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An efficient and practical approach for the synthesis of indoloquinolines and indolo/pyrroloquinoxalines *via* a Cu-catalyzed Ugi-C/Ugi-*N*-arylation sequence†

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A Cu-catalyzed tandem transformation of Ugi adducts through CH/NH bond functionalization reactions was reported for synthesizing a broad spectrum of indolo/pyrrolo-[1,2-*a*]quinoxaline-6/4-carboxamide, 7*H*-indolo[2,3-*c*]quinoline-6-carboxamide, and 1-(cyclohexylamino)-14*H*-indolo[2,3-*c*][1,4]oxazino[4,3-*a*]quinolin-4(3*H*)-one derivatives in moderate to excellent yields. In this protocol the Ugi condensation of aromatic aldehydes, anilines, acids, and isocyanides leads to the formation of bis-amides in methanol at room temperature. This approach employed simple reaction conditions, including Ugi product as starting material, CuI, L-proline as a ligand, and cesium carbonate, in DMSO for 8 h. This method demonstrated efficiency in synthesizing fused-nitrogen-containing heterocycles through a convenient pathway.

Introduction

Organic compounds are usually synthesized through several reaction steps. During this process, it is necessary to separate and purify the intermediates before they can be used in the following reaction. However, the overall yield of the final product decreases significantly with each subsequent step of the iterative synthesis.[1] Powerful transformations and multicomponent reactions have been effectively utilized for the synthesis of various synthetic intermediates, natural products, and bioactive agents.[2–4] Multicomponent reaction techniques enable the rapid and efficient synthesis of complex and diverse molecules, resulting in reduced costs, waste, and time, thus promoting green chemistry. These techniques are now widely utilized to prepare many high-yield compounds.[5–7] Multicomponent reactions based on isocyanides are gaining increasing interest due to the availability of various starting materials and the abundance of transformations that can be performed.[2] The high efficiency of isocyanides in multicomponent reactions is due to their ability to form reversible bonds by extending their valence.[8] In the last decades, the discovery and development of Passerini and Ugi reaction variations have led to immense growth in Isocyanides-based multicomponent reactions.[2] The Ugi four-component reaction has been extensively studied for the production of multifunctional adducts due to its wide scope, high variability, and mild reaction conditions.[9] N-Heterocycles are one of the most important scaffolds in the structure of natural products, pharmaceuticals, dyes and biologically active molecules.[10,11] For instance, many natural and biologically active compounds contain the indole and pyrrole ring.[12–14] Quinoline alkaloids, which are typically found in plants of the *Haplophyllum A. Juss*, exhibit a wide range of biological properties.[15,16] Additionally, Quinoxaline derivatives have various pharmacological profiles.[17]

Quinoxalines are found in marketed drugs with antibacterial, antiviral, antibiotic, antitumor, antimicrobial, antifungal and anti-inflammatory activities (Fig. 1).[18]

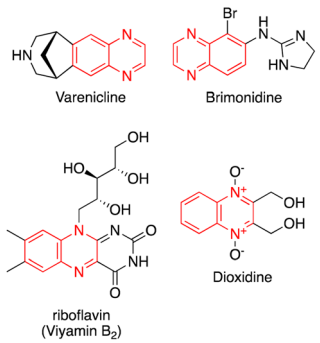

Fig. 1 Representative bioactive and naturally occurring quinoxalines.

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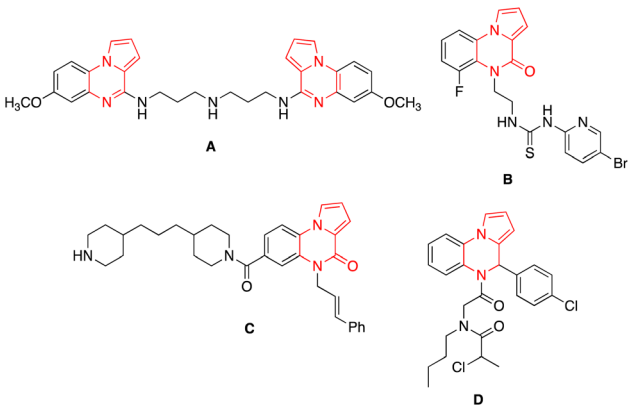


Fig. 2 Some important pyrrolo[1,2-*a*]quinoxalines.

