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Synthesis of fused polycyclic nitrogen-containing heterocycles via cascade cyclization☆

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Abstract—A novel strategy for the synthesis of fused polycyclic-nitrogen containing heterocycles via cascade cyclization is described. The methodology involves condensation of 1-(2-aminophenyl)-9*H*-β-carboline-3-carboxylic acid amide with isothiocyanates followed by in situ treatment of the resulting thioureas with $HgCl_2$ for 1 h at rt. The one-pot cascade cyclization leads to interesting changes in molecular structure and an increase in molecular complexity. A mechanistic rationale for the cascade cyclization is discussed.

Natural products have had a profound impact upon both chemical biology and drug discovery. One such example is the tetrahydro-β-carbolines, which are found abundantly in the plant and animal kingdom, and many of them exhibit potent biological activities.[1–5] This group of indole alkaloids are widely distributed among 23 angiosperm plant families, the original source being *Peganum harmala*.[1] In addition to the diverse biological activity of the naturally occurring compounds, synthetically derived β-carbolines also exhibit significant bioactivity.[6] The reported effects of this class of compound comprise antineoplastic (tubulin binding),[6,7] anticonvulsive, hypnotic and anxiolytic (benzodiazepine receptor ligands),[8,9] antiviral,[1] antimicrobial[5] as well as topoisomerase-II inhibition[10] and inhibition of cGMP-dependent processes.[11] In addition to this, the β-carboline nucleus is also present in a variety of alkaloids isolated both from terrestrial plants[12] and marine organisms[13] with antiplasmodial activity. Waldmann and co-workers[14] strongly advocate the need for staying close to natural products when it comes to designing small-molecule chemical probes. The rationale behind this philosophy is that natural products have gone through the evolutionary process, and thus serve as a useful guiding principle for developing clinical candidates.

In view of our continued interest in the development of novel antimalarial agents derived from natural products,[15,16] we were interested in the synthesis and screening of β-carboline derivatives for which we required intermediate **Ia** (Scheme 1). However, our attempts to synthesize **Ia** led to fused polycyclic nitrogen-containing heterocycles via cascade cyclizations. The details of our findings are presented in this letter.

The synthesis of **Ia** was attempted by treating 1-(2-amino-phenyl)-9*H*-β-carboline-3-carboxylic acid amide **1a** (1 equiv) with isothiocyanate (1.2 equiv) in DMSO at room temperature (Scheme 1, route 1). The progress of the reaction was monitored by both TLC and HPLC. The reaction was found to be complete within 2 h and the product was found to be a mixture of two components with traces of unreacted isothiocyanate as the third component. The HPLC exhibited a major peak in 82% yield (area under the curve) and a minor component in 8% yield. The reaction was worked-up by precipitating the product with water followed by extraction with ethyl acetate. The organic layer was dried over Na_2SO_4 and during its evaporation on a rotavapor, the foul smell of H_2S was noted. This led us to reexamine the purity of the crude product by TLC and HPLC, which showed an increase in the concentration of the minor component to 67% from 8% before work-up.

Keywords: β-Carbolines; Fused polycyclic indoles; Cyclodesulfurization; Cascade cyclization.
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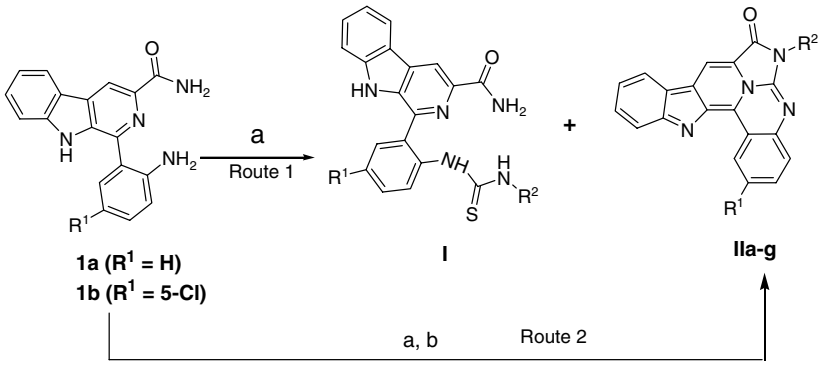


Scheme 1. Reagents and conditions: (a) R^2NCS (1.2 equiv), DMSO, rt, 2 h; (b) $HgCl_2$, Et_3N, rt, 1 h.

