


 Cite this: *RSC Adv.*, 2023, 13, 16963

Highly regioselective and diastereoselective synthesis of novel pyrazinoindolones *via* a base-mediated Ugi-*N*-alkylation sequence†

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An efficient base-mediated/metal-free approach has been developed for the synthesis of 1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole-3-carboxamide derivatives *via* intramolecular indole *N*-H alkylation of novel bis-amide Ugi-adducts. In this protocol the Ugi reaction of (*E*)-cinnamaldehyde derivatives, 2-chloroaniline, indole-2-carboxylic acid and different isocyanides was designed for the preparation of bis-amides. The main highlight of this study is the practical and highly regioselective preparation of new polycyclic functionalized pyrazino derivatives. This system is facilitated by Na₂CO₃ mediation in DMSO and 100 °C conditions.

Received 29th March 2023

Accepted 24th May 2023

DOI: 10.1039/d3ra02065g

rsc.li/rsc-advances

Introduction

Nitrogen-containing heterocycles are really important structural motifs with large applications in medicinal,^{1,2} pharmaceutical,³ and synthetic organic chemistry.⁴ Among them the indole ring is present in many important natural products^{5,6} and is a basic skeleton of a number of drugs.^{2,7} Additionally, fused indole rings have the affinity to bind to receptors.^{8,9} Hence, the preparation of fused and derived indoles has attracted much attention from organic chemists for many years.^{10–13}

Indole and pyrrole fused-piperazine and piperazinone derivatives are significant heterocycle compounds used as pharmacophores due to their potential medicinal activities.^{14,15} Investigations on these tricyclic nucleuses started in 1994, when they were studied from two points of view: synthetic and potency in medical science.^{16–18} In this class, pyrazino[1,2-*a*]indolones are very important tricyclic backbones, such as indole joined into a piperazinone ring. These analogues are under great consideration due to their therapeutic uses.¹⁹

Pyrazino[1,2-*a*]indol-1-one derivatives are impressive pharmacophores in the treatment of various diseases.¹⁹ Several of them have potent inhibitory¹⁹ and anti-cancer activities (Fig. 1A, C and D),^{10,19,20} and some of them have anti-infection,²¹ anti-

allergenic²² and anti-viral properties (Fig. 1B).²³ Compounds containing pyrazinoindolone frames have been reported as potent mitogen-activated protein kinase-2 (MK₂) inhibitors.^{24,25}

Despite the importance of indole-fused structures, a few effective procedures have been reported for their synthesis. A series of substituted-3,4-dihydropyrazinoindol-1(2*H*)-one was

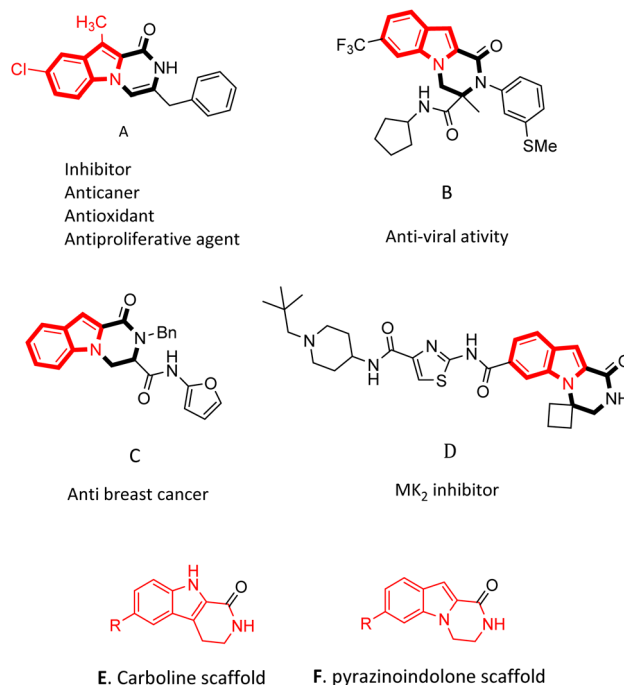


Fig. 1 A library of biologically active pyrazino[1,2-*a*]indol-1-one derivatives.