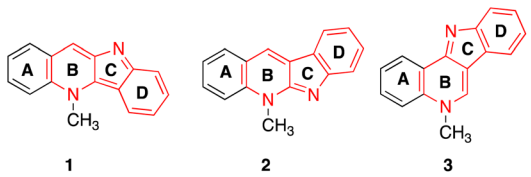
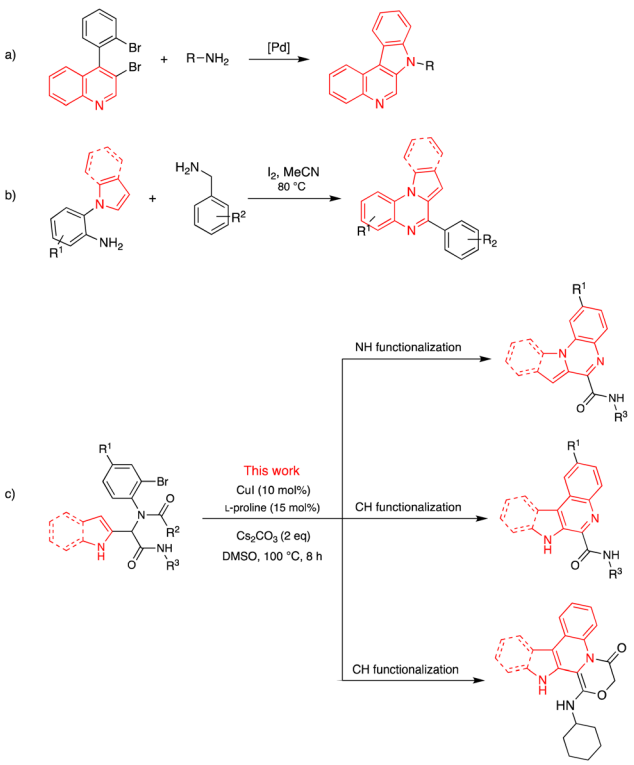


Fig. 3 Cryptolepine (**1**), neocryptolepine (**2**) and isocryptolepine.



Scheme 1 Previous works for the synthesis of 7*H*-indolo[2,3-*c*]quinolines (a), indolo- and pyrrolo[1,2-*a*]quinoxalines (b) and present work (c).

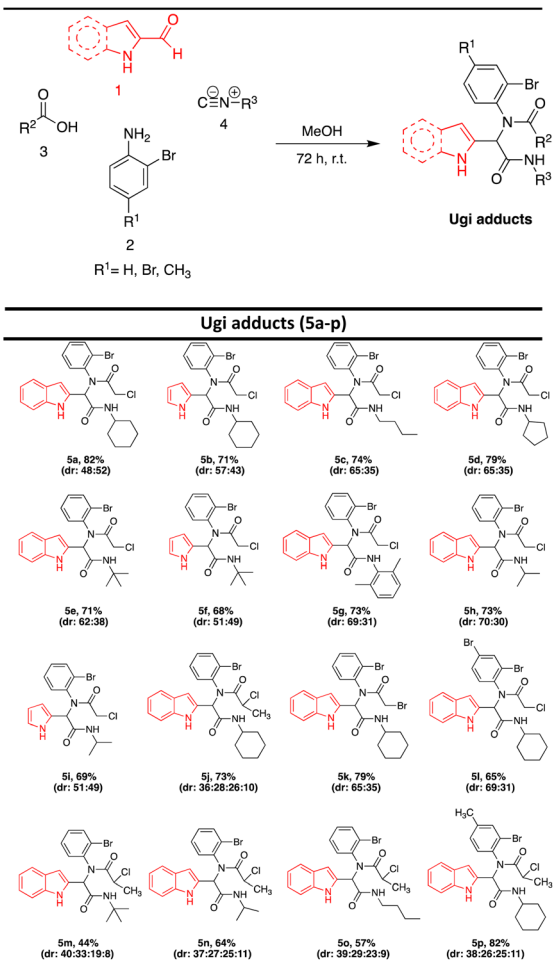
Pyrrole/indole-fused heterocycles are abundant in numerous natural products, as well as medicinal chemistry for lead compounds and drug prospects.[19] Amidst the many compounds, pyrrole/indole-fused quinoxaline derivatives have long been of great interest due to their remarkable biological activities and intriguing structures.[19] Among them, indolo[1,2-*a*]quinoxaline analogues have shown promising anti-fungal properties[17] and pyrrolo[1,2-*a*]quinoxaline subunits are present in various biologically and medicinally useful molecules. Several of its derivatives are antimalarial agents **A**, anti-HIV agents **B**, anticancer agents **C**, and antagonist agents **D** (Fig. 2).[20]

