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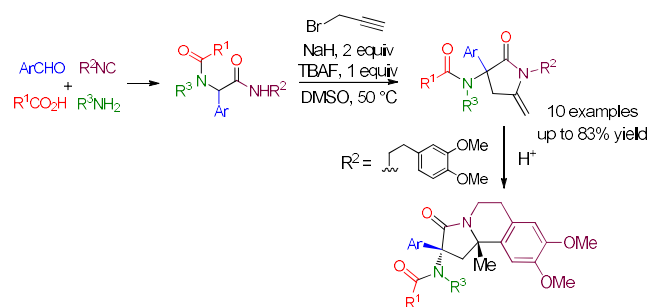
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Propargylation of Ugi amide dianion: An entry into pyrrolidinone and benzoindolizidine alkaloid analogues

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S Supporting Information



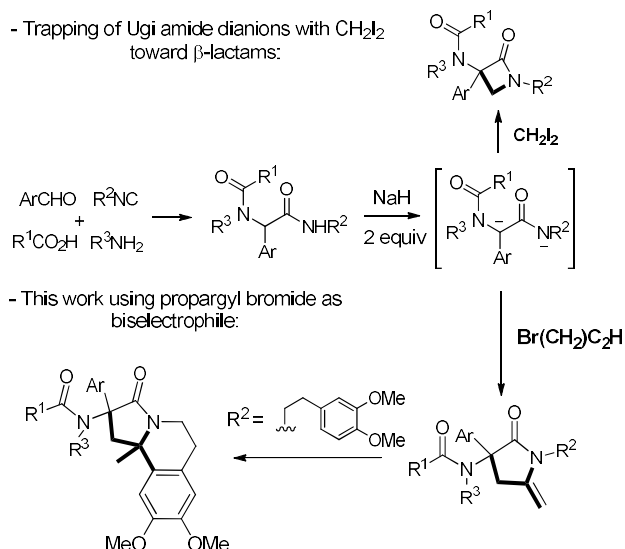
ABSTRACT: Propargylation of Ugi adducts under the addition of excess sodium hydride in DMSO leads to direct formation of pyrrolidinone enamides, which are useful precursors of iminium intermediates and may be trapped by various nucleophiles. This approach has been applied to the formation of benzoindolizidine alkaloids with high diversity via a Ugi/propargylation/Pictet-Spengler cyclization.

Although the Ugi reaction may be considered one of the most efficient 4-component couplings,¹ it continues to suffer from important limitations when the aldehyde starting materials are replaced by ketones. Aliphatic ketones lead to couplings in poor to moderate yields under prolonged reaction times, and simple arylketones are not sufficiently electrophilic to participate as the carbonyl component. A possible umplung strategy to circumvent this issue involves the reaction of an aromatic aldehyde, followed by alkylation of the resulting Ugi intermediate. Indeed, Ugi adducts derived from aromatic aldehydes are relatively acidic at the newly formed peptidyl position, and these adducts may be easily deprotonated under basic conditions. The resulting anion can be trapped by various electrophiles.² However, due to steric reasons, most of these studies have been limited to intramolecular alkylations.^{2(a)-2(f)} We recently used a large excess of strong base to form dianionic Ugi intermediates with enhanced nucleophilicity, leading to easier alkylation at room temperature.³ Selecting biselectrophiles may afford cyclic derivatives via a domino process that involves the formation of C-C and C-N bonds. This two-fold alkylation has been demonstrated in the straightforward 5-component preparation of β -lactams under alkylation of Ugi adducts with diiodomethane (Scheme 1).³

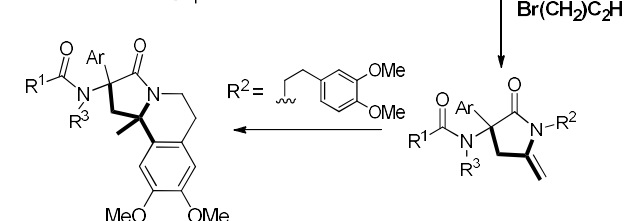
The success of these cyclizations encouraged us to evaluate other electrophiles in similar sequences. Herein, we report the formation of cyclic enamides using propargyl bromide, along with the potential of these additions for the formation of alkaloid analogues with high diversity (Scheme 1).

Scheme 1. Trapping of Ugi amide dianions with biselectrophiles.

