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Vivek T. Humne, Mahavir S. Naykode, Monica H. Ghom, Pradeep D. Lokhande

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Graphical Abstract

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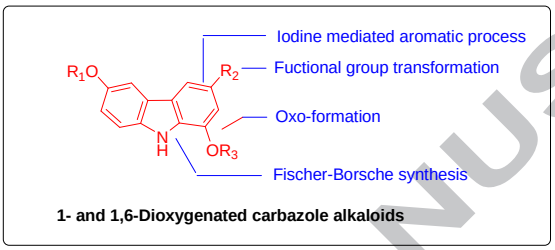

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Total synthesis of diverse oxygenated carbazoles by modified aromatization using molecular iodine

Vivek T. Humne,* Mahavir S. Naykode, Monica H. Ghom, Pradeep D. Lokhande*

Center for Advance Studies, Department of Chemistry, Savitribai Phule Pune University (Formerly University of Pune), Pune-411007, India

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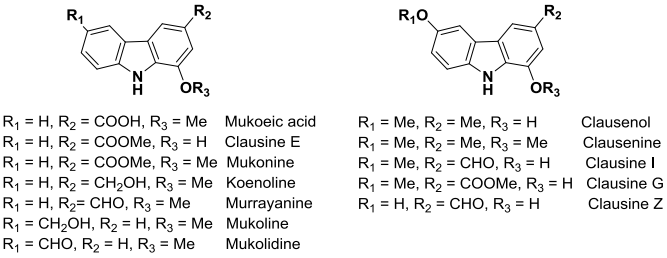
ABSTRACT

A convenient route has been developed for mono and dioxygenated carbazole alkaloids from 1-oxotetrahydrocarbazoles. The key step of the synthetic route is the aromatic process of 1-oxotetrahydrocarbazoles using molecular iodine. To our knowledge, this is the first report to manifest a direct synthesis of clausine E, mukonine, mukoeic acid and mukoline, from readily available ester-containing building blocks by using Fischer-Borsche method.

Carbazole alkaloids are the important class of nitrogen containing heterocycles present in many natural products and pharmaceutical ingredients.[1] Fischer-Borsche is the widely use practical method of its metal-free protocol, good regiospecificity, high yield and easy purification.[2] This process involves the condensation of phenylhydrazine with cyclohexanone, followed by aromatization. Moreover, applications of the Fischer -Borsche synthesis has been abound in various total synthesis of complex natural products.[3]

The oxygenated carbazoles are attracted a great interest due to their diverse and significant biological activities.[4] Many synthetic approaches has been carried out for oxygenated carbazoles by using transition metals[5] but very few routes has been known from Fischer-Borsche method in the literature. However, following drawbacks are noticed in the conventional process of Fischer-Borsche process; (a) difficult to introduce oxygen functionality at the appropriate position of carbazole scaffold, (b) longer reaction time and high temperature are required in the final step of aromatization, (c) protection and deprotection steps are required, and (d) low overall yield. Therefore, most of the research groups divert their synthesis from Fischer-Borsche protocol. We reasoned that the readily available precursor would constitute diversity oriented new approach to this important class of compound. Therefore, development of aromatic process of 1-oxotetrahydrocarbazole and their utility to construct the diverse 1- and 1, 6-dioxygemated carbazole alkaloid is exceedingly desirable.

Mukoeic acid, the first carboxylic acid derivative of 1-oxygenated carbazole was isolated from the bark of *Murraya koenigii* and their ester derivatives such as mukonine and clausine E were isolated from the plants of the *Rutaceae* family.[6]