Indolo- and pyrroloquinoline alkaloids can be ascertained among multiple natural products and exhibit a wide range of biological activities.[21–23] Indoloquinolines are found in the roots of *Cryptolepis sanguinolenta*, the west African plant.[24] Cryptolepine (**1**), neocryptolepine (**2**) and isocryptolepine (**3**) are three of thirteen identified alkaloids of the root (Fig. 3).[25]

Pyrroloquinolines, as another class of important N-heterocycles, were discovered in marine natural products.[21] Tryptophan has been suggested for many years to yield the pyrroloquinoline alkaloid.[26]

In the past years, different methods have been reported for the synthesis of indolo[2,3-*c*]quinoline. These methods

Table 1 Synthesis of Ugi-adducts[a,b]



[a] Reaction conditions: aldehydes (1 mmol), anilines (1 mmol), acids (1 mmol) and isocyanides (1 mmol) in 5 mL methanol at r.t., 72 h. [b] Isolated yield.

include: the chemoselective Suzuki reaction, the Pd-catalyzed intramolecular arylation under microwave irradiation and the third method of including two steps that the first step involved a Cu-catalyzed coupling reaction and the second utilized a Pd-catalyzed intramolecular arylation reaction.[21,25,27]

Among the various synthetic approaches for the preparation of indolo[1,2-*a*]quinoxaline, the following methods can be mentioned: the Pictet–Spengler approach using Brønsted acid-catalyzed, the Pd-catalyzed regioselective C–H olefination/cyclization sequence, the transition metal-free process, the Pd-catalyzed intramolecular C–N bond formation, the modified Pictet–Spengler reaction using Lewis acid-catalyzed, the Domino approach involving spirocyclic ring opening, the Pt(IV)-catalyzed hydroamination triggered cyclization, the tandem one-pot reductive cyclization-oxidation, and oxidative reaction.[17–20,28–32] A series of 7*H*-indolo[2,3-*c*]quinolines was synthesized by Langer *et al.* by the chemoselective Suzuki reaction followed by a ring-closing two-fold Buchwald–Hartwig reaction of 3-bromo-4-iodoquinoline (Scheme 1a).[21] A series of indolo- and pyrrolo[1,2-*a*]quinoxalines were synthesized by Jayaprakash *et al.* from the corresponding 2-(1*H*-indol/pyrrol-1-yl) anilines promoted by molecular iodine (Scheme 1b).[33]

In our ongoing investigation, three different products were synthesized, including indolo/pyrrolo-[1,2-*a*]quinoxaline-6/4-carboxamides, 7*H*-indolo[2,3-*c*]quinoline-6-carboxamides, and 1-(cyclohexylamino)-14*H*-indolo[2,3-*c*][1,4]oxazino[4,3-*a*]quinolin-4(3*H*)-one, all with a high yield (Scheme 1c).

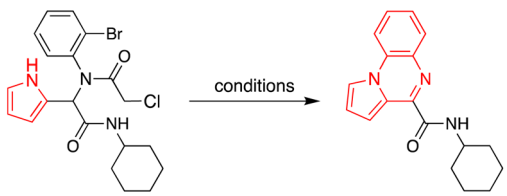
Results and discussion

In continuation of our research interest on multicomponent reactions and indole/pyrrol chemistry,[5,12,34–45] we focused on the preparation of three different products including indolo/pyrrolo [1,2-*a*]quinoxaline, 7*H*-indolo[2,3-*c*]quinoline, and 14*H*-indolo [2,3-*c*][1,4]oxazino[4,3-*a*]quinolin-4-one, using the post-transformation of Ugi adducts under a copper catalyst. In the first step, the Ugi condensation of aromatic aldehydes, anilines, acids, and isocyanides leads to the formation of bis-amides in methanol at room temperature (Table 1).

For the post-transformation of Ugi adducts, the starting material **5b** (2-formyl indole, 2-bromoaniline, 2-chloropropanoic acid, and cyclohexyl isocyanide) was reacted with CuI as a catalyst in the presence of L-proline as ligand, Cs_2CO_3 as base, and DMSO as solvent. The desired product **6a** was obtained in 79% yield (entry 1, Table 2).

