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Unprecedented $SnCl_2{\cdot}2H_2O$-mediated intramolecular cyclization of nitroarenes via C–N bond formation: a new entry to the synthesis of cryptotackieine and related skeletons ☆

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ABSTRACT

A mild, efficient, and one-pot protocol for the intramolecular cyclization of 2-substituted nitroarenes via C–N bond formation using $SnCl_2{\cdot}2H_2O$ is described. The versatility of the method has been demonstrated by synthesizing two sets of polycyclic structures based on privileged structures of indole and pyrrole, and of the alkaloid cryptotackieine associated with antimalarial activity. Our new approach provides a powerful entry into polycyclic structures related to an alkaloid.

In recent years, N-containing polycyclic structures based on privileged templates[1] have drawn significant interest owing to their ability to act as natural product-like chemical probes[2] that may be useful for drug discovery. Besides structural analogy to natural products, other interesting features involve: (1) rigid and planar molecular frameworks; (2) hybrid structures derived from two to three privileged structures; (3) annulation of heterocyclic templates leading to new polycyclic motifs and (4) generation of almost unlimited combinations of annulated heterocyclic structures, resulting in polycyclic skeletons with diverse physical, chemical and biological properties. In the literature, synthetic N-rich fused polyheterocyclic systems have been reported to be associated with a wide range of biological activities[3] including antimalarial activity.[4] Therefore, development of an efficient method for the construction of fused polyheterocyclic ring systems in few steps is highly desirable, particularly in the field of medicinal chemistry.

Recently, we disclosed a novel procedure for generating annulated polycyclic structures using the modified Pictet–Spengler reaction.[5] The latter is a reaction where an aryl amine, when linked covalently to either an activated or deactivated heterocyclic ring, after forming an iminium ion with an aldehyde in the presence of a Bronsted acid, furnishes intermediates having both nucleophilic (Nu) and electrophilic (El) centres. The resulting intermediate eventually leads to the formation of polycyclic structures via intramolecular (*endo*) cyclization. We have successfully applied this modified strategy[5] for the synthesis of several novel N-containing polycyclic motifs with combinations of 5-, 6- and 7-membered rings in a given skeleton.

During one such study, we proposed to apply our modified approach for the Pictet–Spengler reaction to bisindole derivatives having a covalently linked aryl amine, based on substrate **1,** with the view to generate bisindole-based polycyclic structures **2** (Fig. 1) for our ongoing antimalarial programme. Bisindole motifs are known to be widely distributed in nature and are important building blocks for a variety of biologically active natural products.[6] An attempt to obtain **2** was made by treating indole with *o*-nitrobenzaldehyde to give **3** followed by reduction of the aryl nitro group with $SnCl_2{\cdot}2H_2O$. However, to our surprise, reduction of the NO_2 group in **3a** furnished a new product **4a** within an hour in greater than 95% purity (HPLC) and in >85% isolated yield, instead of the expected product **1**.

Chemical characterization of the resulting product using NMR and HRMS led to the identification of a polycyclic structure, 6*H*-indolo[2,3-*b*]quinoline **4a**. A literature search revealed a close structural resemblance to cryptotackieine **5** (5-*N*-methyl-5*H*-indolo[2,3-*b*]quinoline; Fig. 1), an alkaloid with antimalarial activity isolated from the West African shrub *Cryptolepis sanguinolenta*.[7] The alkaloid **5** was found to be a *N*-methyl derivative of the linear indolo[2,3-*b*]quinoline ring system. A careful analysis on the formation of our product **4a** from **3a** revealed that an intramolecular cyclization via C–N bond formation may have occurred resulting in