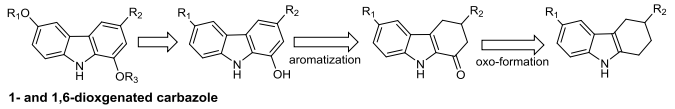
R_1 = H, R_2 = COOH, R_3 = Me	Mukoeic acid	R_1 = Me, R_2 = Me, R_3 = H	Clausenol
R_1 = H, R_2 = COOMe, R_3 = H	Clausine E	R_1 = Me, R_2 = Me, R_3 = Me	Clausenine
R_1 = H, R_2 = COOMe, R_3 = Me	Mukonine	R_1 = Me, R_2 = CHO, R_3 = H	Clausine I
R_1 = H, R_2 = CH_2OH, R_3 = Me	Koenoline	R_1 = Me, R_2 = COOMe, R_3 = H	Clausine G
R_1 = H, R_2= CHO, R_3 = Me	Murrayanine	R_1 = H, R_2 = CHO, R_3 = H	Clausine Z
R_1 = CH_2OH, R_2 = H, R_3 = Me	Mukoline		
R_1 = CHO, R_2 = H, R_3 = Me	Mukolidine		

Figure 1. Natural occurring 1- and 1, 6-dioxygenated carbazoles

A cytotoxic carbazole alkaloid; koenoline[7] and their easily oxidizable murrayanine derivative were obtained from the Indian *M. koenigii*.[8] Mukoline and Mukolidine were isolated from *Murraya koenigii* Spreng, and their extract exhibited antibacterial activity (Figure 1).[9] Recently, mukoline and mukolidine has been synthesized from aryl amine with the combine treatment of palladium (II) acetate and copper (II) acetate in pivalic acid.[10] Including, Nozaki and his co-workers investigated the double *N*-arylation of primary amines with 2,2'-biphenylylene ditriflates for mukonine.[11a] Mal and his co-workers[11b,c] introduced [4+2] annulation process starting from furoindolones and dimethyl maleate. Traditionally, Saha et al[11c,d] attempted 1-oxygenated carbazoles using Japp-Klingemann method.

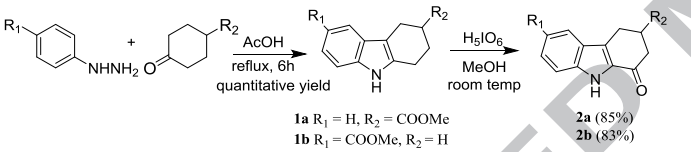
Of particular interest are 1,6-dioxygenated carbazoles, Chakraborty et al isolated clausenol and clausenine from the dried stem bark of *Clausena anisata* (Figure 1).[12] Both alkaloids show antibiotic activities, among these clausenol was found to be more active, and their inhibition against other bacteria can be compared

to streptomycin. Despite these intensive investigations, there are only four synthetic reports are documented: (a) condensation of substituted cyclohexanone with 4-methoxybenzene diazonium chloride under Japp-Klingemann condition,[12] (b) Lin and Zhang derived biscarbazoles *via* the formation of clausenol by Suzuki cross-coupling,[13] (c) Knölker et al attempted Buchwald–Hartwig amination followed by palladium(II)-catalyzed oxidative cyclization,[14] (d) Fagnou and his co-workers described the palladium based coupling protocol for clausenine.[15]



Scheme 1. Retrosynthetic analysis

A concise retrosynthetic analysis of oxygenated carbazole alkaloids is represented in scheme 1. We designed the diverse 1- and 1, 6-dioxygenated carbazoles from 1-oxotetrahydrocarbazole, as a key intermediate. The aromatic process of 1-oxotetrahydrocarbazole could furnish the respective target molecules followed by functional group transformations. The appropriate tetrahydrocarbazoles could conceive from the commercial available starting materials by Fischer-Borsche method. The elegant of our synthesis is to introduced hydroxyl and ester-functionality at the appropriate position of carbazole scaffold.



