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β -Carbolinone Analogues from the Ugi Silver Mine

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Abstract

Here we describe a facile, tandem synthetic route for β -carbolinones, a class of natural products of high biological significance. Commercially available building blocks yield highly diverse analogues in just two simple steps.

Keywords

Ugi-reaction; Multicomponent reactions; Isocyanide; B-Carboline; Propargyl

Introduction

Synthetic strategies to obtain natural products, and analogues/skeletons thereof, are at the very heart of synthetic organic chemistry.^[1] Approaches achieving atom economy are highly sought after, offering various advantages, minimization of waste, time and resources. Multicomponent reaction chemistry is such a group of synthetic transformations allowing via short synthetic routes, access to large libraries of analogues of many different scaffolds from common building blocks, finally minimizing waste, time and resources.^[2] Natural products containing the β -carbolinone scaffold show diverse biological and pharmacological activities,^[3] such as anticancer, inhibition of human leukocyte elastase, and the modulation of effects associated with depression, anxiety disorders and muscle spasms, just to name a few.^[4]

Conventional methods towards the synthesis of β -carbolin-one analogues require multiple steps, including complicated steps to prepare starting materials.^[5] To access this significant scaffold, methods such as dehydrogenative annulations,^[6a] intramolecular Heck,^[6b] and cycloisomerization^[6c] were established. Recently, a silver-catalyzed oxidative cyclization of prop argylamide-substituted indoles towards phosphorated indolo-azepinones was described.^[6d] On the other hand, Ugi adducts are easily accessible, however, transforming such adducts into potentially biologically active molecules remains challenging, even in light of considerable recent advances.^[7] In particular, the use of propargylamine as an amine source

Conflict of Interest

The authors declare no conflict of interest.

in Ugi-reactions is limited to date. Recently, propargylamine was used as the amine component in an Ugi reaction, and via a three-step synthesis using palladium catalyzed cyclization, resulted in aza-polyheterocycles.^[7b] Moreover, Eycken and co-workers developed a gold-catalyzed approach for the synthesis of cyclo-pentapyridinones and spirocyclopentapyridinones using prop-argylamine as an amine source.^[7c] The same group recently described a gold-catalyzed synthesis of pyrrolopyridines and azepinoindoles starting from propargylamines.^[7d] Chauhan and co-workers described interesting β -carbolinone and indolo-pyrazinone analogues based on an Ugi-four-component reaction (Ugi-4CR) with aminodimethylacetal as amine source. However, this reaction requires stoichiometric amounts of PTSA and it produces a side product along with the β -carbolinones.^[8] Synthesis of oxopyrazino[1,2-*a*] indoles was developed by the Shafiee group using potassium *tert*-butoxide, in which cyclization takes place at the more nucleophilic nitrogen of the Ugi product, resulting in oxopyrazino[1,2-*a*]indoles (Scheme 1).^[9] Although the above methods are useful, there is still room for improvement regarding the establishment of a mild synthetic approach with high diversity for the β -carbolinone scaffold.

Here, our aim is to use propargylamine in Ugi-four-component reactions followed by a tandem/sequential AgOTf-catalyzed carbocyclization of the Ugi-products towards β -carbolin-one analogues. In this synthetic approach, 6-*exo-dig* carbocyclization takes place to form the six-membered indole annulated pyrido-1-one in fair to very good yields.