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† Electronic supplementary information (ESI) available. CCDC 2249611. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3ra02065g>



synthesized by Toche *et al.*²⁶ from the cyclization reaction of ethyl 1-(2-bromoethyl)-1*H*-indole-2-carboxylate and primary amines. In another work, Youssif *et al.*¹⁰ prepared open-chain indole-2-carboxamides and then performed consequential oxidation and cyclodehydration using PTSA which resulted in the production of benzyl pyrazino[1,2-*a*]indol-1(2*H*)-ones. In 2017, Kim *et al.*²⁰ reported on the preparation of biologically active 1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole-3-carboxamide analogs in three steps.

Because of the application of pyrazinoindolones in drug discovery, designing a novel and efficient pathway for their synthesis is tempting enough for synthetic chemists. Currently, Ugi four-component reaction has provided good conditions to synthesize diverse N-heterocyclic structures.^{27–29} This name reaction in combination with other reactions is converted to a remarkable tool to prepare new fused scaffolds.³⁰ Since the beginning of the 21st century, various examples have been reported using this combinatory protocol – as post-Ugi process. These strategies include Ugi/Heck,^{31,32} Ugi/Diels–Alder,³³ Ugi/Buchwald–Hartwig,³⁴ Ugi/Knoevenagel condensation,^{35,36} *etc.*

There are a few examples for the synthesis of pyrazinoindolones using Ugi reaction. A modified Ugi-type reaction was developed by Ilyn group³⁷ to obtain novel indole-fused 1-oxo-1,2,3,4-tetrahydropyrazines based on a cyclization key step. An Ugi-3CC strategy was presented in 2012, for the synthesis of *N*-alkyl-3-oxo-2-aryl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole-1-carboxamide derivatives. It was the first use of 2-(2-formyl-1*H*-indol-1-yl)acetic acid in the aforementioned reaction.³⁸

Results and discussion

In continuation of our efforts to indole chemistry and multi-component reactions,^{39–41} we focused on the preparation of tetrahydro-pyrazino[1,2-*a*]indol-1-ones using the post-transformation of Ugi adducts, under metal-free conditions.

Despite the positive effect of the presence of transition metals on the yield of many organic reactions^{42,43} these reactions suffer from some limitations such as the high costs of metals and their removal from the reaction medium.²⁹ Considering these disadvantages and the low efficiency of the procedure in the absence of transition metals, we have reported an efficient base-mediated strategy for the preparation of new 1-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole-3-carboxamides.

In the first step, the Ugi condensation of aromatic aldehydes like cinnamaldehyde derivatives, anilines, 1*H*-indole-2-carboxylic acid and diverse isocyanides led to the formation of bis-amides in methanol (Table 1).

The prepared bis-amide products are unique due to the presence of several potent nucleophilic sites (Scheme 1a–e) and the leaving groups (Scheme 1f–h) that are located on Ugi products, so they are highly predisposed to intramolecular condensation. Because of the presence of these active sites, we tried to do a post sequential reaction of these Ugi adducts. Initially, the reaction was studied with **5a** (derived from cinnamaldehyde, 2-chloroaniline, 1*H*-indole-2-carboxylic acid and cyclohexyl isocyanide) as the model in the presence of Pd(OAc)₂/Ph₃P, K₂CO₃ under CH₃CN reflux conditions, but we did not

obtain any products (Table 2, entry 1). Changing the solvent to DMSO, provided **6a** with 80% yield (Table 2, entry 2). After the identification of the product, it was determined that only indole N–H alkylated one was formed among the possible products (based on their nucleophilic and electrophilic positions) (Scheme 1).