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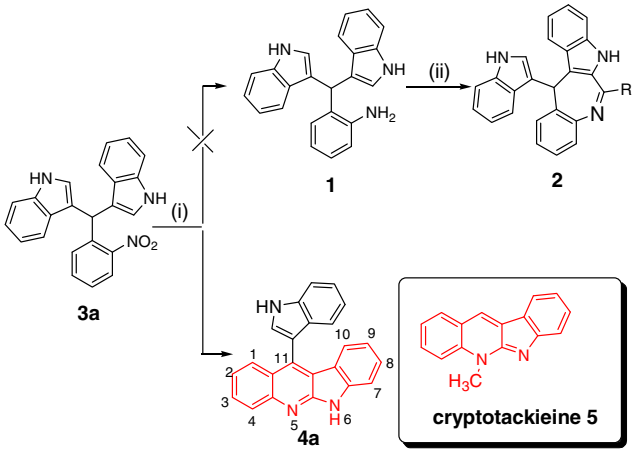


Figure 1. Reagents and conditions: (i) $SnCl_2{\cdot}2H_2O$, MeOH, reflux and (ii) RCHO, *p*-TsOH, toluene, reflux.

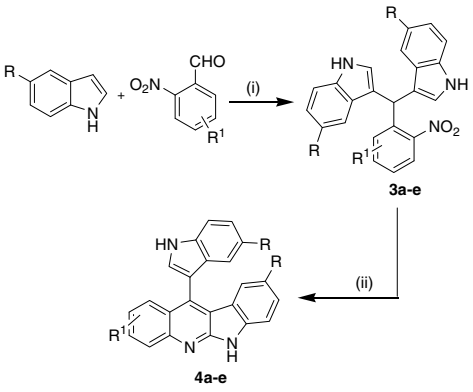
a tetracyclic structure. Interestingly, catalytic reduction of the nitro substrate **3a** using Pd–C furnished amine **1** (Fig. 1) as the only product without any detectable cyclization (**4a**) as evident by HPLC. This suggests that formation of product **4a** could result from either of the nitroso and hydroxylamine intermediates formed during reduction of the nitro group using $SnCl_2$. Although Pd-catalyzed reduction (Pd/C) also proceeds via the same intermediate, it is possible that conversion of amines may be occurring on the catalyst's surface without concomitant release of intermediates at any stage, thus furnishing amine **1** and not the cyclized product **4a**.

A careful survey of the literature revealed a few reports dealing either with the synthesis of 6*H*-indolo[2,3-*b*]quinolines[8] (a precursor to cryptotackieine) or with the synthesis of cryptotackieine **5**.[9] Timári et al.[9e] have described the synthesis of cryptotackieine in five steps in which the key intermediate, 3-(2-aminophenyl)-*N*-methyl-2-quinolone, was obtained via palladium-catalyzed cross-coupling between a 3-bromo-2-quinolone derivative and (2-*N*-pivaloylaminophenyl)boronic acid. Molina et al.[9b] reported an eight-step synthesis of cryptotackieine **5** via a key intermediate, 1-methyl-3-(*o*-azidophenyl)quinolin-2-one. This intermediate was directly converted into cryptotackieine via an intramolecular aza-Wittig reaction with trimethylphosphine. Wang and co-workers[8c] reported biradical-mediated thermolysis of *N*-[2-(1-alkynyl)phenyl]-*N*′-phenylcarbodiimides, obtained via aza-Wittig reaction between 4-methoxyphenyl isocyanate and iminophosphoranes, leading to the corresponding 6*H*-indolo[2,3-*b*]quinoline (a precursor of cryptotackieine). Ila and co-workers[9f] described a five-step synthesis of cryptotackieine **5** using conjugate addition of an enolate anion from cyclohexanone (or 4-methylcyclohexanone) to bis[(methylsulfanyl)-methylene]-2-oxindole followed by heterocyclization in the presence of ammonium acetate. The 11-methylsulfanyl group in the initial precursor was then either desulfurized (Raney Ni) or replaced by methyl/phenyl groups via a nickel-catalyzed cross-coupling reaction using appropriate Grignard reagents. Recently, Tilve and co-workers[9g] reported an interesting method for the synthesis of cryptotackieine via a Perkin reaction, a tandem double reduction-double cyclization reaction followed by methylation at the quinoline nitrogen. Thus, the reported strategies for cryptotackieine not only involved multi-step synthetic routes for both precursors based on **4** and **5**, but also involved harsh and stringent reaction conditions. In contrast, our method is based on a two-step procedure involving mild reaction conditions for intramolecular cyclization. Nevertheless, **5,** despite exhibiting strong antimalarial activity, has not yet been subjected to lead optimization studies through analogue synthesis. This led us to study the scope and limitation of our strategy by carrying out the synthesis of a mini-library based on 6*H*-indolo[2,3-*b*]quinolines **4** and pyrroloquinolines **7** followed by application of our strategy for the synthesis of cryptotackieine **5**.