Interestingly, the major peak observed before work-up was now reduced to 23%. We envisaged that evaporation of the solvent at 50 °C may have triggered the transformation. The two components were separated by column chromatography and characterized by FAB mass, NMR and X-ray diffraction crystallographic studies. One of the components with a lower R_f on TLC was obtained in 16% isolated yield (mass of 450 Da) and was found to be thiourea **Ia** (Scheme 1, route 1). The second component with a higher R_f was obtained in 56% isolated yield (mass of 400 Da) and was identified by X-ray diffraction crystallographic studies as a fused polycyclic nitrogen-containing heterocyclic compound **IIa** (Scheme 1) probably derived from **Ia** via cascade cyclization. Of these two, thiourea **Ia** had only moderate stability, because even after purification, it had a tendency to undergo slow conversion to the cyclized product **IIa**. The X-ray structure of **IIa** is depicted in Figure 1.[17]

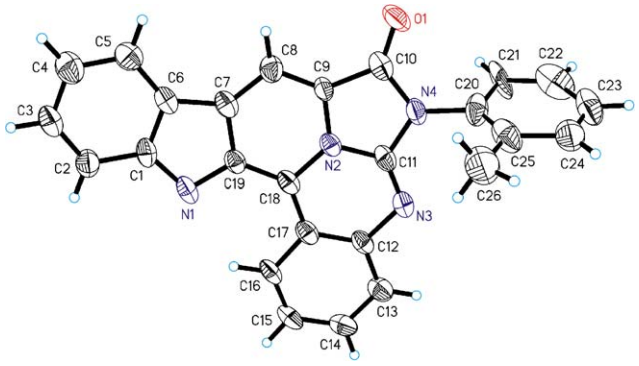


Figure 1. ORTEP plot of the molecular structure of compound **IIa** (at 30% probability level).

A survey of the literature revealed **IIa** to be a new family of indole based polycycles produced by sequential intramolecular guanylation via cyclodesulfurization followed by transamidation/cyclization in one-pot. A plausible mechanism for the formation of **IIa** from **Ia** is depicted in Figure 2. The reaction commences with nucleophilic attack on the thioureido carbon, which results in an intermediate with a delocalized positive charge (represented by two canonical forms). This then triggers the release of a proton from N_a and allows the formation of the quinazoline ring with the release of H_2S. This is then followed by a second cyclization between the carboxamide and the NH attached to the quinazoline ring via transamidation with the release of NH_3. Since by HPLC we could not observe the quinazoline intermediate **III** (Fig. 2) arising from the first cyclization, this led us to believe that intermediate **III**, though formed slowly from **Ia**, appears to be highly reactive. The second cycli-