The *N*-alkylation and arylation of indole are a noteworthy tool for carbon–nitrogen bond formation, because of the vast application of N-heterocycles in natural products and bioactive drugs.^{44–46} To date, there have been several attempts at designing mild strategies towards *N*-alkylated indoles, under metal-catalyzed or catalyst-free conditions.^{46–48}

To continuation the optimization process, different metals/ligands like PdCl₂/Ph₃P and CuI/*L*-proline were studied, but no preference was observed compared to Pd(OAc)₂/Ph₃P (Table 2, entries 4 and 5).

Surprisingly, performing the reaction in the absence of metal/ligand did not show a significant decrease in the product yield (Table 2, entry 6, 78% yield for **6a**). In the next step, different temperatures of 50 °C, to 120 °C were investigated. According to the results, there was no remarkable yield difference between the reactions at 100 and 120 °C, but decreasing the temperature to 50 °C or to RT lowered the yields of the reactions (Table 2, entries 6–9). Then, the influence of diverse solvents was examined and the presence of DMSO showed the best effectiveness (Table 2, entries 7 and 10–12). Some alkaline metal bases were examined in order to comprehend the effect of the base nature. The metal bases mentioned in Table 2 (Na₂CO₃, K₂CO₃, Cs₂CO₃, KOH, KO*t*-Bu) showed very good positive results (entries 13–16), but a negative effect on yield was observed in the presence of triethylamine and diazabicyclo [2,2,2] octane (DABCO) as the organic bases, negative effect on the yield was observed (Table 2, entries 17 and 18). Additionally, performing the reaction in the absence of base led to the desired product **6a** with the yield of 32% (Table 2, entry 19).

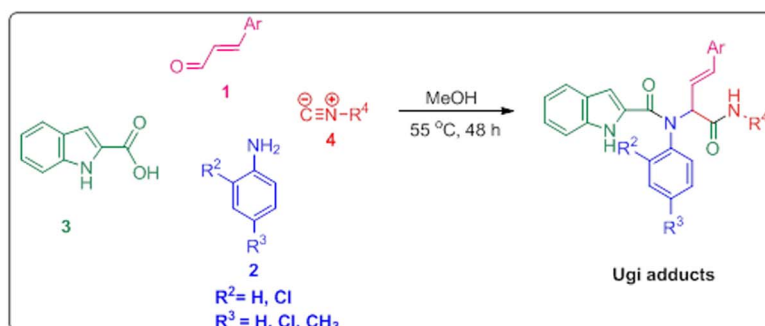
The scope of this Ugi-*N*-alkylation sequence process was explored under optimized reaction conditions (2 equiv. of Na₂CO₃ as base, DMSO as solvent, 100 °C temperature, 4 h) (Table 2, entry 7). The results are summarized in Table 3.

Ugi products (Table 3) containing electron-withdrawing and electron-donating substituents, reacted under optimum conditions to produce the desired product with moderate to excellent yield. Generally, the best results were obtained using electron-donating groups on cinnamaldehyde part (**6b**), and less bulky groups on isocyanide part (**6d**). Ugi products with bulky isocyanide like isopropyl and *t*-butyl showed less reaction efficiency (**6e**, **6f**). Product **6j** was also separated with excellent yield, but because of its low solubility in DMSO it could not be identified.

