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Synthesis of Calothrixins and Its Analogs Using $FeCl_3$-Mediated Domino Reaction Protocol

Bose Muthu Ramalingam, Velu Saravanan, and Arasambattu K. Mohanakrishnan*

Department of Organic Chemistry, School of Chemistry, University of Madras, Guindy Campus Chennai 600 025, Tamil Nadu, India

mohanakrishnan@unom.ac.in

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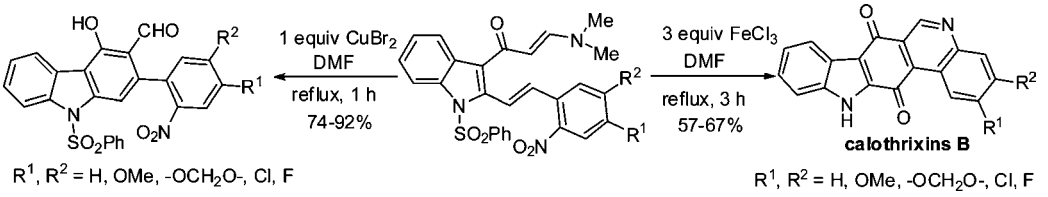
ABSTRACT



A novel one pot synthesis of calothrixin B and its analogs is achieved involving an $FeCl_3$-mediated domino reaction of enamines in dry DMF at reflux. Alternatively, the enamines upon interaction with $CuBr_2$ in DMF at reflux led to the formation of 1-phenylsulfony-2-(2′-nitroaryl)-4-hydroxycarbazole-3-carbaldehydes in excellent yields.

Ellipticine **1**, a pyrido[4,3-*b*]carbazole alkaloid, has been well explored for its anticancer properties (Figure 1).[1] The synthesis of a quino[4,3-*b*]carbazole **2**, a benzo- analog of ellipticine is reported from this laboratory by using thermal electrocyclization as a key step.[2] Subsequently, Rickard et al.[3] isolated calothrixin A **3** and calothrixin B **4** from *Calothrix cyanobacterium*. The carbazoloquinones **3** and **4** exhibit potent antimalarial activity, anticancer properties, and inhibition of RNA polymerase.[3,4] The promising biological activity of calothrixins prompted several groups to explore their synthesis. Ross Kelly et al.[5] reported the first synthesis of calothrixin A and B through the attachment of a *N*-protected indole-3-carboxaldehyde with *N*,*N*-diethylquinoline-4-carboxamide involving a directed lithiation protocol.

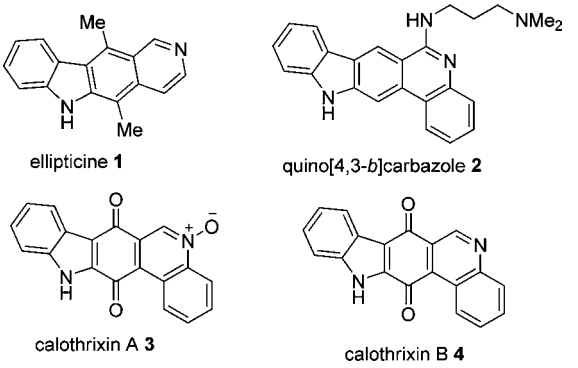


Figure 1. Structures of pyrido[4,3-*b*]carbazoles.

Synthetic pathways outlined to date for calothrixins are prominently based on carbazole intermediates employing either a regioselective hetero Diels–Alder reaction[6]

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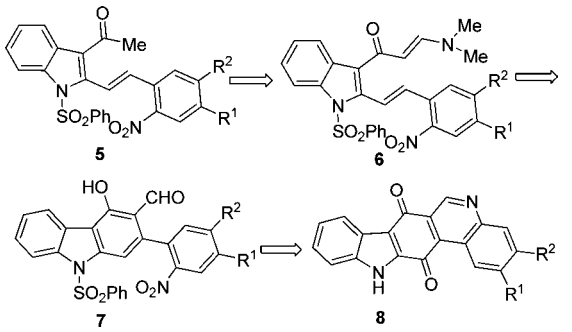
or Pd-mediated intramolecular arylation.[7–9] Substituted quinolines and indoles are the starting material for calothrixins which involve lithiation,[5,10] Friedel–Crafts acylation followed by cyclization,[11] and allene-mediated electrocyclization.[12] Moody and co-workers achieved the synthesis of calothrixins involving a biomimetic protocol.[13] Despite, the many multistep synthesis procedures available, there remains a need for an efficient route that will more readily provide diverse calothrixin analogues for biological screening.

