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Expedient one-pot synthesis of indolo[3,2-*c*]isoquinolines via a base-promoted *N*–alkylation/tandem cyclization

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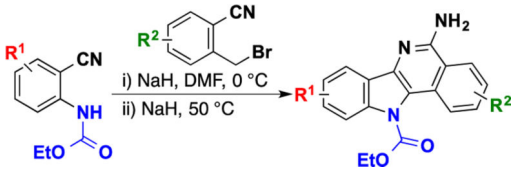
Abstract

A transition metal-free, one-pot protocol has been developed for the synthesis of 11*H*-indolo[3,2-*c*]isoquinolin-5-amines via the atom economical annulation of ethyl (2-cyanophenyl)carbamates and 2-cyanobenzyl bromides. This method proceeds via sequential *N*–alkylation and base-promoted cyclization. Optimization data, substrate scope, mechanistic insights, and photoluminescence properties are discussed.

Graphical Abstract



Keywords

indolo[3,2-*c*]isoquinoline; one-pot; tandem cyclization; photoluminescence; domino process

1. Introduction

Indoles and quinolines are ubiquitous heterocyclic scaffolds appearing in numerous natural products and synthetic pharmaceuticals. The family of indoloquinoline alkaloids depicted in Figure 1 has been isolated from the root bark extracts of *Cryptolepis sanguinolenta* (Asclepiadaceae), a Ghanaian medicinal shrub native to West Africa.[1] Well-recognized as components in traditional folk remedies for malaria, these alkaloids display interesting

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Supplementary Material

Experimental procedures and characterization data for novel compounds; X-ray structure of compound **9a**. This material is available free of charge via the Internet at http://dx.doi.org/10.1016/j.tetlet####.

pharmacology – for example, expressing hypotensive, antibacterial, anti-fungal, anti-plasmodial, antipyretic, and anti-inflammatory activities.[2] Further, recent studies have shown that cryptolepine is a potent cytotoxic agent, which binds to DNA in a base-stacking intercalation mode.[3]

Because of their remarkable therapeutic potentials, the synthesis of indoloquinoline derivatives has attracted considerable attention from the synthetic community.[4] In this report, we were particularly interested in 11*H*-indolo[3,2-*c*]isoquinoline, a close relative of cryptolepine and isocryptolepine. Our literature survey revealed only a few synthetic approaches to this unique motif, and further functionalized derivatives are rarely reported.[5] These existing methods generally require multiple prefunctionalizations of requisite indole or isoquinoline starting materials (Scheme 1). For example, Black and co-workers demonstrated a flexible route to **1** via the acid-catalyzed cyclization of 3-amido-2-phenylindoles[5a] and Timari presented a concise synthesis of **2** by thermal cyclization of 2-azidophenylisoquinoline.[5b] Both are effective, but utilize moderately harsh conditions and involve multi-step precursor preparations.

With the ascendency of organometallic catalysis in modern organic synthesis, metal-catalyzed cross-coupling C–N/C–C bond formations have become a powerful tool for constructing heterocyclic structures.[6] In that context, the Maes group described an interesting assembly of **2** in two steps via a Buchwald–Hartwig amination followed by a Pd-catalyzed intramolecular arylation.[5c] Importantly, the Kalugin group reported the transition metal-free two-step synthesis of benzofuro[3,2-c]isoquinolin-5-amine **3** from 2-cyanophenol.[5d] Building on that work, we believed that an appropriate method could be developed for the facile construction of indolo[3,2-c]isoquinoline from readily available reagents.

Recently, our group has exploited the atom and step-economy of tandem/domino and multicomponent reactions to assemble complex heterocyclic skeletons.[7] These strategies provide a rapid means to introduce molecular complexity by enabling multiple bond forming events to occur in one simple operation – thus avoiding the inconvenience of intermediate purifications.[8] Herein, we report the base-promoted tandem annulation of ethyl (2-cyanophenyl)carbamate derivatives with 2-(bromomethyl)benzonitriles as a one-pot route to amine-functionalized indoloisoquinolines (Scheme 2a). To the best of our knowledge, this is the first report on the synthesis of 11*H*-indolo[3,2-*c*]isoquinolin-5-amines.