After the identification of compound **6a**, the optimization of the reaction conditions including catalyst, base, ligand, solvent, and temperature were investigated. First, various catalysts such as CuI, CuCl, $CuSO_4$, and $CuCl_2$ were investigated and CuI was identified as the best catalyst (entries 1–4, Table 2). Then, various bases such as Cs_2CO_3, K_2CO_3, KO*t*-Bu,

Table 2 Scope of optimization conditions for the synthesis of **6a**[a,b]

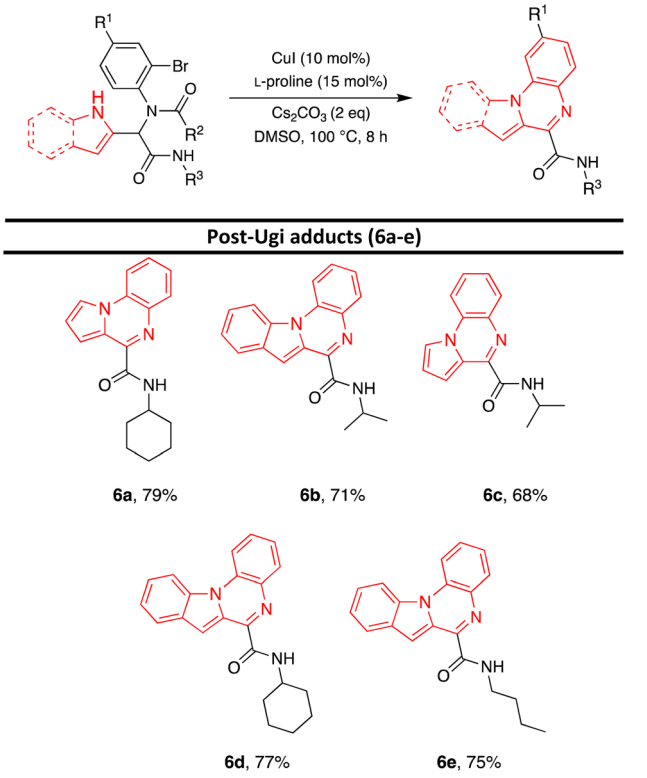


5b **6a**

Entry	Catalyst	Ligand	Base	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	**CuI**	**L-proline**	**Cs_2CO_3**	**DMSO**	**100**	**8**	**79**
2	CuCl	L-proline	Cs_2CO_3	DMSO	100	24	40
3	$CuSO_4$	L-proline	Cs_2CO_3	DMSO	100	24	53
4	$CuCl_2$	L-proline	Cs_2CO_3	DMSO	100	24	27
5	CuI	L-proline	K_2CO_3	DMSO	100	8	70
6	CuI	L-proline	KO*t*-Bu	DMSO	100	8	75
7	CuI	L-proline	KOH	DMSO	100	8	67
8	CuI	L-proline	Et_3N	DMSO	100	8	—
9	CuI	Phen	Cs_2CO_3	DMSO	100	8	22
10	CuI	TMEDA	Cs_2CO_3	DMSO	100	8	72
11	CuI	Ph_3P	Cs_2CO_3	DMSO	100	8	64
12	CuI	L-proline	Cs_2CO_3	Dioxane	100	8	—
13	CuI	L-proline	Cs_2CO_3	THF	Reflux	8	—
14	CuI	L-proline	Cs_2CO_3	CH_3CN	Reflux	8	—
15	CuI	L-proline	Cs_2CO_3	CH_2Cl_2	Reflux	8	—
16	CuI	L-proline	Cs_2CO_3	DMSO	Rt	8	12
17	CuI	—	Cs_2CO_3	DMSO	100	8	74
18	CuI	L-proline	—	DMSO	100	8	—
19	—	—	Cs_2CO_3	DMSO	100	24	21
20	$Pd(OAc)_2$	Ph_3P	Cs_2CO_3	DMSO	100	8	68