Initially, we synthesized four congeners based on **4b–e** by varying the indole and *o*-nitrobenzaldehyde (Scheme 1). The synthesis commenced with the formation of **3a–e** by treating indole with *o*-nitrobenzaldehyde in the presence of iodine.[10] The resulting nitro derivatives **3b–e** were then treated with $SnCl_2{\cdot}2H_2O$ to give **4b–e** in high yields.[11]

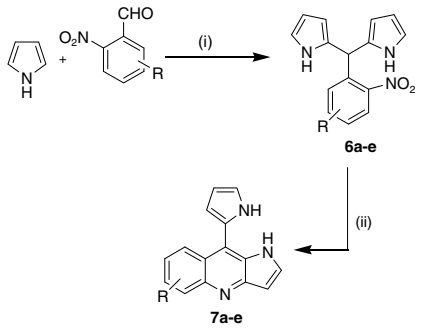
After successfully demonstrating the efficacy of our strategy on indoles, we expanded the repertoire of substrates for generating polycyclic structures by replacing indole (benzopyrrole) with pyrrole (Scheme 2). The synthesis commenced with the formation of nitro intermediates **6** by treating pyrrole with *o*-nitrobenzaldehyde derivatives using the procedure reported in the literature.[12] The resulting nitro derivatives **6a–e** were then treated with $SnCl_2{\cdot}2H_2O$ in methanol under reflux to give **7a–e** in moderate to excellent yields.

We also extended our strategy to the synthesis of the indole-based natural product cryptotackieine **5** with the view to probe the substitution at position 11 in **4a–e.** Our synthesis (Scheme 3) for **5** commenced with the synthesis of nitro intermediate **8** by treating indole with 2-nitrobenzyl bromide in the presence of Na_2CO_3.[13] The resulting product **8** was then subjected to reduction by refluxing in methanol in the presence of $SnCl_2{\cdot}2H_2O$. The crude product was a mixture of three components as was evident by both HPLC and TLC. The product with t_R = 14.035 min (R_f = 0.31, 9:1 hexane/EtOAc) corresponded to the desired tetracyclic 6*H*-indolo-[2,3-*b*]quinoline[8c] **9**. The second component with t_R = 13.194 min (R_f = 0.28, 9:1 hexane/EtOAc) was characterized as the amine **10,** a reduced product of **8.** The third component with t_R = 19.434 min (R_f = 0.56, 9:1 hexane/EtOAc) was characterized as spiroindole **11**. The isolation of stable spiroindole **11** in traces, during the reductive cyclization, is probably the first experimental evidence in support for the plausible mechanism[14] where the C-3 in the indole has been implicated as the most preferred position for initial intramolecular electrophilic attack thereby forming an unstable 'spiroindolenin',[14a] which then quickly undergoes rearrangement to the C-2 of the indole. Thus, reductive cyclization of **8** in the absence of



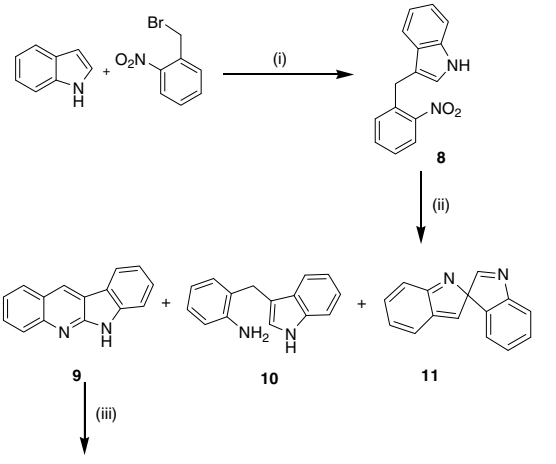
Entry	R	R^1	Product	Yield (%)	Mass (M^++H)	HPLC t_R=min
1	H	H	**4a**	89	334.6	22.675
2	H	5-Cl	**4b**	91	368.4	21.277
3	H	5-F	**4c**	80	352.4	19.483
4	5-OMe	H	**4d**	82	394.3	18.460
5	5-OMe	5-Cl	**4e**	84	428.3	21.294