Results and Discussion

Isocyanide-based multicomponent reactions (IMCRs) have attracted a lot of attention, due to the fact that versatile functional groups can be introduced in the MCR adducts, which can undergo further condensations or cyclizations reactions leading to an array of structurally diverse scaffolds.^[10] In this study, starting from the Ugi-4CR of propargylamine **1a** as an amine source, benzaldehyde **2a**, indole-2-carboxylic acid **3a** and *tert*-butyl isocyanide **4a** in methanol at room temperature resulted to the corresponding Ugi adduct **5a** in a good yield of 83 % after 12 h. With compound **5a** in hand, we were keen to investigate the intramolecular hydroarylation. The initial investigation with Al(OTf)₃ (20 mol-%) in CH₃CN at 75 °C gave the desired product **6a** but in a low yield of 21 %, whereas no product was detected with CuI, PTSA, TfOH, KOTf, and NaOTf. On the other hand, the usage of ZnCl₂ as Lewis-acid catalyst (20 mol-%) led to an isolated yield of **6a** in 40 %. The application of catalysts like Sn(OTf)₂, In(OTf)₃, Zn(OTf)₂ in the reaction at 75 °C gave the isolated yield of 42 %, 56 %, and 56 % respectively. Finally, the yield was increased to 75 % when the reaction was carried out in the presence of AgOTf (20 mol-%) at 75 °C (Table 1, entry 11). After selecting the catalyst, we extensively screened different solvents to achieve the best conditions. A one-pot cyclization was also explored since it could add considerable value to our synthetic approach. To our delight, using methanol as a solvent for 12 h at room temperature for the Ugi reaction and then adding AgOTf (20 mol-%) and heating the reaction mixture to 75 °C for 3 h was proven to be the best condition (Table 1, entry 15).

With the optimized one-pot reaction conditions in hand, the scope of the “Ugi-4CR/ cyclization” reaction was further investigated by reacting propargylamine with different

aldehydes/ket-ones, isocyanides and indole-2-carboxylic acid in methanol followed by AgOTf catalyzed cyclization to furnish the corresponding β -carbolinone library **6a–v**. All the substrates **1**, **2**, **3** and **4** led to the expected β -carbolinone products **6a–v** in 49–77 % yields in one-pot. Substituted benzyl isocyanides with electron-donating groups like *p*-methoxy (**4b**), 3,4,5-trimethoxy (**4d**) reacted smoothly with 65 % and 63 % yields, respectively. Electron withdrawing substituents like cyano and chloro reacted nicely to give the cyclized products in good yields (**6c**, **6e**, Table 2). The commercially available 5-chloro substituted indole-2-carboxylic acid (**3i**) reacted to give the expected product **6i** in 59 % yield. Similarly, 2,6-dimethyl benzyl isocyanide and aliphatic branched isocyanides also furnished the different β -carbolinone products in good yields. Table 2 clearly indicates that there are no electronic or steric effects on the outcome of the reaction.

After successfully demonstrating the one-pot cyclization reactions with different isocyanides, we then focused on different aldehydes and ketones. As shown in Table 3, also, in this case, the one-pot approach results in very good yields. For instance, in case of *ortho/para* bromo-substituted benzaldehydes, the corresponding products were obtained in 77 % and 67 % yields respectively, which unlocks interesting opportunities for further functionalization of the bromo-products via palladium catalysis (Table 3, **6j**, **6k**). Furthermore, keeping in mind the intriguing physicochemical properties of fluoro and trifluoromethyl substituents, we intentionally performed the reactions with **2l**, **2m** and **2n** to get the desired products in good yields (Table 3, **6l**, **6m**, **6n**). Strong +M groups, as well as –M groups containing benzaldehydes, reacted well to give fair yields (Table 3, **6p**, **6q**, **6r**, **6s**, **6t**). Even aliphatic aldehyde also efficiently (**2u**) reacted to give 70 % yield of expected cyclized product **6u**. It is worth mentioning that cyclic ketone reacted without any interruption to obtain decent yield (Table 3, **6v**).

A plausible mechanism of the cyclization path was explained based on the previous reports as shown in Scheme 2.^[11] After getting the Ugi adduct, silver attacks the alkyne to give the intermediate **A**, which undergoes a 6-*exo-dig* cyclization to give intermediate **B**, which upon rearomatization/protodemetalation gives the β -Carbolinone product **6**.