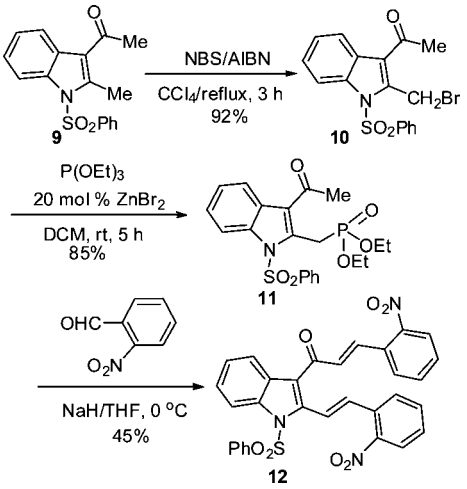
We have recently outlined the synthesis of carbazoles involving an *in situ* generated enamine[14] as well as a Lewis acid mediated domino reaction.[15] In further continuation of our work on carbazole alkaloids,[16] we report herein a novel synthesis of calothrixin B and its analogs using a Lewis acid mediated domino reaction strategy. The methodology involves a Lewis acid mediated cyclization of an enamine **6** followed by reductive cyclization, hydrolysis, and oxidation of carbazole **7** to afford the target compound **8** (Scheme 1).

Scheme 1. Schematic Pathway for Calothrixins



Our synthesis route began with allylic bromination of 1-phenylsulfonyl-3-acetyl-2-methylindole **9**[14b] using an NBS and a catalytic amount of AIBN in CCl_4 at reflux (Scheme 2). The Lewis acid mediated Arbuzov reaction[17] of resulting bromo compound **10** with triethyl phosphite in the presence of 20 mol % anhydrous $ZnBr_2$ at room temperature led to phosphonate ester **11**. Contrary to our expectation, the Wittig–Horner reaction of the phosphonate ester **11** with 2-nitrobenzaldehyde using NaH in dry THF led to the isolation of bis(2-nitrophenyl)vinylene **12**. An attempt to control the undesirable condensation reaction using K_2CO_3 as a base in THF was also found to be problematic, providing only the divinylindole **12** as a major product (Scheme 2).

Scheme 2. Wittig–Horner Reaction of Phosphonate Ester **11**



Next, we turned our attention to employing the Wittig reaction to procure the required 1-phenylsulfonyl-3-acetyl-2-(2′nitrophenyl)vinylindole. Accordingly, the bromo compound **10** upon refluxing with triphenylphosphine in dry THF followed by the reaction of resulting phosphonium salt with K_2CO_3 in dry DCM at room temperature led to the isolation of a stable ylide **13**. As expected the ylide **13** upon refluxing with 2-nitroaryl aldehydes **14a–g** in dry DCM/1,2-DCE furnished 2-nitroarylvinylenes **15a–g** in good yields (Scheme 3).

A subsequent reaction of the 3-acetyl-2-nitroarylvinylenes **15a–g** with DMF·DMA in the presence of 50 mol % glycocyamine[18] as a catalyst at 100 °C for 3–4 h followed by aqueous workup furnished the respective enamines **16a–g** as yellow/orange solids (Scheme 4).

As a representative case, thermal electrocyclization of the enamine **16a** was carried out in refluxing xylenes without any success. However, when the electrocyclization of the enamine **16a** was performed with 1 equiv of $ZnBr_2$ in xylenes at reflux for 24 h following workup,

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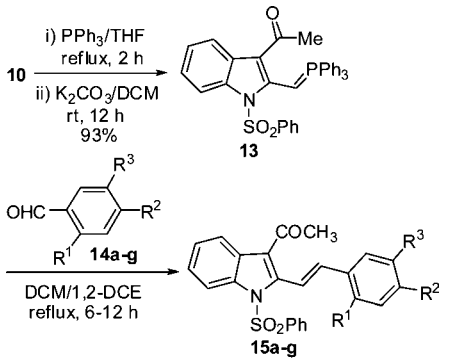
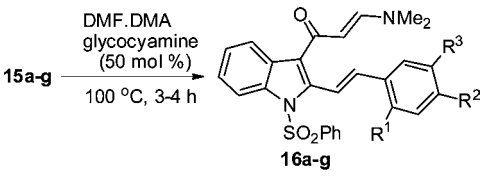
Scheme 3. Synthesis of 2-Nitroarylvinylene Using Wittig Reaction



15	R^1	R^2	R^3	yield (%)
a	NO_2	H	H	92
b	NO_2	OMe	OMe	88
c	NO_2	-OCH_2O-		90
d	NO_2	Cl	H	94
e	NO_2	F	H	93
f	NO_2	Cl	Cl	93
g	Cl	Cl	H	88

