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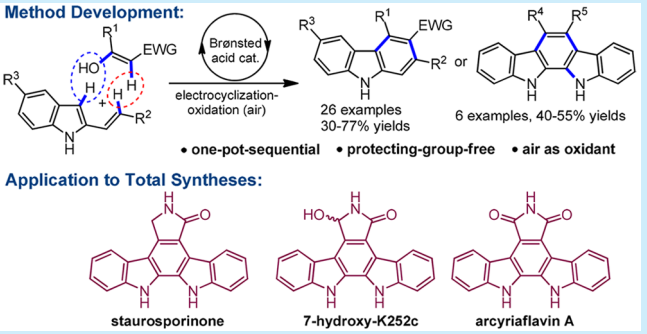
Brønsted Acid Catalyzed One-Pot Benzannulation of 2-Alkenylindoles under Aerial Oxidation: A Route to Carbazoles and Indolo[2,3-*a*]carbazole Alkaloids

Shuvendu Saha, Ankush Banerjee, and Modhu Sudan Maji*

Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721302, West Bengal, India

Supporting Information

ABSTRACT: A one-pot, protecting-group-free benzannulation of 2-alkenylindoles with readily available 1,3-dicarbonyls is demonstrated to construct structurally diverse carbazoles. The use of a cheap Brønsted acid catalyst and air as the sole oxidant exemplifies the economic viability of this protocol. The execution of four different reactions successively to generate the medicinally important indolocarbazole core is also achieved. This one-pot protecting-group-free method paved the way for the total synthesis of three medicinally important alkaloids, namely staurosporinone, arcyriaflavin A, and 7-hydroxy-K252c.



Indolocarbazoles and carbazoles are commonly occurring heterocycles present in alkaloids of therapeutic importance.[1,2] To date, more than 110 indolo[2,3-*a*]carbazole alkaloids have been isolated from nature,[3] and many of those are undergoing clinical trials for the treatment of cancer, diabetic retinopathy, and Parkinson's disease.[4] In 2017, midostaurin was approved as drug to treat patients diagnosed with a form of blood cancer known as acute myeloid leukemia (Figure 1).[5] Synthesis of diversely functionalized indolo[2,3-*a*]carbazoles was generally accomplished by Fischer indole cyclization of functionalized cyclohexanones prepared by tedious synthetic efforts[6] or via C−C coupling using expensive transition-metal catalysts followed by Cadogan cyclization.[7,8] Limited and complicated methods for the synthesis of indolocarbazoles[9] demand a profound synthetic route to access both symmetrical and even challenging unsymmetrical indolo[2,3-*a*]carbazoles and related alkaloids.

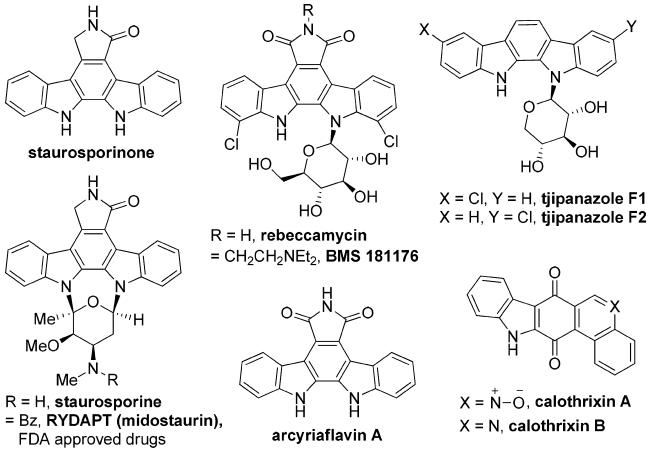
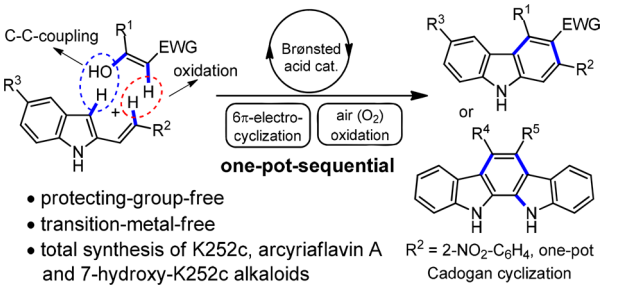


Figure 1. Indolocarbazoles of medical importance.

