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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-cyano-phenyl)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.

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 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 Letter, we were particularly interested in 11*H*-indolo[3,2-*c*]isoquinoline, a close relative of cryptolepine and cryptosanguinolentine (also know as 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-

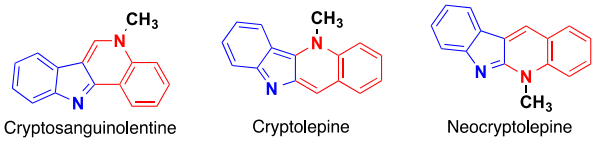
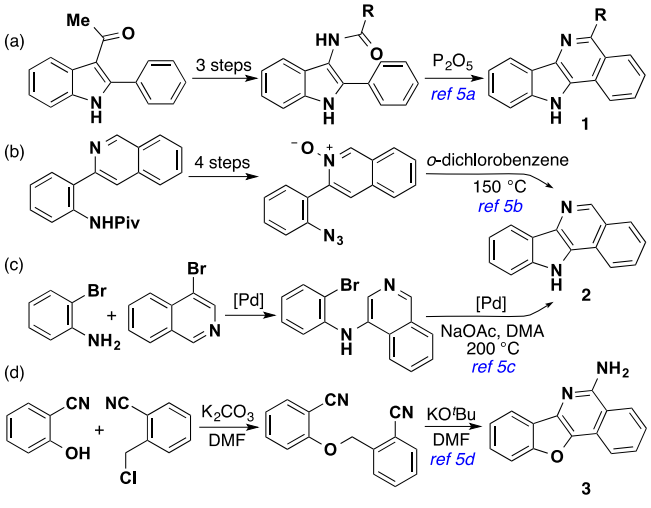


Figure 1. Bioactive examples of indoloquinoline alkaloids.



Scheme 1. Reported indolo[3,2-*c*]isoquinoline and benzofuro[3,2-*c*]isoquinolin-5-amine synthetic methods.

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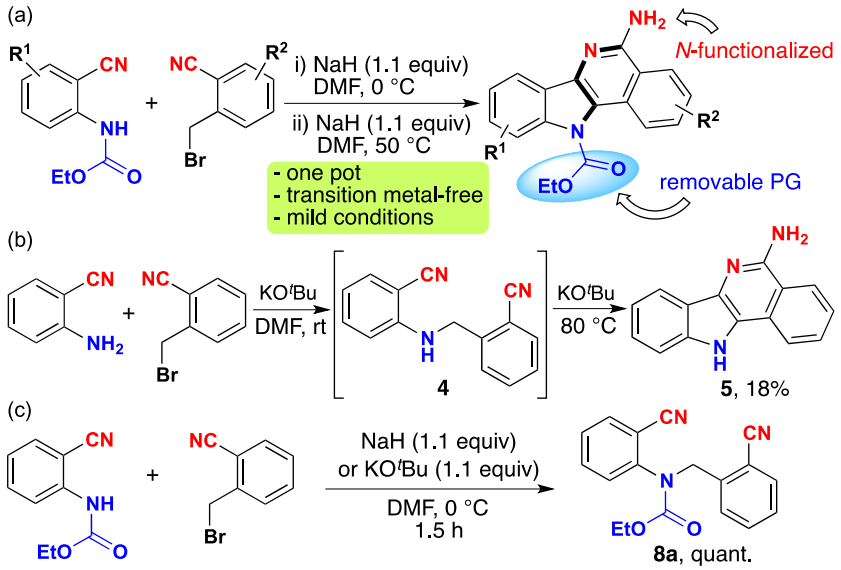


Scheme 2. (a) Overall transformation; (b) initial approach; and (c) preparation of ethyl (2-cyanobenzyl)(2-cyanophenyl)carbamate.

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.

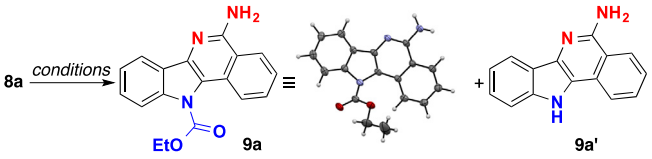
With the ascendency of organometallic catalysis in modern organic synthesis, metal-catalyzed cross-coupling C–N/C–C bond formations have become a powerful tool for constructing heterocyclic structures.[6] In that context, the Maes group described an interesting assembly of **2** in two steps via a Buchwald–Hartwig 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 Letter on the synthesis of 11*H*-indolo[3,2-*c*]isoquinolin-5-amines.

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^{t}Bu 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^{t}Bu. 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

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	—

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