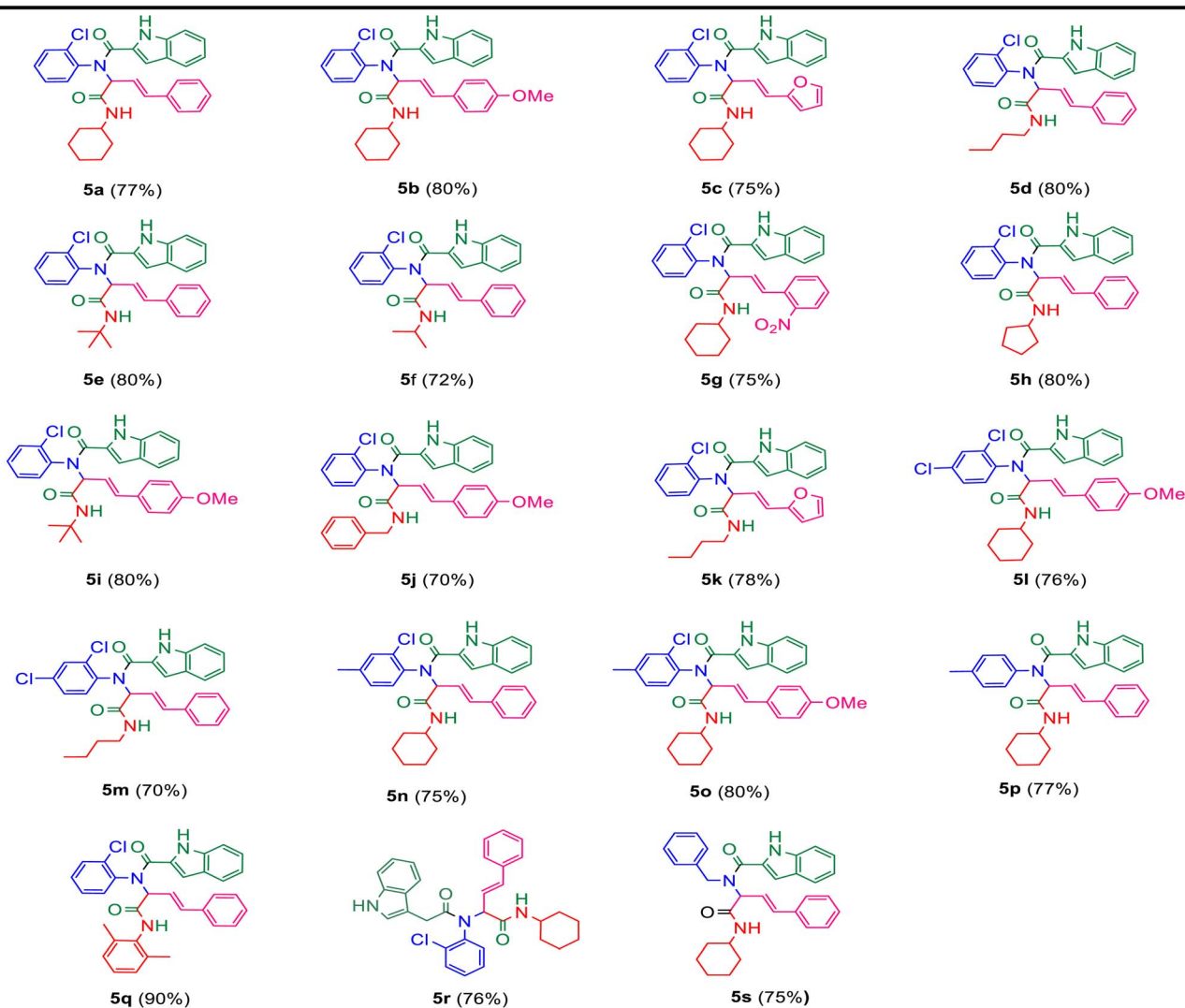
In order to investigate the possibility of the reaction in the absence of chlorine substitution on the aniline ring, we applied *p*-toluidine as amine instead of 2-chloroaniline in the Ugi reaction and product **5p** was obtained. This substrate, was treated with Na₂CO₃ under optimized reaction conditions and generated post-Ugi product **6p** with good efficiency.

Due to the presence of two chiral centers, two diastereomeric isomers were formed in the corresponding products, except for



Table 1 Synthesis of Ugi-adducts^{a,b,c}

Ugi adducts (5a–s)

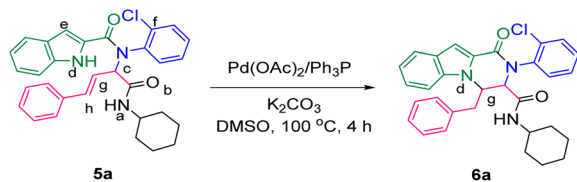


^a Reaction conditions: enals (1 mmol), anilines (1 mmol), 1H-indole-2-carboxylic acid (1 mmol) and isocyanides (1.1 mmol) in 5 mL methanol at reflux for 48 h. ^b Yields are reported for isolated products. ^c For 5r we used indole-3-acetic acid instead of indole-2-carboxylic acid.

the compounds **6m** and **6p**, in which only one diastereomer was obtained. It is worth mentioning that indole N-H alkylation was successfully performed without protection of the second N-H

function group. This issue is evident from the elimination of the indole N-H peak in the ¹H NMR spectrum.