Scheme 1. Reagents and conditions: (i) I_2, CH_3CN, 20 min; (ii) $SnCl_2{\cdot}2H_2O$, MeOH, reflux.



Entry	R	Product	Isolated Yield (%)	Mass (M^++H)	HPLC t_R=min
1	H	**7a**	87	234.4	15.327
2	5-Cl	**7b**	92	268.3	18.249
3	5-F	**7c**	81	252.4	16.495
4	3-OMe	**7d**	53	264.2	18.440
5	4,5-Di-OMe	**7e**	51	294.2	15.978

Scheme 2. Reagents and conditions: (i) Cat. TFA, N_2, rt, 30 min; (ii) $SnCl_2{\cdot}2H_2O$, MeOH, reflux.



Product	HPLC (%)	Isolated Yield (%)	Mass (M^++H)	HPLC t_R=min
9	45	35	219.5	14.035
10	35	27	223.0	13.194
11	15	10	219.5	19.434

Scheme 3. Reagents and conditions: (i) Na_2CO_3, 80% acetone in H_2O, 70 °C, 36 h, 83%. (ii) $SnCl_2{\cdot}2H_2O$, MeOH, reflux. 1 h. (iii) MeI, toluene, 130 °C, sealed tube, 4 h, 82%.

any substitution at the methylene leads to incomplete intramolecular cyclization and competes with the formation of **10** and **11**. The use of other reductive procedures[15] involving Zn, NH_4Cl, H_2O, EtOH and Zn, NaOH, H_2O, EtOH, reflux failed to offer any improvement in terms of yield/selectivity. This is in contrast to our findings on substrates **3a–e** and **6a–e** with substituents at their respective methines resulting in products **4a–e** and **7a–e.** The surprising result of incomplete reductive cyclization in **8** is indicative of the crucial role of the substituents at the methines in **3** and **6,** respectively. Substituents at the methines could be playing a role by restricting rotation of the C–C bond in a manner that brings the nitro group in close proximity to C-2 of the indole thereby facilitating complete cyclization via the formation of a C–N bond.

Finally, for the synthesis of crytotackinene **5, 9** was subjected to N-methylation using CH_3I in toluene to give the desired N-methylated product[9f] **5** in excellent yield.

In conclusion, we have described the first example of $SnCl_2{\cdot}2H_2O$-mediated intramolecular cyclization of 2-substituted nitroarenes via C–N bond formation under mild conditions. The generality of the method has been established by synthesizing two sets of polycyclic structures based on indole and pyrrole, and the alkaloid cryptotackieine. Thus, our new approach provides a powerful entry into polycyclic structures related to an alkaloid.