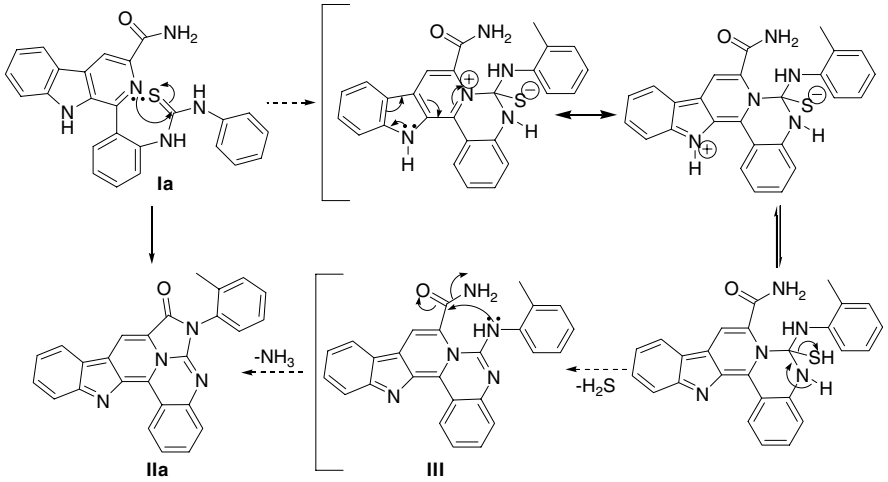


Figure 2. Proposed mechanism for the formation of **IIa** from **Ia**.

Table 1. Optimization of **IIa** formation from **1a**

Entry	Reaction conditions	**IIa**[a] (%)	**Ia**[a] (%)
1	**1a** + *o*-Tolyl isothiocyanate, at 80 °C, 12 h	68	26
2	**1a** + *o*-Tolyl isothiocyanate + $HgCl_2$ (1 equiv) heating at 60 °C, 6 h	70	20
3	**1a** + *o*-Tolyl isothiocyanate, 2 h then $HgCl_2$ (1 equiv), rt, 6 h	82	12
4	**1a** *o*-Tolyl isothiocyanate, 2 h then $HgCl_2$ (1 equiv), Et_3N (2 equiv), rt, 1 h	93	0

[a] Based on HPLC of the crude reaction product.

zation furnishing the polycyclic framework **II** from **III**, however, appears to be both easy and rapid. Polycyclic indolic compounds are the targets of extensive synthetic interest, partly because there are many biologically active natural products of this type, and also because the polycyclic frameworks lead to relatively rigid structures that might be expected to show substantial selectivity in their interaction with enzymes or receptors. This prompted us to develop a suitable strategy to effect cascade cyclization in quantitative yields.

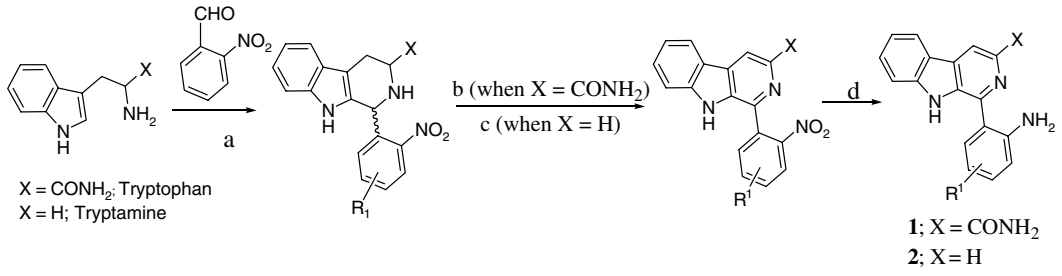
In view of the slow and incomplete conversion of **I** to **III**, we directed our efforts towards this cyclization involving guanylation via cyclodesulfurization. In the first instance, based on our initial observation that heating triggered the cascade cyclization, we treated **1a** with isothiocyanate at 80 °C and monitored the progress of the reaction by HPLC. Unfortunately, even after prolonged heating for 24 h, the final product **IIa** could still only be obtained in 68% yield along with **Ia** (Table 1, entry 1). This led us to add reagents that are known to catalyze guanylation via desulfurization and accordingly we selected $HgCl_2$ for this purpose.[18] We carried out the reaction of **1a** with isothiocyanate (1.2 equiv) in the presence of $HgCl_2$ and monitored the progress of reaction by HPLC. Optimization of the reaction led to room temperature conditions in two steps (Table 1, entry 4).