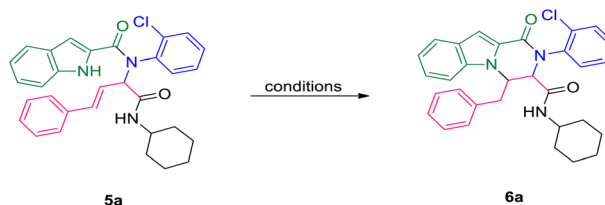
Scheme 1 Oxo-tetrahydro-pyrazino[1,2-*a*]indole-3-carboxamides synthesis. The nucleophilic sites are marked as (a–e), while the leaving groups are marked as (f–h).

The structure of compound **6b** was determined by X-ray crystallographic analysis to get a better view about the composition structure of these products. The X-ray diffraction data analysis revealed that **6b** got crystallized in monoclinic space group *P2₁/n*. The asymmetric unit is composed of two **6b** molecules (A and B) but, one of them (A) is partially disordered and thus only one molecule (B) is presented in Fig. 2. In the crystal structure, the 1*H*-indole-2-carboxylic, 2-chloroaniline and cinnamaldehyde derivative (4-methoxybenzene) rings are flat. The 2-chloroaniline and the 4-methoxybenzene rings are rotated from the plane of 1*H*-indole-2-carboxylic ring by 82.36(2) and 35.43(2)°, respectively. The planes of 2-chloroaniline and the 4-methoxybenzene are set at an angle of 64.41(2)° to each other. The Cremer and Pople ring-puckering parameters⁴⁹ *Q*, *θ* and *φ* (0.58 Å, 1.47°, 358.65° and 0.58 Å, 177.87°, 127.99° for molecule

A and B, respectively) calculated using program PLATON⁵⁰ for six-membered *N*-cyclohexylamide ring indicate its chair conformation. In the crystal structure, the molecules of **6b** are linked into chains running along the *b*-axis by N3–H3⋯O1ⁱ hydrogen bond [H⋯A = 2.01 Å, D⋯A = 2.867(5) Å, D–H⋯A = 164°, (i) *x*, *y* + 1, *z*] involving the atom H3 of the *N*-cyclohexylamide NH group as a donor and the carbonyl O1 atom of 1*H*-indole-2-carboxylic group as an acceptor (Fig. 3).

The analysis using PLATON⁵⁰ showed aromatic π–π stacking interactions were observed in the **6b** crystal between the centroids of 2-chloroaniline [C1A–C6A (Cg1A), C1B–C6B (Cg1B)] rings [Cg1A⋯Cg1B = 3.6965(17) Å, Cg1A⋯Cg1Bⁱ = 3.7408(17) Å, Cg1Aⁱⁱ⋯Cg1B = 3.7408(17) Å, (i) *x*, *y* + 1, *z*, (ii) *x*, *y* – 1, *z*]. A comparatively short distance was also found between the centroids of the 1*H*-indole-2-carboxylic [C10B–C15B (Cg2)] rings from the adjacent molecules [Cg2⋯Cg2ⁱⁱⁱ = 3.5383(16) Å, (iii) *x*, *y* + 1, *z*]. The crystal structure of **6b** compound is also stabilized by a few weak C–H⋯π interactions between the C14 atoms of the six-membered 1*H*-indole-2-carboxylic rings and the centroids of the 4-methoxybenzene [C26–C31 (Cg3)] rings: C14A–H14A⋯Cg3A [H⋯A = 2.93 Å, D⋯A = 3.4549(16) Å, D–H⋯A = 116°], C14B–H14B⋯Cg3B [H⋯A = 2.92 Å, D⋯A = 2.9991(15) Å, D–H⋯A = 105°]. As mentioned earlier, molecule A is partially disordered in the **6b** crystal structure and this disorder includes the 4-methoxybenzene ring (C26C–C31C, Cg3C). Thus, the following C–H⋯π interaction was also