Scheme 4. Preparation of Enamine **16a**–**g** Using DMF·DMA

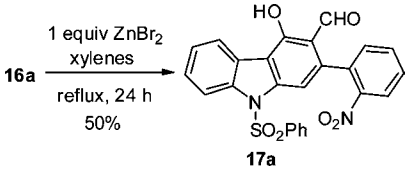


16	R^1	R^2	R^3	yield (%)
a	NO_2	H	H	89[a]
b	NO_2	OMe	OMe	97[b]
c	NO_2	-OCH_2O-		85[a]
d	NO_2	Cl	H	92[a]
e	NO_2	F	H	91[a]
f	NO_2	Cl	Cl	88[a]
g	Cl	Cl	H	98[b]

[a] Isolated yield. [b] Crude yield.

2-(2′-nitroaryl)-4-hydroxy carbazole-3-carbaldehyde **17a** was isolated in 50% yield (Scheme 5).

Scheme 5. Lewis Acid Mediated Cyclization of Enamine **16a**



The Lewis acid mediated cyclization of the enamine **16a** was then carried out using different Lewis acids, and the results obtained are presented in Table 1. In general, the reaction was found to be successful with all the Lewis acids. Use of 3 equiv of $ZnBr_2$ in xylenes at reflux slightly enhanced the yield of the carbazole **17a** (entry 2). Relatively, carbazole formation was found to be better and faster in DMF than xylenes confirming the involvement of ionic intermediates. Among the Lewis acids employed, the maximum yield for the carbazole **17a** was obtained using $CuBr_2$ (entries 4, 8, and 9). Surprisingly, the electrocyclization reaction was found to be successful even under moderate temperatures affording the carbazole **17a** in 75% yield (entry 9). Finally, the use of 1 equiv of $FeCl_3$ in DMF at reflux for 1 h led to the isolation of **17a** in low yield (entry 10).

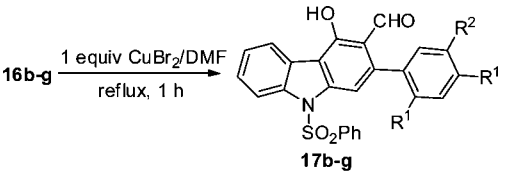
Table 1. Effect of Catalyst on Lewis Acid Mediated Cyclization of Enamine **16a**

entry	catalyst	condition	yield (%)[a]
1	1 equiv of $ZnBr_2$	xylenes, ref, 24 h	50
2	3 equiv of $ZnBr_2$	xylenes, ref, 24 h	55
3	1 equiv of $InBr_3$	xylenes, ref, 24 h	35
4	1 equiv of $CuBr_2$	xylenes, ref, 6 h	73
5	1 equiv of $ZnBr_2$	DMF, ref, 16 h	63
6	1 equiv of $InBr_3$	DMF, ref, 18 h	60
7	1 equiv of $CeCl_3$	DMF, ref, 8 h	65
8	1 equiv of $CuBr_2$	DMF, ref, 1 h	89
9	1 equiv of $CuBr_2$	1,2-DCE, ref, 6 h	75
10	1 equiv of $FeCl_3$	DMF, ref, 3 h	10

[a] Isolated yields of carbazole **17a**.

Having established a facile transformation of the enamine **16a** into the carbazole **17a** using $CuBr_2$, adopting similar conditions, the rest of the enamines **16b**–**g** were also converted into the respective 4-hydroxycarbazoles **17b**–**g** in excellent yields (Scheme 6). The structures of the 4-hydroxycarbazoles **17a**–**g** were confirmed by ^1H NMR, ^{13}C NMR, and HRMS analyses. As a representative case, the structure of the carbazole **17d** was confirmed by a single crystal X-ray analysis.[19]

Scheme 6. $CuBr_2$-Mediated Domino Reaction of Enamines **16b**–**g**



17	R^1	R^2	R^3	yield (%)
b	NO_2	OMe	OMe	74
c	NO_2	-OCH_2O-		87
d	NO_2	Cl	H	91
e	NO_2	F	H	89
f	NO_2	Cl	Cl	92
g	Cl	Cl	H	78

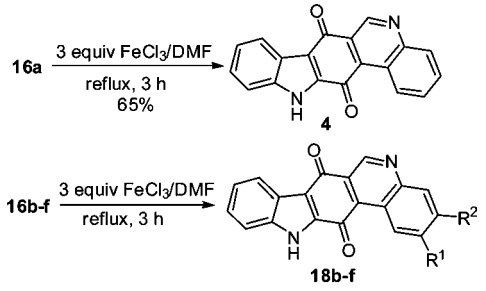
The low yield formation of carbazole **17a** using $FeCl_3$ (Table 1, entry 10) prompted us to study the reaction in a

detailed manner. It should be noted that under these conditions the enamine **16a** was fully consumed.