- Trapping of Ugi amide dianions with CH_2I_2 toward β -lactams:

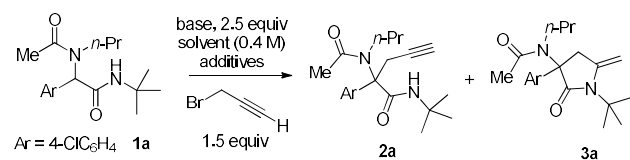


- This work using propargyl bromide as bis-electrophile:



When Ugi adduct **1a**, which was obtained in 89% yield from 4-chlorobenzaldehyde, propylamine, acetic acid and *tert*-butylisocyanide, was treated with equimolar amounts of sodium hydride and propargyl bromide in DMSO at rt, the new propargylic amide **2a** was obtained in a poor 30% yield. An increase in the temperature to 50 °C afforded a better 51% yield, but 32% of the starting Ugi adduct remained (Table 1, entry 1). When the amount of base was increased to 2.5 equiv, we were delighted to observe the new formation of enamide **3a** after 4 h at rt. In addition, when the reaction was performed at 50 °C, the same enamide was produced in less time with a comparable yield (entries 2,5). Under these conditions, we could not isolate any of starting **1a** or intermediate **2a** as side products. When the solvent or base was changed, no improvement in the reaction yield was observed (entries 3,4). Thus, to improve both the yield and selectivity, we decided to examine the effect of various catalysts that are known to activate the addition of nucleophiles to alkynes.⁴ Among the various trials performed with silver, zinc and ytterbium salts, which were added in 10 to 20 mol % ratios, silver carbonate appeared to be the best catalyst based on better overall yields, as well as better selectivity for **3a** when the reaction was performed at 50 °C (entry 12). The use of 1 mol % of SPhosAuNTf₂ was less satisfying. However, better yields were obtained using ammonium salts as additives to enhance the nucleophilicity of the anionic intermediates.⁵

Table 1. Optimization of the conversion of Ugi adduct **1a** to **3a**.



| Entry | base | solvent | additive | 2a (%) | 3a (%) |
|----------------|----------------|---------|----------|------------------|------------------|
| 1 ^a | NaH 1 equiv | DMSO | - | 51 | 0 |
| 2 ^b | NaH | DMSO | - | 0 | 54 |
| 3 ^a | NaH | THF | - | 25 | 15 |

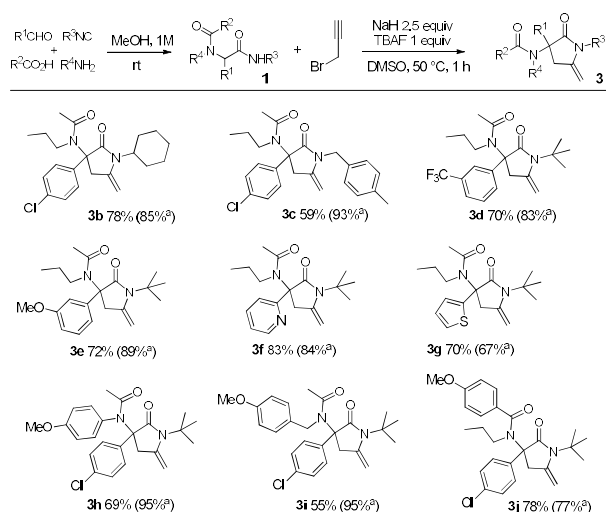
| | | | | | |
|-----------------|--------|------|---|----|----|
| 4 ^a | LiHMDS | THF | - | 15 | 0 |
| 5 ^c | NaH | DMSO | - | 0 | 52 |
| 6 ^b | NaH | DMSO | Ag(OTf) 0.1 equiv | 0 | 65 |
| 7 ^b | NaH | DMSO | Zn(OTf) ₂ 0.1 equiv | 48 | 24 |
| 8 ^b | NaH | DMSO | Yb(OTf) ₃ 0.1 equiv | 17 | 51 |
| 9 ^b | NaH | DMSO | Ag ₂ CO ₃ 0.1 equiv | 21 | 61 |
| 10 ^b | NaH | DMSO | SPhosAuNTf ₂ 0.01 equiv | 22 | 47 |
| 11 ^b | NaH | DMSO | Ag ₂ CO ₃ 0.2 equiv | 0 | 70 |
| 12 ^c | NaH | DMSO | Ag ₂ CO ₃ 0.1 equiv | 0 | 68 |
| 13 ^c | NaH | DMSO | Ag ₂ CO ₃ 0.1 equiv TBAI 1 equiv | 0 | 78 |
| 14 ^c | NaH | DMSO | TBAI 1 equiv | 0 | 77 |
| 15 ^c | NaH | DMSO | TBABr 1 equiv | 0 | 57 |
| 16 ^c | NaH | DMSO | TBACl 1 equiv | 0 | 66 |
| 17 ^c | NaH | DMSO | TBAF 1 equiv | 0 | 81 |
| 18 ^c | NaH | DMSO | TBAF 0.5 equiv | 0 | 74 |
| 19 ^c | NaH | DMSO | TBAF 1 equiv 1 equiv | 52 | 0 |

^aReaction at 50 °C for 4 h. ^bReaction at rt for 4 h. ^cReaction at 50 °C for 1 h.