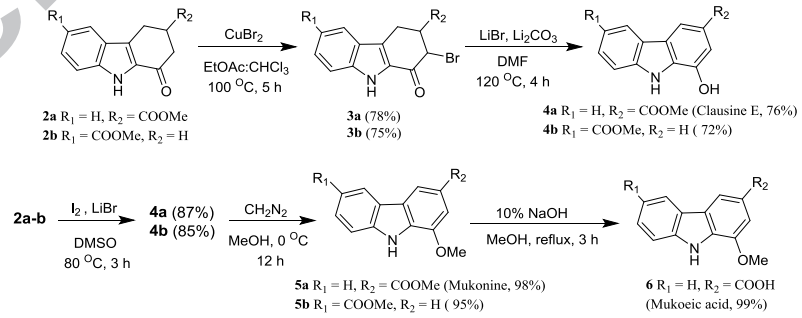
Scheme 2. Synthesis of 1-oxotetrahydrocarbazole

We started our experiment from commercially available phenylhydrazine and cylcohexanone, which readily converted to appropriate tetrahydrocarbazoles by Fischer-indolization. The 1-oxo-tetrahydrocarbazole-6-methylcarboxylate **(2a-b)** was obtained from **1a-b** by treating with periodic acid in methanol in good yield.[16] Initially, **2a** was our model substrate to study the efficacy of the aromatic process. In continuous of our work based on iodine-mediated transformations,[17a,b] recently, we reported the aromatization of tetrahydrocarbazoles using a catalytic amount of molecular iodine.[17c,d] When similar condition was employed, no remarkable change was observed. Previously, it was found that Oliveria et al. aromatized the similar kind of motif in two steps; (a) introduction of bromo group at α-position of 1-oxotetrahydrocarbazole and, (b) followed by aromatization using $LiBr/Li_2CO_3$ in DMF.[18] To accompany Oliveria protocol, we synthesized α-bromo requisite (**3a)** was aromatized by using $LiBr/Li_2CO_3$ in DMF to lead clausine E **(4a)** with 76% yield. On careful search of a literature, Sissouma et al[19] proposed the total synthesis of Calothrixin B without protection of indole nitrogen by using enolate formation, followed by dehydrogenation. Enolate of substrate **2a** was trapped by triflate and dehydrogenated *in situ* (Table 1, entry b). In this case, the aromatic product **4a** was isolated with moderate yield after deprotection process.

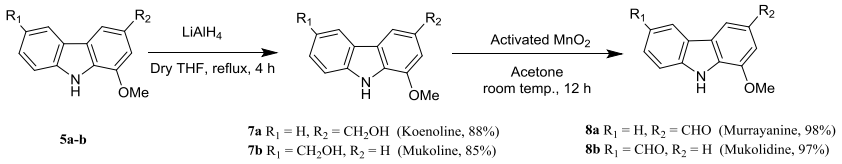
Table 1. Aromatization of 1- oxotetrahydrocarbazole under different reaction conditions

Entry	Condition	Time (h)	Yield (%)[a] 3a/4a
a[18]	LiBr, Li_2CO_3, DMF, 120 ºC	2	ND[c]/69
b[19]	LiHMDS, THF:HMPA, -78 ºC then $PhNTf_2$ in THF	1	ND/48
c	I_2, KBr, DMSO, 100 ºC	8	ND/ND
d	I_2, NaBr, DMSO, 100 ºC	6	47/ND
e	I_2, LiBr, DMSO, 80 ºC [b]	1	ND/87

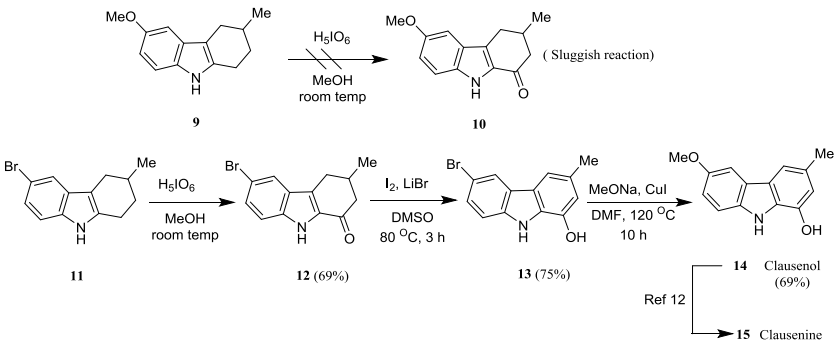
[a] Isolated yield
[b] Different proportion of I_2 and LiBr were screened
[c] ND = Not determine