As already mentioned, β -carbolinones possess diverse biological activities and evident from the report by Bracher et al. in 2011.^[12] Derivatives of 7,8-dichloro-1-oxo- β -carbolinones, which were based on the alkaloid Bauerine C showed kinase inhibitory activity. A co-crystal structure with DAPK3 was obtained, shedding light into the molecular interactions and indicating an unusual, non-ATP mimetic binding mode. Using the PDB code 3BHY, we were interested in docking our β -carbolin-one derivatives. Interestingly, we observed a good overlap of the indole parts with the original ligand and our compounds fitted nicely into the pocket. Although in the original crystal structure, the two chloro substituents of the indole ring participate in halogen bonds, this feature is missing from our derivatives. However, in our case, the indole rings are oriented in a similar manner and the amide moieties of the side chains were able to form hydrogen bonds. Halogen bonds are weaker than the hydrogen bonds that we observed while docking the compounds and we thus hypothesize that these compounds could have potential as kinase inhibitors (Figure 1).

Conclusions

To sum up, we have successfully established a mild and facile one-pot procedure for the synthesis of β -carbolinones, starting from commercially available starting materials. Diversity can be achieved mainly through, the isocyanide and the aldehyde component and to a smaller extent the indole-carboxylic acid. Regarding potential applications, docking studies indicate that these types of derivatives could be useful as kinase inhibitors and biological work is ongoing, will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Docking poses. Up left: Overlap of compound **6p** (yellow sticks) with the ligand (green sticks) of PDB 3BHY. Up right: hydrogen bonds (black dots) of compound **6p** (yellow sticks) with Lys141 and Ser21 (cyan sticks). Below: 2D structures of ligand of PDB 3BHY and compound **6p**.

Scheme 1.

Synthesis of carbolinones: present and previous work.

Scheme 2. Anticipated mechanistic pathway for 6-*exo-dig* cyclization reaction.

Table 1.Optimization of the intramolecular hydroarylation.^[a,b]

S.No.	Catalyst (20 mol%)	Solvent	Product yield 6
1.	PTSA	CH ₃ CN	nd
2.	CuI	CH ₃ CN	nd
3.	TfOH	CH ₃ CN	nd
4.	Al(OTf) ₃	CH ₃ CN	21% yield
5.	KOTf	CH ₃ CN	nd
6.	NaOTf	CH ₃ CN	nd
7.	ZnCl ₂	CH ₃ CN	40% yield
8.	Sn(OTf) ₂	CH ₃ CN	42% yield
9.	In(OTf) ₃	CH ₃ CN	56% yield
10.	Zn(OTf) ₂	CH ₃ CN	56% yield
11.	AgOTf	CH ₃ CN	75% yield
12.	AgOTf	Toluene	52% yield
13.	AgOTf	Acetone	67% yield
14.	AgOTf	MeOH	76% yield
15.	AgOTf	MeOH	69% yield^c
16.	AgNO ₃	MeOH	57% yield

^[a] The Ugi-reaction was carried out using **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol) and **4a** (1.0 mmol) in MeOH for 12 h at room temperature. Pure product **5a** was subjected to cyclization under indicated catalysis in a sealed tube with an indicated solvent for 3 h at 75 °C.

^[b] Isolated yield.

^[c] Reaction was carried out one-pot (Ugi-reaction followed by cyclization).

Table 2.

Synthesis of β -carbolinones: Variation in isocyanide part.^[a,b]

^[a] The reactions were run using **1a** (1.0 mmol), **2b** (1.0 mmol), **3** (1.0 mmol) and **4a–i** (1.0 mmol) in MeOH as solvent for 12–24 h at room temperature. After Ugi-reaction, AgOTf (20 mol-%) followed by extra MeOH was added to the reaction mixture and the whole mixture was heated to 75 °C for 3 h in a sealed tube.

^[b] Isolated yield.

Table 3.

Synthesis of β -carbolinones: Variation in aldehyde/ketone part.^[a,b]

^[a] The reactions were run using **1a** (1.0 mmol), **2** (1.0 mmol), **3a** (1.0 mmol) and **4a** (1.0 mmol) in MeOH as solvent for 12–24 h at room temperature. After Ugi-reaction, AgOTf (20 mol-%) followed by extra MeOH was added to the reaction mixture and the whole mixture was heated to 75 °C for 3 h in a sealed tube.

[b] Isolated yield.

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