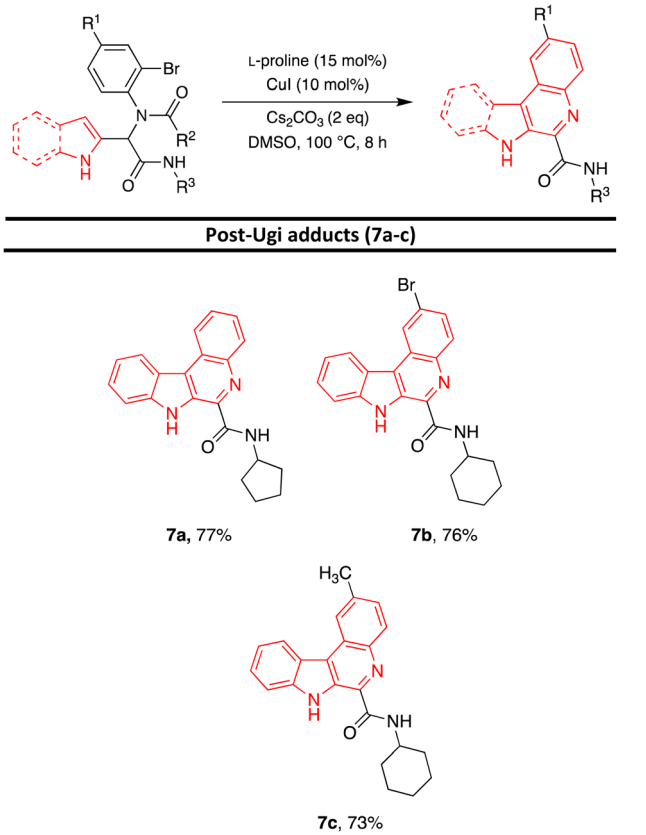
[a] Conditions: **5b** (0.5 mmol), catalyst (10 mol%), ligand (15 mol%), base (2 equiv.), solvent (3 mL). [b] Isolated yields.

Table 3 Synthesis of post-Ugi adducts[a,b]



[a] Reaction conditions: 5 (1 mmol), Cs_2CO_3 (2 mmol), CuI (10 mol%), L-proline (15 mol%) in 5 mL DMSO at 100 °C, 8 h. [b] Isolated yield.

Table 4 Synthesis of post-Ugi adducts[a,b]

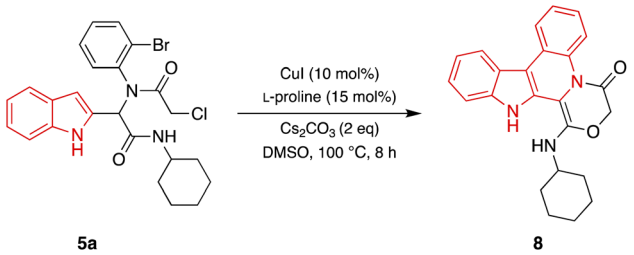


[a] Reaction conditions: 5 (1 mmol), Cs_2CO_3 (2 mmol), CuI (10 mol%), L-proline (15 mol%) in 5 mL DMSO at 100 °C, 8 h. [b] Isolated yield.

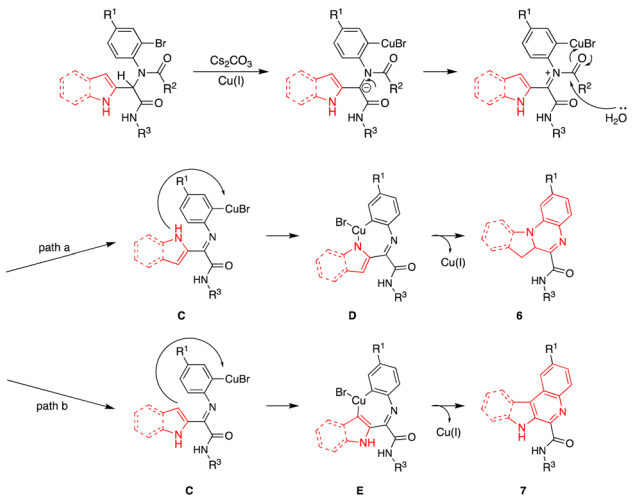
KOH, and Et_3N were investigated. Cs_2CO_3 was found to be the best catalyst (entries 1, 5–8, Table 2). Various ligands such as L-proline, 1,10-phenanthroline, TMEDA, and Ph_3P were applied for this transformation and the results showed that the best yield was obtained when L-proline was utilized (entries 1, 9–11, Table 2). Running the reaction in the different solvents such as dioxane, THF, CH_3CN, CH_2Cl_2, and DMSO revealed that the best yield was obtained using DMSO as solvent (entries 1, 12–15, Table 2). The impact of temperature on the reaction was also studied and 100 °C was selected as the optimum temperature (entries 1, 15–16, Table 2). Additionally, running the reaction without a ligand or ligand and catalyst, led to a decrease in the reaction efficiency (entries 17,19, Table 2). No product was obtained when the reaction was performed without base (entry 18, Table 2). Furthermore, after changing the catalyst and ligand to $Pd(OAc)_2$ and Ph_3P, the desired product was obtained with a lower yield (Entry 20, Table 2). According to the obtained results, the highest yield was detected with CuI as a catalyst, L-proline as a ligand, and Cs_2CO_3 as a base in DMSO as solvent at 100 °C for 8 hours (entry 1, Table 2). Under optimized reaction conditions, various Ugi adducts were applied to explore the scope of the reaction. Unexpectedly, we procured three different types of products. Post-Ugi adducts **6a–e**were obtained using Ugi adducts **5b**, **5h**, **5i**, **5j**, and **5o** under optimized reaction conditions (Table 3). On the other side, when Ugi adducts **5d**, **5l**, and **5p** were reacted under mentioned optimized reaction conditions, post-Ugi adducts **7a–c**were formed (Table 4) while using Ugi adduct **5a**, final product **8** in 81% yield was generated (Scheme 2). The best results were obtained using less bulky groups on the isocyanide part (**8**, **6a**, **7a**) and electron-donating groups on the acid part (**6d**). Ugi products with bulky isocyanide-like isopropyl showed less reaction efficiency (**6c** and **6b**). A satisfactory result was obtained using electron-withdrawing groups on the amine part (**7b**).