Alongside indolocarbazole, synthesis of carbazole, another privileged heterocycle, primarily relied on complicated starting materials, expensive catalysts, and longer reaction sequences.[10,11] Despite merits of these methods,[12] synthesis of this heterocycle starting with simple precursors by using a cheap and commonly available catalyst is highly attractive and desirable. Recently, the benzannulation strategy has emerged as one of the most powerful tools for the synthesis of carbazoles bearing unique substitution patterns.[13] In our ongoing research interest,[14] we envisioned that carbazole can be constructed in one pot[15] by annulation of 2-alkenylindoles and appropriate 1,3-dicarbonyls using Brønsted acid catalyst under aerial oxidation (Scheme 1).[16] Advancing a step further,

Scheme 1. Working Hypothesis for the Synthesis of Carbazoles and Indolo[2,3-*a*]carbazoles



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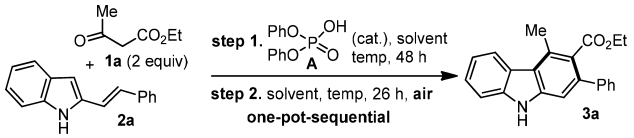
upon extending this one-pot strategy by employing intermediately formed carbazoles bearing a 2-nitroaryl moiety at the C2-position, valuable indolo[2,3-*a*]carbazoles can be synthesized by performing an in situ Cadogan cyclization. More importantly, on choosing the required 2-alkenylindole along with 1,3-dicarbonyls as annulating partners, several indolo[2,3-*a*]carbazole alkaloids can also be synthesized in fewer steps via a protecting-group-free route. It is important to note that 2-alkenylindoles have been utilized as 1,3-dienes for the [4 + 2]-cycloaddition reactions to obtain octahydrocarbazoles.[17] Herein, we disclose one-pot synthesis of carbazoles and indolocarbazoles by using benzannulation protocols and their application to the synthesis of indolocarbazole alkaloids.

At the onset of our optimizations, first, 2.0 equiv of ethylacetoacetate (EAA) **1a** was reacted with **2a** in ethyl acetate solvent by employing 20 mol % of diphenylphosphoric acid catalyst to generate intermediate 2,3-dialkenylindole. After completion of the alkenylation (step 1), decalin was added, and 6π-electrocyclization was carried out at 130 °C under air as sole oxidant to provide carbazole **3a** in 53% yield (Table 1, entry 1). Yield of **3a** was enhanced to 65% on increasing the catalyst loading to 25 mol % (entry 2). Employing other Brønsted acid catalyst or increasing the EAA amount did not provide better results (entries 3 and 4). On conducting the first step in other solvents, the yield decreased (entries 5−7). A similar yield was recorded when step 2 was conducted in xylene (entry 8). Air was sufficient for the oxidative aromatization reaction, as the yield of **3a** did not improve when the reaction was conducted under molecular oxygen (entry 9). Finally, on increasing the temperature for the step 1, the highest yield of **3a** was obtained at 110 °C (72%, entries 10 and 11). The (*E*)-2-alkenyl indoles **2a** was more effective as the corresponding (*Z*)-isomer provided **3a** in 52% yield.

Table 1. Optimization of the Reaction Conditions[a]