Scheme 3. Synthesis of Clausine E, Mukonine and Mukoeic acid



Scheme 4. Synthesis of Koenoline, Mukoline, Murrayanine and Mukolidine



Scheme-5. Synthesis of Clausenol

The enolation of substrate **2a** followed by oxidative dehydrogenation by molecular iodine could reduce the total steps and increase the overall yield. We screened the different set of reaction conditions to aromatize the substrate **2a** (Table 1)**.** To avoid the expensive catalyst and harsh condition, we tried different types of readily available salts, but these salts did not afford the desired product **4a**. However product **3a** was isolated with 47% by the combined treatment of NaBr and iodine in DMSO at 100 ºC (Table 1, entry d). The combination of LiBr (1 equiv.) and molecular iodine (25 mol%) in DMSO at 80 ºC lead to increase the yield of clausine E **4a** (Table 1, entry e, 87%). Further increase the amount of molecular iodine did not significantly affect the reaction yield. In the next step, *o*-methlyation was carried out by diazomethane in methanol to afford mukonine **(5a)** in 98% yield.[20] Treatment of **5a** with 10% NaOH in methanol accomplished the mukoeic acid **(6)** with excellent yield. However, under similar optimal condition, we have successfully achieved isomer **5b** from **2b.**

To our delight, **5a-b** on our hand, we turn our synthesis to diverse structure of carbazoles from a single precursor. The substrates **5a-b** were reduced to their corresponding alcohols **7a-b** by lithium aluminium hydride in THF under reflux condition.[21a] Furthermore, under oxidation by activated MnO_2 in acetone, **7a-b** gets converted to murrayanine **8a** (98%) and mukolidine **8b** (97%).[21b]

Encouraged by the findings discussed above, we have drawn the total synthesis of 1, 6- dioxygenated carbazole such as clausenol **(14)**. In this case, we smoothly achieved substrate **9** by the condensation of 4-methoxyphenylhydrazine and 4-methyl cyclohexanone under reflux condition. When substrate **9** was employed to periodic acid in methanol for 6 h at -20 ºC, the oxo-product **10** was isolated with low yield (16%). However, the reaction was sluggish at 0 ºC and room temperature. Therefore, we changed our strategy and started with appropriate 1-oxotetrahydrocarbazole **12**. In this case, 4-bromophenylhydrazine and 4-methylcyclohexanone was allowed to undergo in Fischer-Borsche method to give tetrahydrocarbazole **11**. The resulting compound **11** was treated with periodic acid in methanol, the corresponding oxo-product **12** was accomplished with 69% yield. A mixture of molecular iodine and lithium bromide was subjected to **12** in dimethyl sulfoxide at 80 ºC to afforded aromatic product **13** in 75% yield. In the next step, bromo group of substrate **13** was displaced by methoxy group using CuI/MeONa[22] in DMF at 120 ºC, the clausenol **14** obtained in 69% yield. Finally, Phenol **14** on methylation by diazomethane in presence of methanol furnished clausenine **(15)**. The spectroscopic data of all synthesized natural products are in agreement with that reported in the literature.[23]

In conclusion, we have demonstrated a convenient, general and flexible synthesis for the diverse structure of carbazole alkaloids with good to excellent overall yields. In the present approach, construction of a suitably substituted basic carbazole framework in just 4-5 steps by modifying the aromatization process is remarkable. The present method is expedient and elegant furnishes an alternative method to aromatic process. Syntheses of these alkaloids have been accomplished without involving any discrete protection-deprotection steps. Further studies on the synthesis of other carbazole alkaloids and their analogues with additional biological studies are currently in progress and will be reported in due course.

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