TBAF and TBAI⁶ have been reported to trigger the formation of enamide via cyclization of an amide to an alkyne. The best conditions were observed using a combination of 2.5 equiv of sodium hydride and 1.0 equiv of TBAF in DMSO for 1 h at 50 °C (entry 17). The latter condition was selected to evaluate the scope of this new enamide **3** formation from Ugi adducts **1** (Scheme 2).

As shown by the examples displayed in Scheme 2, the sequence may be extended to various aromatic and heteroaromatic aldehydes with comparable yields. Most examples have been performed using aliphatic amines. However, aromatic amines, such as 4-methoxyaniline, can also be involved (Scheme 2, **3h**). The steric hindrance around the amide does not substantially affect the yields and may be considered beneficial based on the higher yields observed with a *tert*-butyl substituent, compared to a cyclohexyl or benzyl group (Scheme 2, **3a**, **3b**, **3c**). The reaction mechanism most likely involves the intermediate formation of dianionic amide derivatives, leading to a higher reactivity toward propargyl bromide. Then, the propargylation step is followed by a fast cyclization of the resulting amide monoanion. The added ammonium salt most likely increases the nucleophilicity of the intermediate anions, but the benefit to both steps or on a single step of the process is difficult to address. When TBAF was added, along with a reduced amount of NaH (1 equiv) under the same conditions (see Table 1, entry 19), propargyl adduct **2a** was isolated in 52% yield, along with 34% of the starting material. The absence of any cyclized product under these conditions was surprising due to the known TBAF triggered cyclization of alkenyl amides.⁵ However, this result can be explained by the progressive conversion of the added TBAF to the less basic TBABr, which demonstrates the importance of using excess sodium hydride.

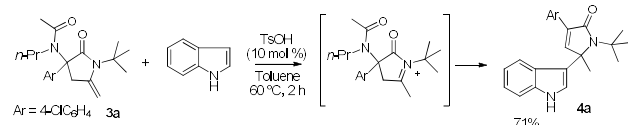
Scheme 2. Scope of the Ugi enamide synthesis.^a



^a Isolated yield of intermediate Ugi adduct.

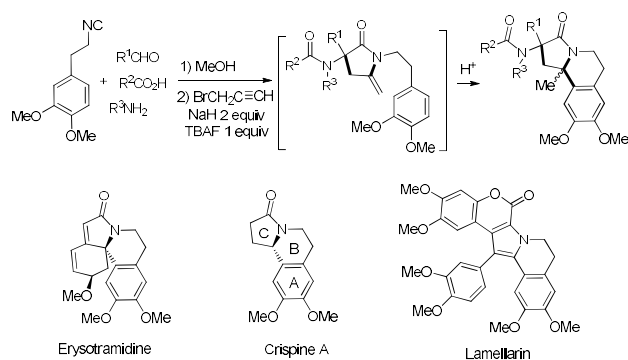
Next, we decided to evaluate the synthetic interest of these new cyclic enamides.^{7,8} Their enamine nature should be associated with potential iminium formation under acidic conditions. This nature can be confirmed by the facile addition of indole to **3a** under treatment with a catalytic amount of tosic acid (10 mol %) in toluene at 60 °C (Scheme 3). Introducing the indole moiety is counterbalanced by the lower diversity associated with the elimination of the starting amino and carboxylic acid Ugi components.

Scheme 3. Bronsted acid-triggered indole addition to **3a**.



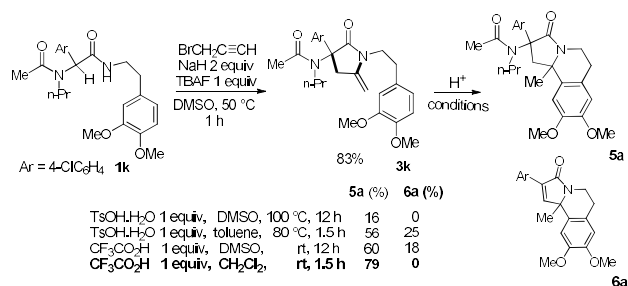
After this first addition, we surmised that an intramolecular reaction could be achieved more readily and prevent the elimination of the amide residue to afford easy access to complex polycyclic derivatives with high diversity. With this goal in mind, a Pictet-Spengler cyclization⁹ of a dimethoxyaryl group tethered on the isocyanide starting moiety was selected due to the biological relevance of the potential benzoindolizine that is formed in the process (Scheme 4). This heterocyclic scaffold is largely represented among natural alkaloids in various compounds, such as Crispine, Erysotramidine or Lamellarin, which exhibit interesting biological activities (Scheme 4).¹⁰

Scheme 4. Ugi strategy toward Crispine and Capsin alkaloids.