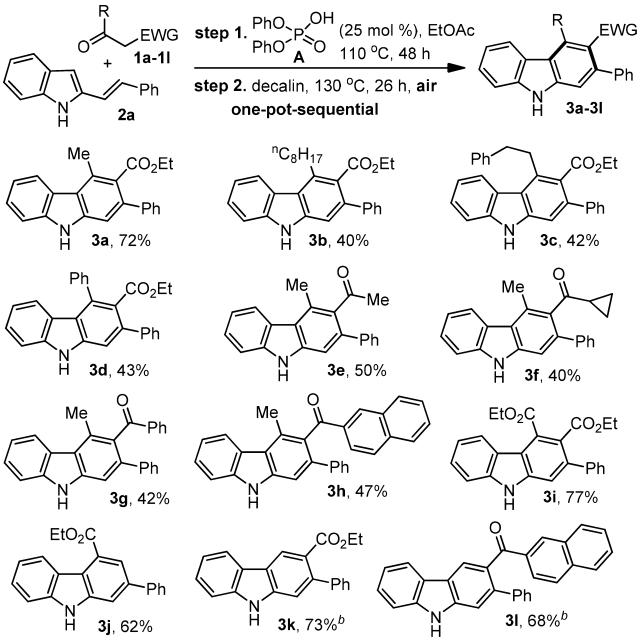


entry	acid cat. (mol %)	solvent step 1/step 2	temp (°C) step 1/step 2	yield of **3a**[b] (%)
1	20	EtOAc/decalin	90/130	53
2	25	EtOAc/decalin	90/130	65
3[c]	25	EtOAc/decalin	90/130	31
4[d]	25	EtOAc/decalin	90/130	62
5	25	$CHCl_3$/decalin	90/130	53
6	25	THF/decalin	90/130	30
7	25	EtOH/decalin	90/130	26
8	25	EtOAc/xylene	90/130	63
9[e]	25	EtOAc/decalin	90/130	53
10	**25**	**EtOAc/decalin**	**110/130**	**72**
11	25	EtOAc/decalin	130/130	66

[a]Reaction conditions: **1a** (0.30 mmol), **2a** (0.15 mmol). [b]Isolated yield. [c]Binolphosphoric acid was used in place of **A**. [d]EAA (2.5 equiv). [e]Step 2 was carried out under oxygen.

With the optimized reaction conditions in hand, we first studied the compatibility of several electrophiles. 4-Heptyl- and 4-benzyl-substituted EAA derivatives provided carbazoles **3b** and **3c** in moderate yields (Scheme 2). Ethyl benzoylacetate is also a suitable annulating partner (**3d**, 43% yield). Acetylacetone also reacted well to furnish carbazole **3e** bearing a ketone functional group at the 3-position. To our delight, unsymmetrical 1,3-diketones reacted exclusively at the less hindered site (**3f−h**, 40−47% yields). Diethyl 2-oxosuccinate furnished diester substituted carbazole **3i** in 77% yield. Ethyl pyruvate also afforded carbazole **3j** bearing an ester functional group at the 4-position. Reactivity of aldehyde over ketone was exploited to obtain carbazole **3l** in 68% yield.

Scheme 2. Scope of Electrophiles[a]



[a]Reaction conditions: step 1, **1** (0.40 mmol), **2a** (0.20 mmol), **A** (25 mol %), 1.3 mL EtOAc, 110 °C; step 2, 2.7 mL of decalin, 130 °C; isolated yield. [b]5 mol % of **A** used.

After successfully employing several electrophiles, the reaction scope was further studied by varying several 2-alkenylindoles **2b−m** (Scheme 3). 2-Alkenylindoles bearing methyl, methoxy, chloride, and bromide functional groups at the 5-position of indole reacted efficiently to afford carbazoles **3m−p** in 52−71% yields. Likewise, several functional groups such as methyl, methoxy, fluoro, and nitro at the phenyl ring of 2-alkenylindoles were tolerated to furnish **3q−v** in 50−68% yields. 1-Naphthyl- and 2-thiophenyl-substituted 2-alkenylindoles were also suitable substrates (**3w−x**, 67−70% yields). The alkyl group at the 2-position of the carbazole can be incorporated, albeit in lower yield (**3y**, 30%). Although one of the key highlights of this annulation strategy is that it is protecting-group-free, if required, the *N*-benzyl-protected carbazole **3z** can also be synthesized in 63% yield. To show the scalability of this method, carbazoles **3t** and **3v** were synthesized on a gram scale.