2. Results and Discussion

We commenced initial screening by examining the feasibility of the reaction between 2-aminobenzonitrile and 2-(bromomethyl)benzonitrile in the presence of strong base (KO^tBu in DMF; Scheme 2b) – conditions adapted from the work of Li et al.[9] Based on Kalugin's work,[5d] we envisioned that S_N2 displacement would lead to intermediate **4**, which would be subsequently deprotonated *in situ* by KO^tBu. The resultant benzylic anion would then attack the aniline ring nitrile and trigger the annulation process in a cascade fashion. Unfortunately, this *N*–alkylation/tandem cyclization furnished the expected tetracyclic core **5** in low yield and as a complicated reaction mixture. LCMS analysis revealed a significant amount of

aniline remained post-reaction, suggesting that weak nucleophilicity of the 2-aminobenzonitrile results in an incomplete S_N2 reaction. Presumably the NH moiety of **4**, exhibiting a lower pK_a than benzylic protons, might undergo deprotonation in this basic environment forming the amide anion, which could then attack electrophilic sites to form side products. In order to circumvent these hypothesized difficulties, we decided to modify the NH_2 moiety on the starting aniline with an appropriate protecting group (PG) – one easy to install, compatible with the desired transformations, and readily removed after cyclization. Among *N*–alkyl, *N*–acyl, and *N*–carbamoyl PGs, we found *N*–ethylcarbamoyl was the most satisfactory as treating ethyl (2-cyanophenyl)carbamate and the benzylic bromide with stoichiometric KO^{t}Bu or NaH in DMF at 0 °C cleanly delivered **8a** in quantitative yield within 1.5 h (Scheme 2c). With this result in hand, we turned our attention to an investigation of optimal conditions for the annulation using **8a** as the model substrate (Table 1).

KO^{t}Bu achieved the desired transformation, but afforded **9a** in only 27% yield (entry 1). Examination of other bases revealed that NaH gave the best efficiency in terms of yield and clean reaction mixture. Cyclization was sluggish with LiHMDS and ineffective with K_2CO_3 and DBU, resulting in low conversion (entries 7–9). Among the solvents tested, DMF was superior to THF and MeCN (entries 5,6). Notably, stoichiometric NaH was essential for complete conversion. Also, prolonged stirring has a detrimental effect on the overall yield (entry 3) with **9a'**, the *N*-deprotected indoloisoquinolines, being the major product. When the reaction was conducted with NaH/DMF at 50 °C for 30 min, the best conversion was achieved with minimal formation of **9a'** (entry 4); therefore, these conditions were found optimal. The structure of tetracyclic product **9a** (Table 1) was unambiguously established by X-ray crystallographic analysis.[10]

This mild and efficient annulation (**8a** → **9a**) encouraged us to explore combining the robust S_N2 reaction with the subsequent cyclization steps to give a one-pot cascade synthesis of **9**. With effective sodium hydride mediation of both steps established (see Scheme 2 and Table 1), we set out to explore the scope and generality of this method for transforming appropriate carbamates **6** and bromides **7** into substituted 11*H*-indolo[3,2-*c*]isoquinolin-5-amines **9**.

We first examined the effects of a variety of R^1 substituents on the one-pot process (Scheme 3). Ethyl (2-cyanophenyl)carbamates possessing either e-donating or e-withdrawing substituents are well-tolerated, affording the desired products in moderate to good yields (**9a**–**h**). Aryl halides (F / Cl / Br) are accommodated by the transformation and provide the possibility of further functionalization via various coupling reactions. It was found, in general, that e-rich anilines displayed retarded reactivity, resulting in lower yields than e-deficient substrates (cf., **9g** in 45% vs **9d** in 57%). A cyclic-*β*-enaminonitrile reacted smoothly to deliver **9i** in 66%, and a pyridyl substrate was converted to 11*H*-pyrido[3',2':4,5]pyrrolo-[3,2-*c*]isoquinolin-5-amine (**9n**) in 68% yield. A limitation of this protocol was revealed with a thiophenyl substrate, which failed to undergo cyclization (→ **9o**) resulting in recovery of the S_N2 intermediate. We next surveyed benzyl bromide R^2 substituents. The presence of an e-withdrawing fluorine substituent slightly lowers yields (**9j-l**) and, in the case of an e-donating methoxy, the S_N2 intermediate leads to **9m** in only a trace amount.[11]

With various analogs of indoloisoquinolines **9** in hand, we set out to establish a practical *N*–deprotection method since most indoles require the free N–H to be biologically active. Fortunately, removal of the *N*–ethylcarbamate group can be achieved by simply treating a solution of **9** with LiOH at ambient temperature, which affords the free indolyl nitrogen in quantitative yield (Scheme 4). These conditions were found to be applicable to substrates with various substituents.