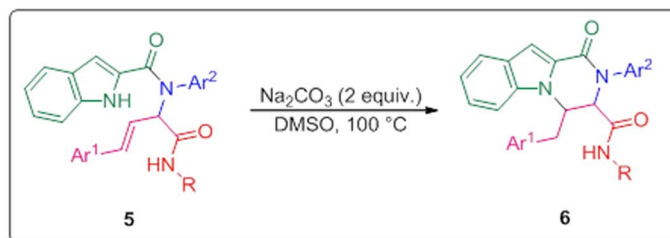
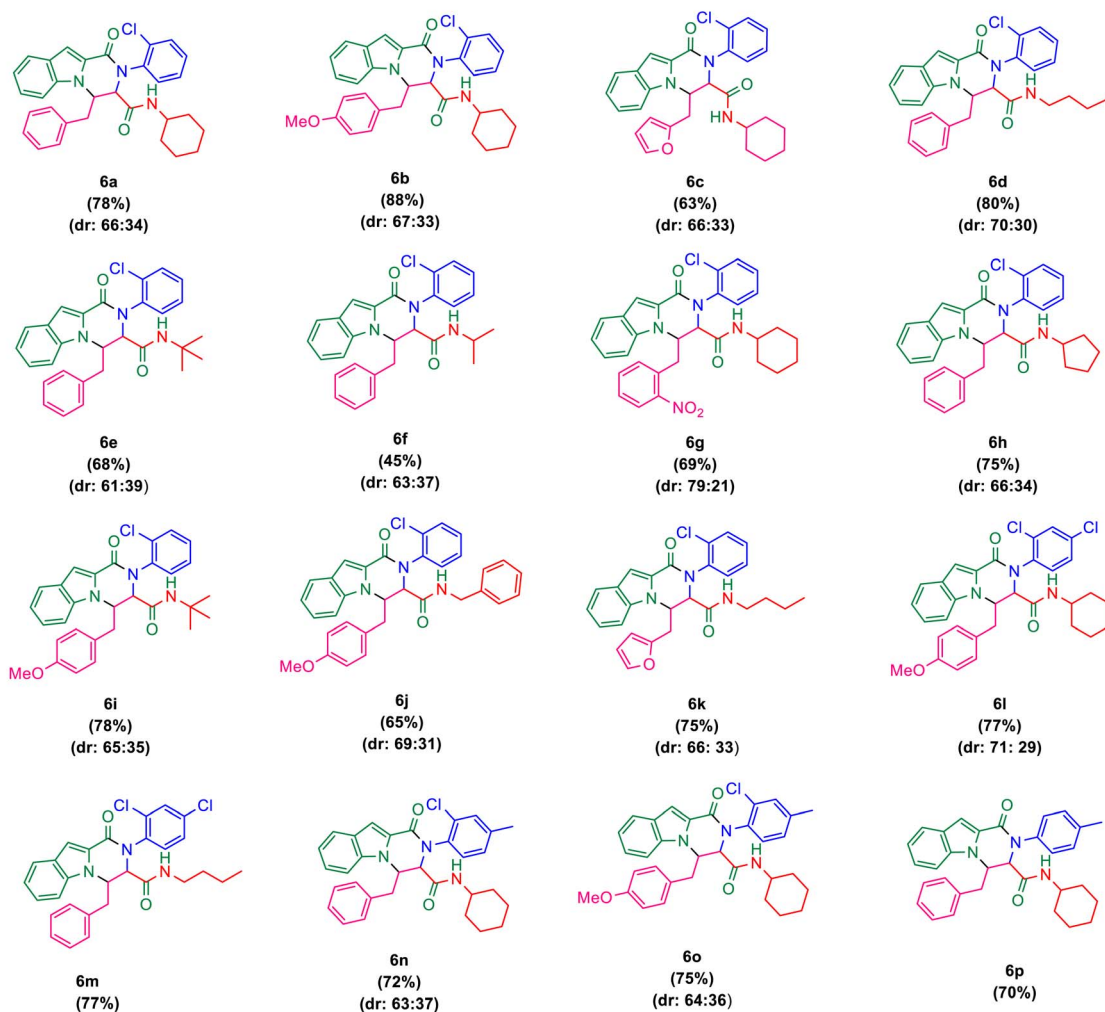
Table 2 Scope of optimization conditions for the synthesis of **6a**^a



