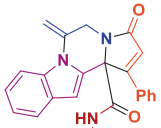
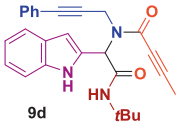
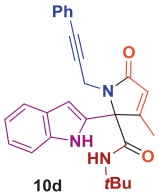
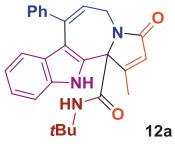
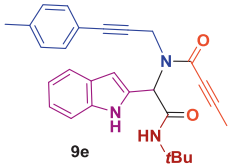
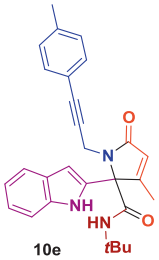
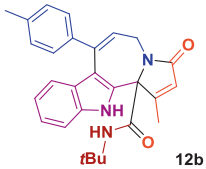



**Scheme 1.** Strategies for sequential assembly of polycyclic frameworks based on post-Ugi transformations.

**Table 1**
Scope of the strategy.

| Entry | Ugi adduct **9** | Yield of **9**, %[a] | Pyrrol-2-one **10** | Yield of **10**, %[a] | Polycyclic product **11**, **12** or **13** | Yield of **11**, **12** or **13**, %[a] |
|---|---|---|---|---|---|---|
| 1 |  **9a** | 83 |  **10a** | 76 |  **11a** | 69 |
| 2 |  **9b** | 83 |  **10b** | 81 |  **11b** | 59 |
| 3 |  **9c** | 80 |  **10c** | 72 |  **11c** | 68 |
| | | | | |  **13** | 11 |
| 4 |  **9d** | 75 |  **10d** | 79 |  **12a** | 85 |
| 5 |  **9e** | 78 |  **10e** | 77 |  **12b** | 85 |