A plausible mechanism for the synthesis of compounds **6** and **7** is presented in Scheme 3. First, by adding Cs_2CO_3 as base and CuI as catalyzed to compound **5**, metal complex **A** is formed, and that this unstable carbanion forms Intermediate **B**. In the next step, nucleophilic attacks of H_2O in DMSO solvent to carbon of the carbonyl group, and the elimination of carboxylic acid group generates intermediate **C**. Then the Ullman reaction on intermediate **C** through path a, leads to C–N bond formation in a new Cu-complex **D**, which undergoes a reductive elimination to generate the product **6**.[46] In path b C–C bond formation on intermediate **C** forms the Cu-complex **E**, which undergoes reductive elimination leads to the formation of product **7**.[47]

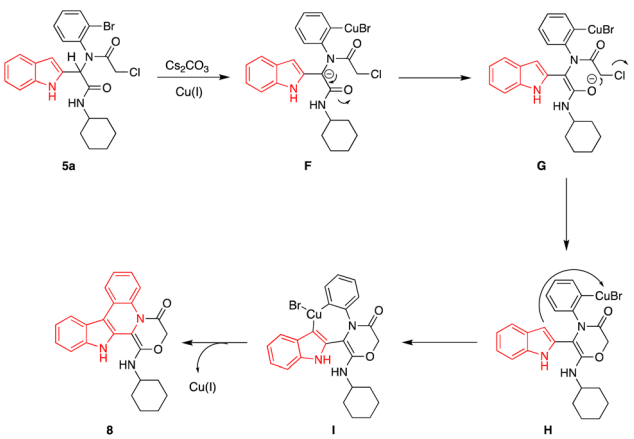
A possible mechanism for the synthesis of compound **8** is presented in Scheme 4. First, the adding of Cs_2CO_3 and Cu(I) to



Scheme 2 Synthesis of post-Ugi adduct 8.



Scheme 3 A plausible mechanism for the synthesis of compounds 6 and 7.



Scheme 4 A plausible mechanism for synthesis of compound 8.

compound **5a**, leads to the formation of metal complex **F**. The unstable carbanion generates intermediate **G** *via* keto–enol tautomerization. Intermediate **G** forms intermediate **H** under intramolecular nucleophilic attack by oxygen *via* cyclization and losing Cl. Nucleophilic attack by carbon atom of the indole part in intermediate **H** produces a new Cu-complex **I**. Finally, the corresponding product **8** was released from **I** through reductive elimination.[47]

Conclusions

In summary, we presented a copper-catalyzed tandem approach for preparation of three different products, including indolo/pyrrolo-[1,2-*a*]quinoxaline-6/4-carboxamides, 7*H*-indolo[2,3-*c*]quinoline-6-carboxamides and 1-(cyclohexylamino)-14*H*-indolo[2,3-*c*][1,4]oxazino[4,3-*a*]quinolin-4(3*H*)-one scaffolds found in some biologically active compounds. In this project, Ugi products were synthesized through the Ugi 4CR reaction using aldehydes, amines, isocyanides and acids in methanol as the solvent at room temperature. The Ugi adducts as starting materials were then used in the next step to diversify various classes of fused-nitrogen-containing heterocycles, in a one-pot/multi-steps effective protocol. The identification of the generated compounds was conducted using analytical techniques including FT-IR, ^{1}H-NMR, ^{13}C-NMR and HRMS.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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