A plausible mechanism for the base-promoted tandem cyclization is depicted in Scheme 5. Initial abstraction of a benzylic hydrogen by NaH generates benzylic anion intermediate **A**, which subsequently attacks the aniline-derived nitrile (→ **B**). Tautomerization furnishes 3-aminoindole **C** through which intramolecular nucleophilic attack onto the benzylic bromide-derived nitrile delivers **D**. Finally, tautomerization (→ **E**) and protonation deliver **9a**.

Finally, we examined the photophysical properties of these novel indoloisoquinolines (UV −vis and fluorescence spectral data for **9a** and **10a** in DCM are illustrated in Figure 2). Compound **9a** has a maximum absorption at 341 nm, which can be ascribed to an aromatic π–π* transition. As expected, removal of the carbamate moiety increases the availability of π-electrons on the indolyl nitrogen for easier conjugation with the isoquinoline, thus possibly explaining the bathochromic shift [**9a** (341 nm) → **10a** (367 nm)]. Both compounds displayed strong fluorescence in the blue-green region (400-500 nm) and a red-shift trend was observed for fluorescence (**9a** → **10a** ‖ 425 nm → 452 nm).

3. Conclusion

In conclusion, a transition metal-free and operationally simple one-pot protocol for the synthesis of 11*H*-indolo[3,2-*c*]isoquinolin-5-amines has been developed starting from readily available ethyl (2-cyanophenyl)carbamates and 2-cyanobenzyl bromides. This mild and efficient method proceeds via base-promoted *N*–alkylation and cyclization steps to forge novel indoloisoquinolines via a domino process that features atom and step economy as well as broad substrate scope. Photophysical studies demonstrate that this class of compounds affords potentially useful fluorophore properties.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors dedicate this work to Roland J. Kurth, a wonderful and gracious mentor, on the occasion of his 89th birthday. Financial support provided by the National Institutes of Health (DK072517 and GM089153) and the National Science Foundation (CHE-080444; for the Dual source X-ray diffractometer). We also thank Teresa A. Palazzo (Kurth Group), Dong hee Chung (Toney Group), Alexandra L. Holmes (Kauzlarich Group) at UC Davis for assistance in the collection of HRMS, UV–Vis, and fluorescence data, respectively.

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10. The X-ray crystal structure revealed intermolecular N–H···O bonding. See SI for details.
11. The cyclization was sluggish even in the presence of 3 equivalents of NaH.