Table 2. Compounds (**II**) prepared via Scheme 1 (route 2)

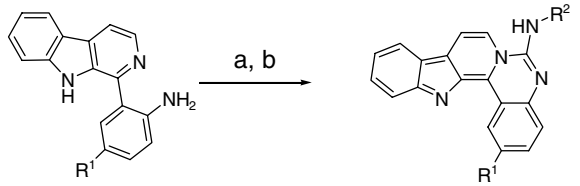
Compound	R^1	R^2	Isolated yield (%)	FAB (M^++1)
IIa	H	2-$CH_3C_6H_4$	85	401
IIb	H	C_6H_5	72	387
IIc	H	4-$FC_6H_4CH_2$	74	419
IId	5-Cl	2-$CH_3C_6H_4$	70	435
IIe	5-Cl	C_6H_5	75	421
IIf	5-Cl	4-$FC_6H_4CH_2$	76	453
IIg	H	*n*-C_4H_9	80	367

In the first step, **1a** is allowed to react with isothiocyanate (1.2 equiv) at rt for 2 h and in the second step, the resulting thiourea **Ia** is treated in situ with $HgCl_2$ (1 equiv) and Et_3N (2 equiv) for 1 h at rt (Scheme 1, route 2).[19] We were pleased to observe complete conversion of thiourea **Ia** into **IIa** within 1 h, along with traces of unreacted isothiocyanate. The crude product was purified by silica gel column chromatography to give **IIa** in 85% isolated yield. The scope and limitation of the method was established by synthesizing six compounds **II** by varying the isothiocyanates (aryl and alkyl) and *o*-nitrobenzaldehydes (Table 2). Starting β-carbolines **1** were synthesized (Scheme 2) by treating Trp-amide with *o*-nitrobenzaldehydes under Pictet–Spengler conditions.[20] The resulting tetrahydro-β-carboline was then oxidized with $KMnO_4$ to give β-carbolines.[21] Subsequently, the nitro group was reduced to the amine by hydrogenation in the presence of Pd/C to furnish **1**. Substitution on the aryl aldehydes or isothiocyanates did not have any affect on the yields and purities of **II**. Next, we extended our methodology to tryptamine, as this would result in compounds **IV** via single cyclization (Scheme 3), again a class of β-carboline derived compounds hitherto unknown. Interestingly, compounds **IV** appear to structurally resemble the yohimbane/reserpine backbone.[22] The precursor 1-(2-aminophenyl)-9*H*-β-carboline **2** derived from tryptamine (Scheme 2) by the literature procedure[23] was treated with isothiocyanates in the presence of $HgCl_2$ to furnish **IV** in high yields (Scheme 3, Table 3).

In summary, we have developed a mild and versatile approach for the synthesis of a structurally unique group of fused polycyclic β-carboline based heterocycles in high yield and purity. The one-pot cascade cyclization



Scheme 2. Reagents and conditions: (a) 2% TFA in DCM, rt, 7 h; (b) $KMnO_4$, THF, 0 °C, 30 min; (c) S, DMSO, 100 °C, 48 h; (d) 10% Pd/C, MeOH, 30 psi, 2 h.



2 (R^1 = H) **IV a-d**

Scheme 3. Reagents and conditions: (a) R^2NCS (1.2 equiv), DMSO, rt, 2 h; (b) $HgCl_2$, Et_3N, rt, 1 h.

Table 3. Compounds (**IV**) prepared via Scheme 3

Compound	R^1	R^2	Isolated yield (%)	FAB (M^++1)
IVa	H	2-$CH_3C_6H_4$	80	375
IVb	H	C_6H_5	77	361
IVc	H	$C_6H_5CH_2$–	74	375
IVd	H	*n*-C_4H_9	79	341

leads to interesting changes in molecular structure and an increase in molecular complexity.