Entry	Cat/ligand	Solvent	Base	Temp (°C)	Time (h)	Yield ^b (%)
1	Pd(OAc) ₂ /Ph ₃ P	CH ₃ CN	K ₂ CO ₃	82	4	—
2	Pd(OAc) ₂ /Ph ₃ P	DMSO	K ₂ CO ₃	120	4	80
3	Pd(OAc) ₂ /Ph ₃ P	DMSO	Na ₂ CO ₃	120	4	80
4	PdCl ₂ /Ph ₃ P	DMSO	Na ₂ CO ₃	120	4	75
5	CuI/ <i>L</i> -proline	DMSO	Na ₂ CO ₃	120	4	76
6	—	DMSO	Na ₂ CO ₃	120	4	78
7	—	DMSO	Na₂CO₃	100	4	78
8	—	DMSO	Na ₂ CO ₃	50	4	50
9	—	DMSO	Na ₂ CO ₃	Rt	4	25
10	—	1,4-Dioxane	Na ₂ CO ₃	100	4	—
11	—	PhCH ₃	Na ₂ CO ₃	100	4	—
12	—	DMF	Na ₂ CO ₃	100	5	63
13	—	DMSO	K ₂ CO ₃	100	4	75
14	—	DMSO	Cs ₂ CO ₃	100	4	70
15	—	DMSO	KO ^{<i>t</i>} -Bu	100	4	70
16	—	DMSO	KOH	100	4	76
17	—	DMSO	Et ₃ N	100	5	46
18	—	DMSO	DABCO	100	5	46
19	—	DMSO	—	100	4	32

^a Conditions: **5a** (0.5 mmol), metal (10 mol%), ligand (20 mol%), base (2 equiv.), solvent (4 mL). ^b Isolated yields.



Table 3 Synthesis of tricyclic products **6** via a post-Ugi cyclization^aPost-Ugi adducts **6a–p** (reaction time–yield^b–diastereomeric ratio^c)

^a Reaction conditions: **5** (0.5 mmol), Na₂CO₃ (1 mmol) in 2.5 mL DMSO at 100 °C. ^b Isolated yields. ^c Diastereomeric ratio was reported from the ¹H NMR spectra.

observed: C14A–H14A...Cg3C [H...A = 2.86 Å, D...A = 3.2470(15) Å, D–H...A = 106°]. Additionally, the atoms of the ordered (molecule B) methoxy group of 4-methoxybenzene part are also involved in a weak C–H...π contact with the centroid of

the five-membered 1*H*-indole-2-carboxylic [N2A–C15A (Cg4A)] ring: C32B–H32E...Cg4A^{iv} [H...A = 2.94 Å, D...A = 3.7385(17) Å, D–H...A = 139°, (iv) $x - 1/2, -y + 1, z - 1/2$].