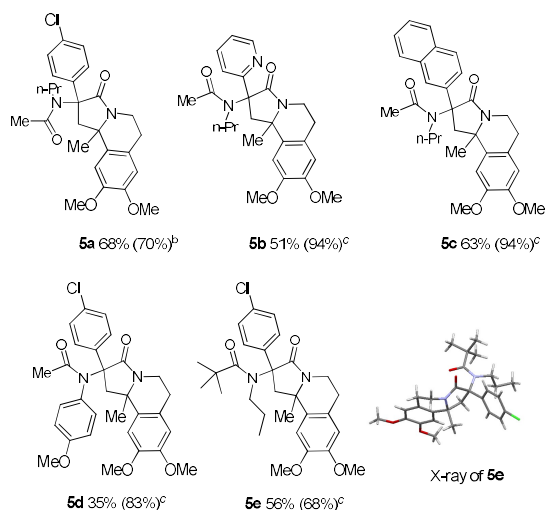
When Ugi adduct **1k**, which was obtained in 92% isolated yield from homoveratryl amine isocyanide, propyl amine, acetic acid and 4-chlorobenzaldehyde, was treated with propargylbromide under our previously optimized conditions, the expected enamide **3k** was formed in an isolated yield of 83% (Scheme 5). The addition of a stoichiometric amount of TsOH to **3k** in DMSO at 100 °C resulted in the formation of **5a** as a single diastereomer in 56% yield, along with alkene **6a** as a side product.¹¹ Toluene afforded a slightly better selectivity in a shorter reaction time (60% of **5a** with 18% of **6a**). When the Bronsted acid was changed to CF₃CO₂H in DMSO at rt, only 16% yield of **5a** was obtained. The best results were obtained using a CF₃CO₂H/CH₂Cl₂ system, which afforded **5a** selectively in 79% yield.

Scheme 5. Optimization of Pictet-Spengler reaction.



Although the choice of this solvent makes a one-pot extension more difficult to achieve, it was selected due to facile cyclization at rt without the formation of elimination product **6a**. The direct transformation of Ugi adduct **1k** to **5a** was attempted with these latter conditions to avoid the purification of intermediate **3k**. Thus, after cyclization in DMSO, water was added, followed by citric acid to achieve neutral pH prior to extraction with dichloromethane. The subsequent cyclization was performed in CH₂Cl₂ using 2 equiv of CF₃CO₂H, leading to indolizine **5a** as a single diastereomer in an overall isolated yield of 68%. In this case, the use of 1 equiv of acid lowered the reaction yield. Different Ugi adducts were treated under the same conditions to afford indolizines **5b-e** in moderate to good yields as single diastereomers (Scheme 6). The relative positions of the substituents in **5a-e** could not be addressed using NMR techniques. However, their stereochemistries were proposed by analogy to compound **5e**, which was crystallized in toluene to obtain its X-ray structure.¹²

Scheme 6. One-pot benzoindolizine **5** synthesis from homoveratryl amine-derived Ugi adducts **1**.^a



^aReaction conditions: Ugi adduct **1** (0.4 mmol), NaH (1.0 mmol), propargyl bromide (0.6 mmol) TBAF (0.4 mmol) in DMSO (0.4 M) at 50 °C for 1 h then CF₃CO₂H (0.8 mmol) in CH₂Cl₂ (0.4 M) at rt for 1.5 h. ^bYield obtained when the reaction was performed on 1 mmol of Ugi adduct **1k** using the same concentration and reagent ratio. ^cIsolated yield of intermediate Ugi adduct.

Nevertheless, refluxing **5a** in toluene for 24 hrs using 1 equiv of TsOH allowed for complete transformation to elimination product **6a**, which was isolated in 87% yield.

In conclusion, we have developed novel multicomponent access to pyrrolidone enamide derivatives. The synthetic sequence is based on Ugi amide dianionic derivatives, which are key intermediates with enhanced nucleophilic behavior. The selectivity of the cascade was improved using TBAF as an additive. The power of the Ugi reaction as the first step was demonstrated by application of this strategy to the straightforward preparation of the heterocyclic core of Crispine alkaloids. Although several Ugi/Pictet Spengler strategies have been previously reported,¹³ most of these approaches require the introduction of an electrophilic moiety on one of the Ugi components, leading to competition issues or the need for protecting groups. Furthermore, the combination of propargylation and the Pictet-Spengler reaction to afford benzoin-dolizines in one step is without precedent. We are continuing to explore this methodology to study the reaction of more complex alkynes, as well as other nucleophilic groups in the final Pictet-Spengler step.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and ¹H and ¹³C spectra for new compounds (PDF)

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Author Contributions

All authors have given approval to the final version of the manuscript.

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