After successfully executing the synthesis of several structurally diverse carbazoles, we further explored this strategy to the synthesis of diversified indolo[2,3-*a*]carbazoles **4** by employing Cadogan cyclization. Notably, to achieve this medicinally important indolocarbazole core structure, four completely different reactions need to be executed sequentially without isolating a single intermediate. For this, a nitro group needed to be appropriately poised in the intermediate carbazole **3** for the subsequent Cadogan cyclization, which was achieved by using (*E*)-2-(2-nitrostyryl)-1*H*-indole as the

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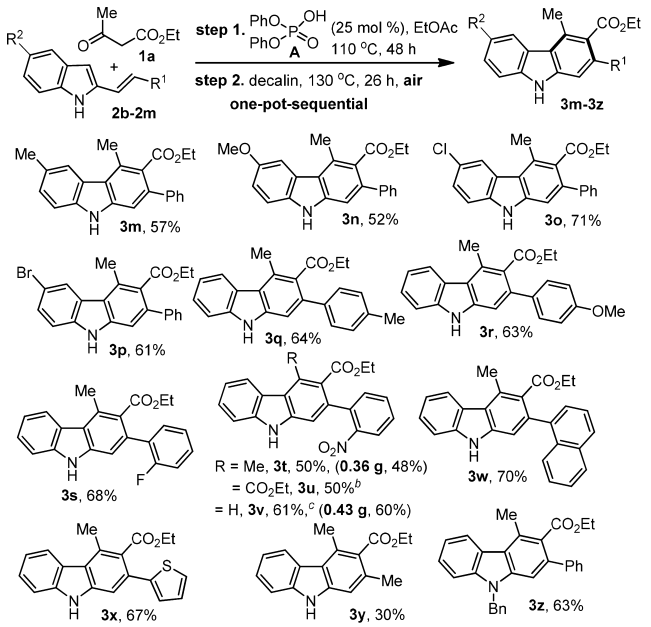
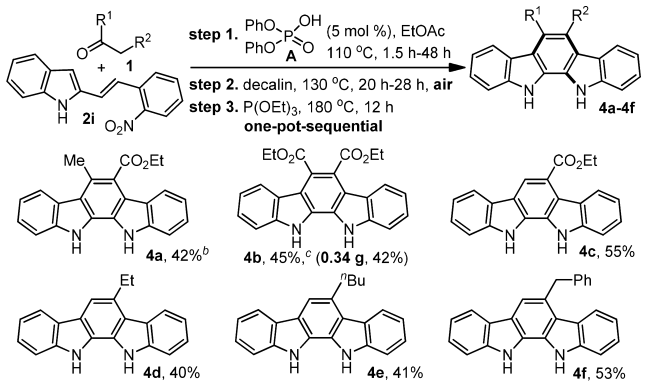
Scheme 3. Scope of 2-Alkenylindoles[a]



[a]Reaction conditions: step 1, **1** (0.40 mmol), **2** (0.20 mmol), **A** (25 mol %), 1.3 mL of EtOAc, 110 °C; step 2, 2.7 mL of decalin, 130 °C; isolated yield. [b]15 mol % of **A** used. [c]5 mol % of **A** used.

annulating partner. Executing this one-pot strategy by employing **1a** as an electrophile provided the indolocarbazole **4a** in 42% yield (Scheme 4). Diethyl 2-oxosuccinate and ethyl

Scheme 4. Scope of Indolocarbazoles[a]

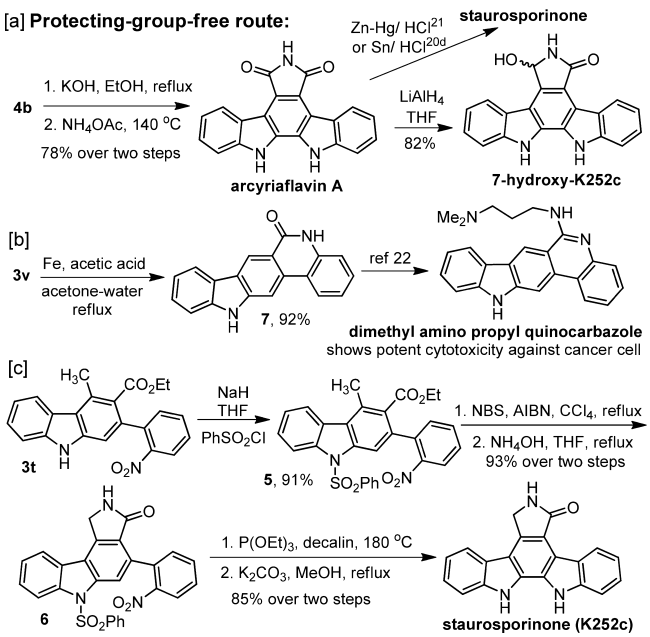


[a]Reaction conditions: step 1, **1** (0.40 mmol), **2i** (0.20 mmol), **A** (5 mol %), 1.3 mL of EtOAc, 110 °C; step 2, 2.7 mL of decalin, 130 °C; step 3, 0.5 mL of $P(OEt)_3$, 180 °C; isolated yield. [b]25 mol % of **A** used. [c]15 mol % of **A** used.