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11. *General procedure*: A solution of **3** or **6** (1 mmol) and $SnCl_2{\cdot}2H_2O$ (5 mmol) in methanol (4 mL) was refluxed for 1 h. The solution was allowed to cool and was then poured into ice. The pH was made slightly basic (pH 8) by addition of 5% aqueous $NaHCO_3$. EtOAc (50 mL) was added to the mixture which was filtered through a bed of Celite®. The organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography using hexane/ethyl acetate to afford products **4** and **7**.
11-(1H-Indol-3-yl)-6H-indolo[2,3-b]quinoline: Compound **(4a)** Yield: 89%; yellow solid; mp > 250 °C; R_f 0.60 (7:3 hexane/EtOAc); IR (KBr) ν_{max} 3399, 1607 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.80 (br s, 1H, NH), 10.86 (br s, 1H, NH), 8.39 (d, 1H, J = 7.7 Hz, ArH), 8.27 (d, 1H, J = 8.2 Hz, ArH), 7.96 (d, 1H, J = 8.0 Hz, ArH), 7.87 (d, 1H, J = 2.5 Hz, ArH), 7.69–7.44 (m, 5H, ArH), 7.31–7.21 (m, 2H, ArH), 7.14 (d, 1H, J = 7.8 Hz, ArH), 7.03 (t, 1H, J = 7.4 Hz, ArH); ^{13}C NMR (50 MHz, DMSO-d_6) δ 145.6, 144.5, 144.4, 136.9, 132.0, 129.7, 129.6, 127.2, 127.0, 126.1, 125.9, 124.8, 122.1, 121.8, 121.6, 120.5, 120.0, 119.8, 119.6, 112.4, 112.2, 107.7; Mass (ES^+) m/z 334.6 (M^++1); HRMS (EI) m/z calcd for [M^+]

333.1266, found 333.1239; Anal. Calcd for $C_{23}H_{15}N_3$: C, 82.86; H, 4.54; N, 12.60. Found: C, 82.78; H, 4.42; N, 12.80.

9-(1H-Pyrrol-2-yl)-1H-pyrrolo[3,2-b]quinoline: **(7a)** Yield: 87%; yellow solid; mp > 250 °C; R_f 0.67 (1:1 hexane/EtOAc); IR (KBr) ν_{max} 3399, 1592 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.57 (br s, 1H, NH), 11.49 (br s, 1H, NH), 8.32 (dd, 1H, J = 8.6, 0.9 Hz, ArH), 7.96 (dd, 1H, J = 8.4, 0.8 Hz, ArH), 7.73–7.70 (m, 1H, ArH), 7.64–7.59 (m, 1H, ArH), 7.43–7.35 (m, 1H, ArH), 7.11–7.09 (m, 1H, ArH), 6.61–6.57 (m, 2H, ArH), 6.38–6.35 (m, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.5, 144.7, 129.7, 127.3, 126.6, 125.7, 125.6, 122.0, 121.0, 119.9, 118.8, 110.9, 108.5, 99.3; mass (ES^+) m/z 234.4 (M^++1); Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.09; H, 4.78; N, 18.13.

Spiroindole (*Compound* **11**): Yield: 10%; yellow solid; mp 103–105 °C; R_f 0.56 (9:1 hexane/EtOAc); IR (KBr) ν_{max} 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.96 (s, 1H, ArH), 8.50–8.44 (m, 2H, ArH), 8.02–7.97 (m, 2H, ArH), 7.66–7.54 (m, 2H, ArH), 7.49–7.42 (m, 2H, ArH), 7.17 (s, 1H, ArH); mass (ES^+) m/z 219.5 (M^++1); HRMS (EI) m/z calcd for [M^+] 218.0844, found 218.0833; Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84. Found: C, 82.43; H, 4.76; N, 12.81.

2-(1H-Indol-3-ylmethyl)aniline: **10** Yield: 27%; white solid; mp 89–90 °C; R_f 0.28 (9:1 hexane/EtOAc); IR (KBr) ν_{max} 3225, 3198, 2946, 2852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (br s, 1H, NH); 7.58 (d, 1H, J = 7.9 Hz, ArH), 7.34 (d, 1H, J = 8.1 Hz, ArH), 7.24–7.06 (m, 4H, ArH), 6.82–6.81 (m, 1H, ArH), 6.79–6.73 (m, 1H, ArH), 6.67 (d, 1H, J = 7.8 Hz, ArH), 4.00 (s, 2H, CH_2), 3.54 (br s, 2H, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.0, 136.5, 129.2, 127.3, 126.5, 124.6, 123.3, 120.9, 118.7, 118.2, 116.2, 114.6, 112.3, 111.4, 26.8; Mass (ES^+) m/z 223.0 (M^++1); Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.12; H, 6.41; N, 12.47.

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