Additionally, the TLC analysis of the crude product indicated the formation of polar components in addition to the aldehyde **17a**. Further, the enamine **16g** which is lacking a NO_2 function can be converted into the respective 4-hydroxycarbazole **17g** using 1 equiv of $FeCl_3$ in DMF at reflux for 1 h in 76% yield.

To our delight, the reaction of enamine **16a** with 3 equiv of $FeCl_3$ in DMF at reflux for 3 h followed by workup led to the isolation calothrixin B **4** in 65% yield (Scheme 7). Under identical conditions, the enamines **16b**−**f** also converted into the corresponding carbazoloquinones **18b**−**f** in good yields. The structures of the calothrixins B **4**, **18b**−**f** were confirmed by ^{1}H NMR, ^{13}C NMR, and HRMS analyses.

Scheme 7. $FeCl_3$-Mediated Cyclization of Enamines **16a**−**f**



18	R^1	R^2	yield (%)
b	OMe	OMe	57
c	-OCH_2O-		60
d	Cl	H	67
e	F	H	64
f	Cl	Cl	65

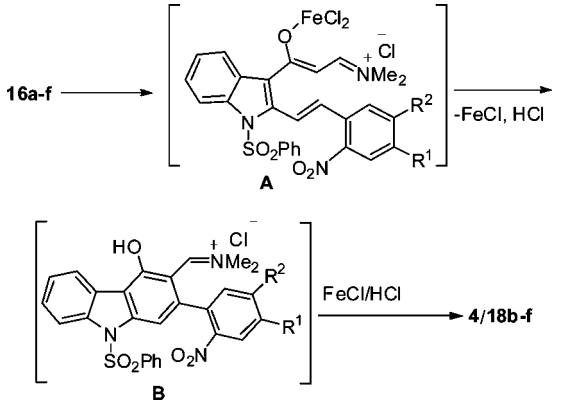
To our knowledge, this type of domino reaction which comprises electrocyclization, reductive cyclization, and oxidation followed by cleavage of the phenylsulfonyl group is highly unprecedented.

It should be mentioned that the reaction of 4-hydroxy-2-*o*-nitrophenylcarbazole-3-carbaldehyde **17a** with $FeCl_3$ in DMF at reflux failed to produce calothrixin B **4**. This clearly confirms the involvement of low valent iron as the transient species in the reduction of the nitro group. Mechanistically, the reaction of enamine with $FeCl_3$ generates a triene intermediate **A**, which upon electrocyclization followed by oxidation led to the 4-hydroxycarbazole iminium ion **B**. Obviously, the FeCl/HCl-mediated reduction of the nitro group followed by an intramolecular cyclization led to a quinoline moiety. The hydroxyquinoline upon oxidation followed by cleavage of the phenylsulfonyl group led to the target compounds **4**/**18b**−**f** (Scheme 8). The observed cleavage of the *N*-phenylsulfonyl group can be visualized through the nucleophilic addition of a dimethylamide anion which was formed during reductive cyclization of the intermediate **B**.

Alternatively, the coordination of $FeCl_3$ with oxygen atoms of sulfonyl and carbazoloquinone units followed by nucleophilic addition of the chloride anion may also support cleavage of the *N*-phenylsulfonyl group.

Finally, as a representative case, the calothrixin B **4** was converted into calothrixin A **3** using an excess of *m*-CPBA in DCM at reflux.[5]

Scheme 8. Mechanistic Hypothesis for Calothrixins **4**/**18b**−**f**



In summary, a novel one pot synthesis of calothrixins and its analogs is achieved involving an $FeCl_3$-mediated domino reaction of the enamines as a key step. The $FeCl_3$-mediated domino reaction protocol reported herein afforded calothrixin B and its analogs in an overall yield of 39−50%. Studies on antimalarial as well as anticancer activities of calothrixins and their analogs are in progress, and the results will be reported in due course.

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Supporting Information Available. Experimental procedure along with characterization data, ^{1}H, ^{13}C NMR spectra of all new compounds, ORTEP diagram and CIF file for **17d**. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) Structure was confirmed by single-crystal X-ray data. CCDC number for carbazole **17d**: 937225 (see the Supporting Information).

The authors declare no competing financial interest.