Acknowledgements

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17. *Crystal data for* **IIa**: $C_{26}H_{16}N_4O$, $M = 400.43$, mp > 300 °C, triclinic, $P1$, $a = 8.468(2)$, $b = 11.229(2)$, $c = 11.557(2)$ Å, $\alpha = 90.13(1)$, $\beta = 109.67(1)$, $\gamma = 111.90(1)°$, $V = 949.8(3)$ Å^3, $T = 293(2)$ K, $Z = 2$, $D_c = 1.400$ g cm^{-3}, $\mu = 0.88$ mm^{-1}, $F_{(000)} = 416$, λ (Mo K_α) = 0.71073 Å, reddish block, crystal size $0.250 \times 0.125 \times 0.050$ mm, 3069 reflections measured ($R_{int} = 0.0676$), 2325 unique, $R1 = 0.0677$ for 819 $Fo > 4\sigma(Fo)$ and 0.2149 for all 2325 data, $S = 0.919$ for all data and 281 parameters. Unit cell determinations and intensity data collection ($2\theta = 44.16°$) were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix-least-squares methods on F^2. Programs: XSCANS [(Siemens Analytical X-ray Instruments Inc.: Madison, Wisconsin, USA 1996) were used for data collection and data processing], SHELXTL-NT [(Bruker AXS Inc.: Madison, Wisconsin, USA 1997) was used for structure determination, refinements and molecular graphics]. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC deposit No. 297367).
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19. *Representative procedure* **IIa/IVa**: To a solution of **1a** or **2** (0.33 mmol) in dry DMSO (5 mL) was added *o*-tolyl phenylisothiocyanate (98 μL, 0.66 mmol) and the mixture was stirred for 2 h. Then, triethylamine (91 μL, 0.66 mmol) and $HgCl_2$ (90 mg, 0.33 mmol) were added to the reaction mixture which was stirred for 1 h. To the mixture was added EtOAc (5 mL) and stirring continued for an additional 5 min. After this, the mixture was poured in cold water and an additional amount of EtOAc (50 mL) was added and the mixture filtered through a bed of Celite®. The organic layer was separated, washed with water and dried over Na_2SO_4. It was then evaporated to dryness under reduced pressure and the crude red residue so obtained was purified by column chromatography on silica gel (100–200 mesh) using chloroform as an eluent to afford **IIa** or **IVa**.
Compound **IIa**: red solid; mp > 300 °C; IR ν_{max} (KBr) 1649 cm^{-1}; ^{1}H NMR (600 MHz, DMSO): $\delta = 8.68$ (d,

$J = 7.8$ Hz, 1H, ArH), 8.14 (d, $J = 8.4$ Hz, 1H, ArH), 8.12–8.10 (overlapped, 2H, ArH), 8.08–8.06 (m, 2H, ArH), 7.72 (t, $J = 7.2$ Hz, 1H, ArH), 7.63 (d, $J = 8.4$ Hz, 1H, ArH), 7.57–7.56 (overlapped, 3H, ArH), 7.50–7.48 (m, 1H, ArH) 7.45 (t, $J = 7.2$ Hz, 1H, ArH), 2.30 (s, 3H, CH_3). Anal. Calcd for $C_{26}H_{16}N_4O$: C, 77.99; H, 4.03; N, 13.99. Found: C, 77.75; H, 4.27; N, 13.84.

Compound **IVa**: brown solid; mp > 250 °C; IR ν_{max} (KBr) 3426 cm^{-1}; ^1H NMR (600 MHz, DMSO): $\delta = 8.90$ (d, $J = 6.6$ Hz, 1H, ArH), 8.57 (d, $J = 7.8$ Hz, 1H, ArH), 8.02 (d, $J = 8.4$ Hz, 1H, ArH), 7.84–7.81 (m, 3H, ArH), 7.59 (br s, 1H, NH), 7.53–7.51 (m, 3H, ArH), 7.37–7.33 (m, 3H, ArH), 7.37 (t, $J = 7.8$ Hz, 1H, ArH), 7.34 (t, $J = 7.2$ Hz, 1H, ArH), 2.67 (s, 3H, CH_3). Anal. Calcd for $C_{25}H_{18}N_4$: C, 80.19; H, 4.85; N, 14.96. Found: C, 80.55; H, 4.77; N, 14.84.

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