3-oxopropanoate were also found to be suitable coupling partners, delivering indolocarbazoles **4b** and **4c** in good yields. To our delight, commercially available aliphatic aldehydes also reacted smoothly to furnish 5-alkylated indolocarbazoles **4d**–**f** in 40–53% yields.

Next, we applied our strategy to the total synthesis of different indolo[2,3-*a*]carbazole alkaloids, namely, staurosporinone,[18] arcyriaflavin A,[19] and 7-hydroxy-K252c,[20] in a protecting-group-free and step-economical way. These naturally occurring alkaloids have gained considerable attention owing to their presence in drugs and importance in medicinal chemistry. For example, arcyriaflavin A manifests as a human cytomegalovirus replication inhibitor.[19a] Besides their own merits, most, if not all, of the existing methods to synthesize these alkaloids have certain limitations such as longer reaction sequences, complicated precursors, additional protection–deprotection steps, and use of expensive transition-metal catalysts. To achieve the total synthesis of arcyriaflavin A, first, saponification of the intermediate **4b** by treatment with KOH in ethanol under reflux conditions provided an anhydride intermediate which in the presence of neat ammonium acetate at 140 °C furnished arcyriaflavin A in 78% yield over two steps and in 35% overall yield over three steps from **2i** (Scheme 5a).[19d] Selective reduction of arcyriaflavin A by using $LiAlH_4$

Scheme 5. Total Synthesis of K252c, Arcyriaflavin A, and 7-Hydroxy-K252c Alkaloids



afforded alkaloid 7-hydroxy-K252c in 82% yield.[20b] The synthesis of staurosporinone from arcyriaflavin A was reported by reduction of one carbonyl group under Sn/HCl or Zn–Hg/HCl conditions,[20d,21] thus completing the synthesis of this alkaloid in four steps from **2i** in 24% overall yield. In addition to staurosporinone, (dimethylamino)propyl quinocarbazole also exhibits potential cytotoxicity against cancer cells.[22] An advanced intermediate **7** for the synthesis of (dimethylamino)-propyl quinocarbazole was achieved in one pot by reduction of **3v** followed by intramolecular amidation in 92% yield (Scheme 5b). Furthermore, compound **7** also resembles the core structure present in the alkaloids calothrixin A and calothrixin B.

To achieve the total synthesis of staurosporinone by a second route, an attempt to brominate the benzylic hydrogen of **3t** was in vain as this resulted in ring bromination at the C6-position. To circumvent this problem, at first the free –NH group of **3t** was sulfonaylated to furnish electron-deficient carbazole **5** (Scheme 5c). The selective benzylic bromination of **5** using NBS and a catalytic amount of AIBN was then successful.[18c] Subsequently, nucleophilic substitution of the benzylic bromide intermediate with ammonia followed by in situ intramolecular amidation afforded **6** in 93% yield. Finally, Cadogan cyclization of **6** and desulfonation completed the

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total synthesis of staurosporinone alkaloid in an improved 36% overall yield over six steps from **2i**.

In conclusion, we developed an elegant method for the construction of polyfunctionalized carbazoles and indolo[2,3-*a*]carbazoles using a benzannulation strategy employing simple starting materials. Transition-metal-free conditions, broad substrate scope, scalability, regioselectivity, aerial oxidation, and readily available Brønsted acid catalyst renders this method practical. The protecting-group-free synthesis of staurosporinone, arcyriaflavin A, and 7-hydroxy-K252c demonstrates the applicability of this method. We presume this strategy will be fruitful for the synthesis of diversified indolocarbazole and quinocarbazole alkaloids relevant to medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03063.

Experimental details, analytical data for all new compounds, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: msm@chem.iitkgp.ac.in.

ORCID

Modhu Sudan Maji: 0000-0001-9647-2683

Notes

The authors declare no competing financial interest.

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