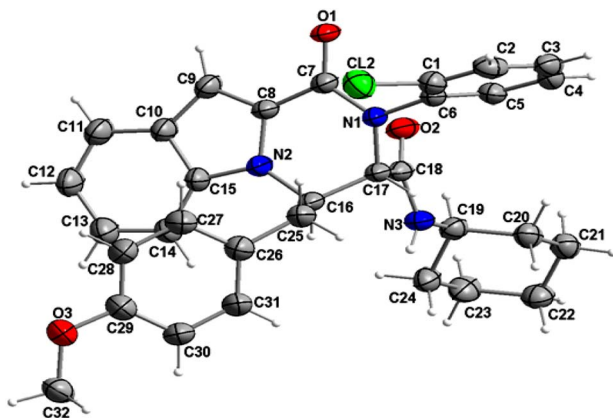


Fig. 2 Crystal structure of the **6b** molecule showing the atom-numbering scheme and displacement ellipsoids drawn at the 50% probability level. The partially disordered molecule A was removed for clarity.⁵¹

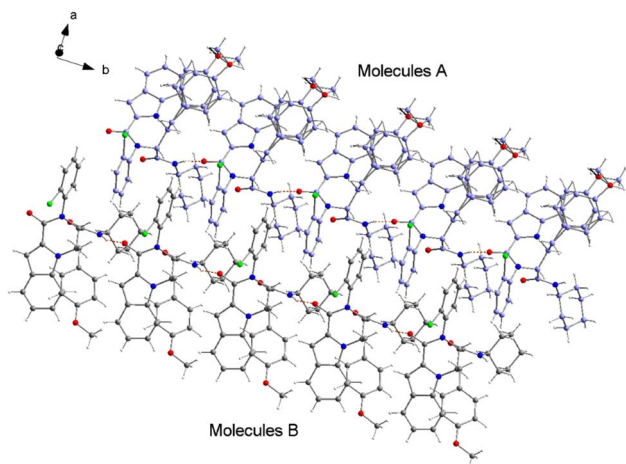
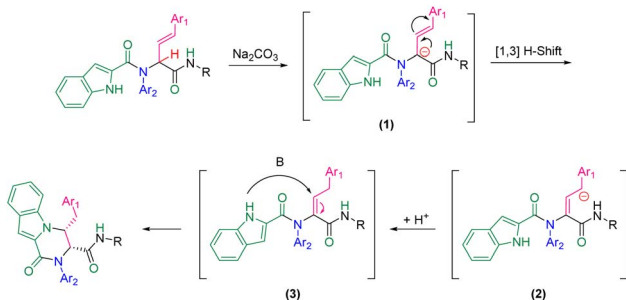


Fig. 3 A part of crystal packing of **6b** showing the chain along *b*-axis formed by N–H...O hydrogen bonds (depicted as orange dashed lines). The carbon atoms are shown in gray for molecules B and in lilac for the partially disordered molecules A.

A plausible mechanism for this diastereoselective cyclization is presented in Scheme 2 based on the experimental results. First, carbanionic intermediate (**1**), is formed by the addition of base to Ugi substrate. The destabilization of carbanion (**1**)



Scheme 2 A plausible mechanism for the cyclization step of Ugi adducts.

followed by neutralization led to intermediate (**3**). This intermediate can undergo intramolecular nucleophilic attack by the nitrogen atom of the indole moiety to generate the final product via a 6-*endo-trig* cyclization.

Conclusion

In summary, we have reported a new sequential Ugi reaction/NH-alkylation for the synthesis of novel tricyclic oxo-tetrahydropyrazino[1,2-*a*]indole-3-carboxamide derivatives. Various enals, anilines and isocyanides were subjected to this protocol and the products were obtained with high selectivity. Simple procedure, high yield of all products, chemo- and diastereoselectivity and metal-free condition are the main advantages of this method that can make it a practical synthetic route for the preparation of pyrazinoindolone derivatives.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors express their gratitude to Alzahra University and the Iran National Science Foundation (INSF) for the financial support of our research project. We are also grateful to Prof. Dr Tadeusz Lis for his assistance in single crystal X-ray data collection and the crystallographic part.

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- 51 CCDC 2249611† contains the supplementary crystallographic data for this paper.