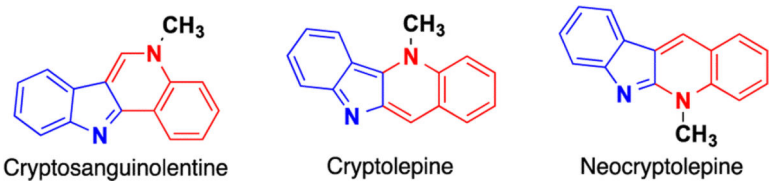
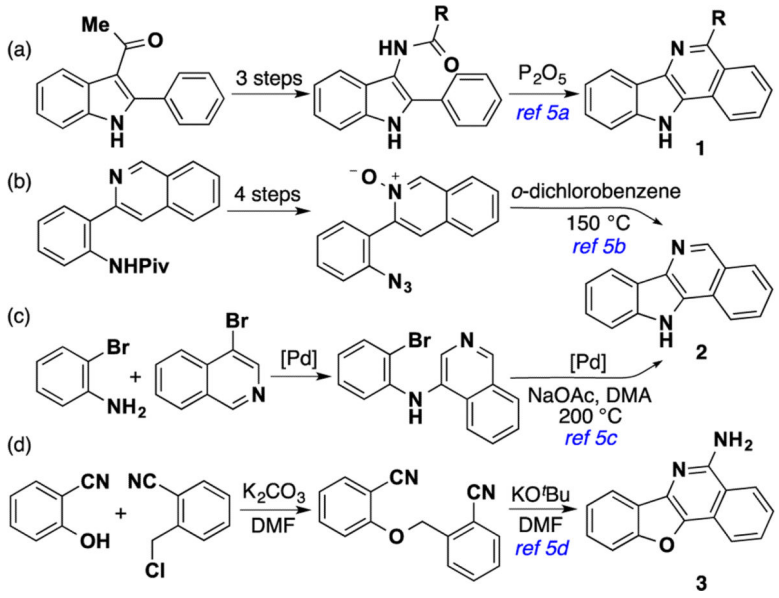
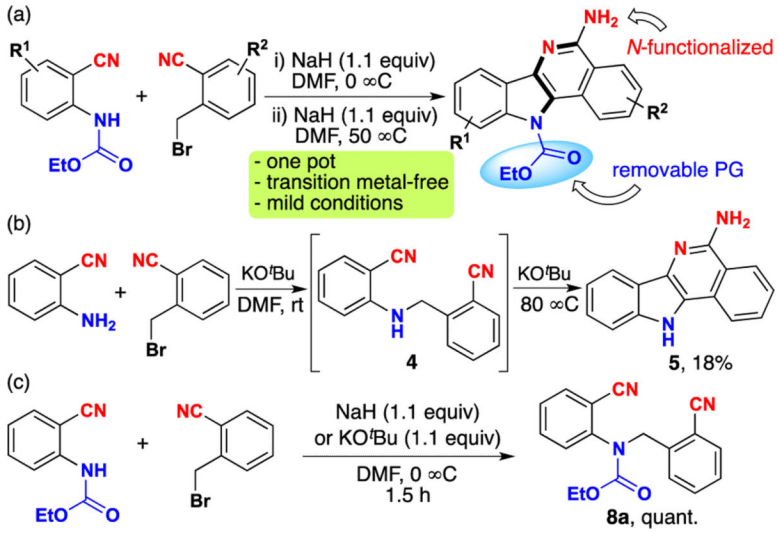


Figure 1.
Bioactive examples of indoloquinoline alkaloids.



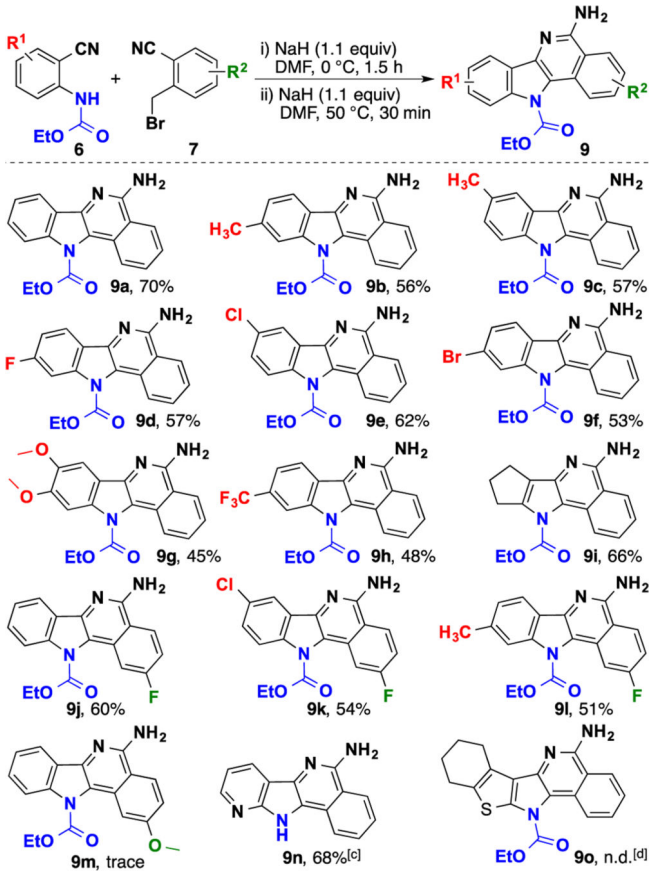
Scheme 1.

Reported indolo[3,2-c]isoquinoline and benzofuro[3,2-c]isoquinolin-5-amine synthetic methods.



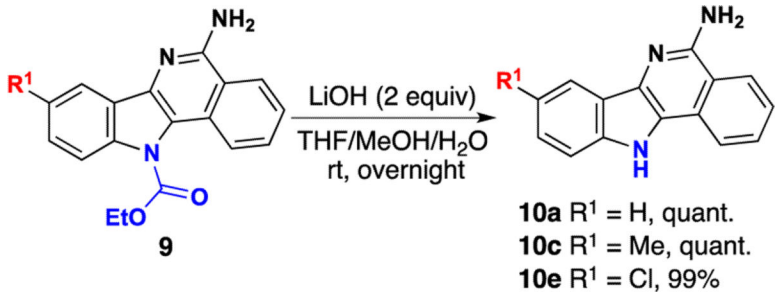
Scheme 2.

(a) Overall transformation; (b) initial approach; and (c) preparation of ethyl (2-cyanobenzyl) (2-cyanophenyl)carbamate.



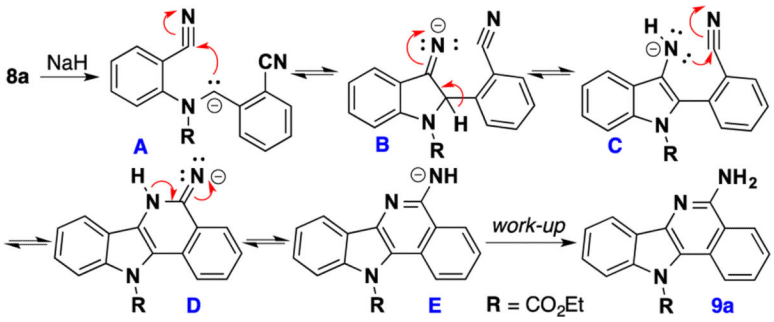
Scheme 3.

One-pot substrate scope: synthesis of 11*H*-indolo[3,2-*c*]isoquinolin-5-amines. [a]See SI for experimental procedures. [b]Isolated yield. [c]Three equivalents of NaH were used. [d]n.d. = not detected.



Scheme 4.

N–Deprotection of indoloisoquinolines **9**.



Scheme 5.
Proposed mechanistic pathway.

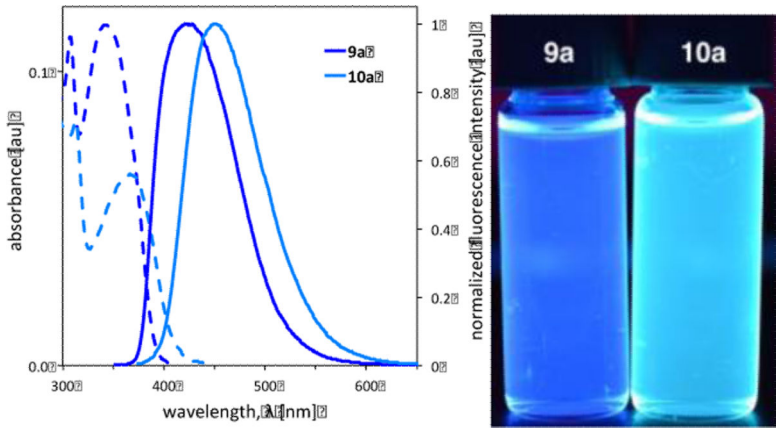
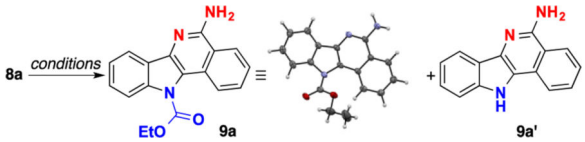


Figure 2.

Absorption (dashed lines) and emission (solid lines) spectra of **9a** and **10a** (c = 10 μM) in DCM (left). Fluorescence of **9a** and **10a** under UV illumination (365 nm) (right).

Table 1

Optimization studies: base-promoted heterocyclization of **8a** to indoloisoquinolines **9a**[a]



Entry	Base	Solvent	t (°C)	Time (h)	9a yield[b] (%)	9a/9a'[c]
1	KO^{t}Bu	DMF	50	1	27	–
2	NaH	DMF	0	1	49	90:10
3	NaH	DMF	rt	24	26	20:80
4	NaH	DMF	50	0.5	70	90:10
5	NaH	THF	80	2	trace	–
6	NaH	MeCN	80	2	trace	–
7	LiHMDS	DMF	rt	24	20	–
8	K_2CO_3	DMF	80	2	NR	–
9	DBU	DMF	rt	24	trace	–

DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene.

[a] Reactions were performed using 8a (0.5 mmol), base (0.55 mmol), and solvent (5.0 mL) at different temperatures and reaction time

[b] Isolated yield.

[c] Determined by HPLC analysis of the crude reaction mixture.