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Copper (II) catalyzed aromatization of tetrahydrocarbazole: An unprecedented protocol and its utility towards the synthesis of carbazole alkaloids

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ABSTRACT

An efficient protocol for the aromatization of tetrahydrocarbazole is described by using catalytic copper (II) chloride dihydrate in DMSO. This newly established methodology has utilized towards the synthesis of naturally occurring carbazole alkaloids, namely 3-methylcarbazole, 3-formyl carbazole, glycozoline, glycozolicine and clauszoline-K. In addition, the protocol is generalized for the aromatization of *N*-substituted tetrahydrocarbazole, 1, 2, 3, 4-tetrahydroquinoline, 1, 2, 3, 4-tetrahydroisoquinoline and 1, 2, 3, 4-tetrahydro β-carboline to give the corresponding heteroaromatic compounds from very good to excellent yield. Moreover, this method has been proven to be tolerant to a broad range of functional groups with excellent yields.

Introduction

Carbazole is important structural motif due to its occurrence in natural products[1a-c] and drugs[1d-i] with a broad range of biological activities. For example, mono-oxygenated carbazole alkaloids like glycozoline,[2a,b] glycozolicine,[2c] and clauszoline-K[2d] isolated from the plants of genera Murraya, Clausena and Glycosmis (family *Rutaceae*) exhibit potent antibacterial, antioxidant, antifungal, anticancer and antifeedent activities. Similarly, 3-methyl carbazole[2d,e] and 3-formyl carbazole[2f] found in *Rutaceae* family possess antibacterial and antifungal properties. Besides this, the tricyclic carbazole scaffold is also important in electroluminescent material chemistry, like polymeric light emitting diode (PLED),[3a] organic light emitting device[3b,3c] and in organic solar cell (OSC).[3d] Thus, upgrading of efficient synthetic routes to the variety of biologically active carbazoles represents a significant objective in organic synthesis.

Several reports for the synthesis of carbazoles are available mainly in three fashion: (I) C-N bond coupling, (II) C-C bond coupling and (III) C-C/C-N bond coupling in one pot manner such as Fe mediated amination of iron complex followed by cyclization,[4a-c] Rh catalyzed[4d] cyclization,[4e] reductive cyclization,[4f] transition-metal-free intramolecular *N*-arylation,[4g] palladium-mediated oxidative cyclization,[4h] visible-light-induced intramolecular cyclization,[4i] reaction of arynes with nitrosoarenes[4j] and palladium-catalyzed Suzuki cross-coupling followed by reductive Cadogan cyclization.[4k] But the above methods required stoichiometric amount of tricarbonyliron,[4a-c] expensive catalyst,[4d] high temperature[4f] and possesses low yield[4h] and low regioselectivity.[4f,4h]

Besides C-C/C-N bond coupling, aromatization of Fischer–Borsche ring is the most intricating task and very few aromatizing reagents are reported which are mainly divided into three categories (a) Pd/C catalyzed aromatization.[5a-d] (b) DDQ and chloranil catalyzed aromatization.[5e-g] and (c) V_2O_5, MnO_2 catalysed aromatization[5h] which posseses many downsides like use of expensive catalyst, high catalyst loading, *N*-protection,[5e-g] higher temperature and frequently produces various side products. Hence development of easy, proficient and conventional method for the aromatization of tetrahydrocarbazole is exceedingly desirable.

Recently, we have developed a protocol in which iodine in DMSO caused aromatization[5i] and its efficacy was presented in the synthesis of different natural carbazole alkaloids.[6a-c] Copper (II) chloride is an inexpensive, environmentally friendly and readily available catalyst. It plays various functions like oxidizing agent for alcohol to aldehyde and ketone, [7a,b] oxidative coupling agent for the synthesis of heterocyclic compounds,[7c] halogenating agent,[7d] acts as a Lewis acid catalyst to promote iodination reaction, dehydrogenating agent for the indole and flavones synthesis,[7e-g] coupling agent for the coupling of terminal alkynes in PEG.[7h] We envisaged that the reaction of tetrahydrocarbazole using catalytic amount of $CuCl_2.2H_2O$ in DMSO allows aromatization.

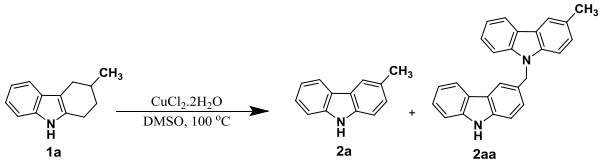
Owing to the need for more environmentally and economically benign processes, in this article we report the synthesis of carbazoles along with its application in the synthesis of naturally occurring carbazole alkaloids such as 3-formyl carbazole and clauszoline-K. Finally, the generality of our methodology was checked by the synthesis of *N*-protected carbazoles, quinoline, isoquinoline and *β*-carboline by using catalytic amount of $CuCl_2.2H_2O$ in DMSO solvent at 100 ^oC in excellent yield.

Results and discussion

We initiated our investigation with the reaction of 3-methyl terahydrocarbazole **1a** with 0.1 equiv of $CuCl_2.2H_2O$ at 80 °C. Under this condition, the product **2a** was isolated in 62% yield (Table 1, entry 2). Consequently, Lower yield was obtained at a lower reaction temperature. When the same reaction was carried out at 100 °C, increased in yield of **2a** to 95% was observed (Table 1, entry 3). Further increase in the temperature did not affect the yield of **2a**. To establish the best reaction condition for the aromatization of 3-methyl tertahydrocarbazole **1a**, the catalyst loading and reaction time were also scrutinized. When the reaction was conducted at lower catalyst loading, it proceeded with a lower product yield (Table 1, entry 1). A higher catalyst loading did not improve the yield, however 12 % of biscarbazole **2aa** was isolated as a side product which was confirmed by ^1H, ^{13}C, DEPT and HRMS (Table 1, entry 6).

Addition of TBHP as an oxidant to the reaction does not affect the yield of the product (Table 1, entry 7). Unsatisfactory results were obtained, when other oxidants such as di-tert-butyl peroxide, $NaIO_4$ and mCPBA were used with 0.10 equiv. of $CuCl_2.2H_2O$. Finally, the use of other solvents, such as DMF, PEG-400, and acetic acid was found to be less effective (Table 1, entry 8-10). However, there was no reaction in MeCN, EtOAc, and toluene. On the whole, we examined that the conditions of entry 3 are optimum for obtaining the desired product **2a** in the best yield.

Table 1 Optimization of the reaction conditions[a]

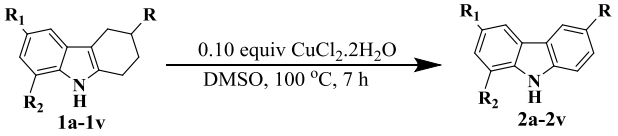


Entry	Catalyst	Conditions	Time	Yield[b] %	
			h	2a	2aa
1	0.05 equiv	DMSO	36	72	ND
2	0.10 equiv	DMSO, 80 °C	24	62	ND[c]
3	**0.10 equiv**	**DMSO**	**7**	**95**	**ND**
4	0.20 equiv	DMSO	4	93	ND
5	1.00 equiv	DMSO	2	88	Trace
6	2.00 equiv	DMSO	1	84	12
7	0.10 equiv	TBHP (0.02 equiv), DMSO	7	93	ND
8	0.10 equiv	DMF	24	58	ND
9	0.10 equiv	Acetic acid	24	60	ND
10	0.20 equiv	PEG 400	24	40	ND

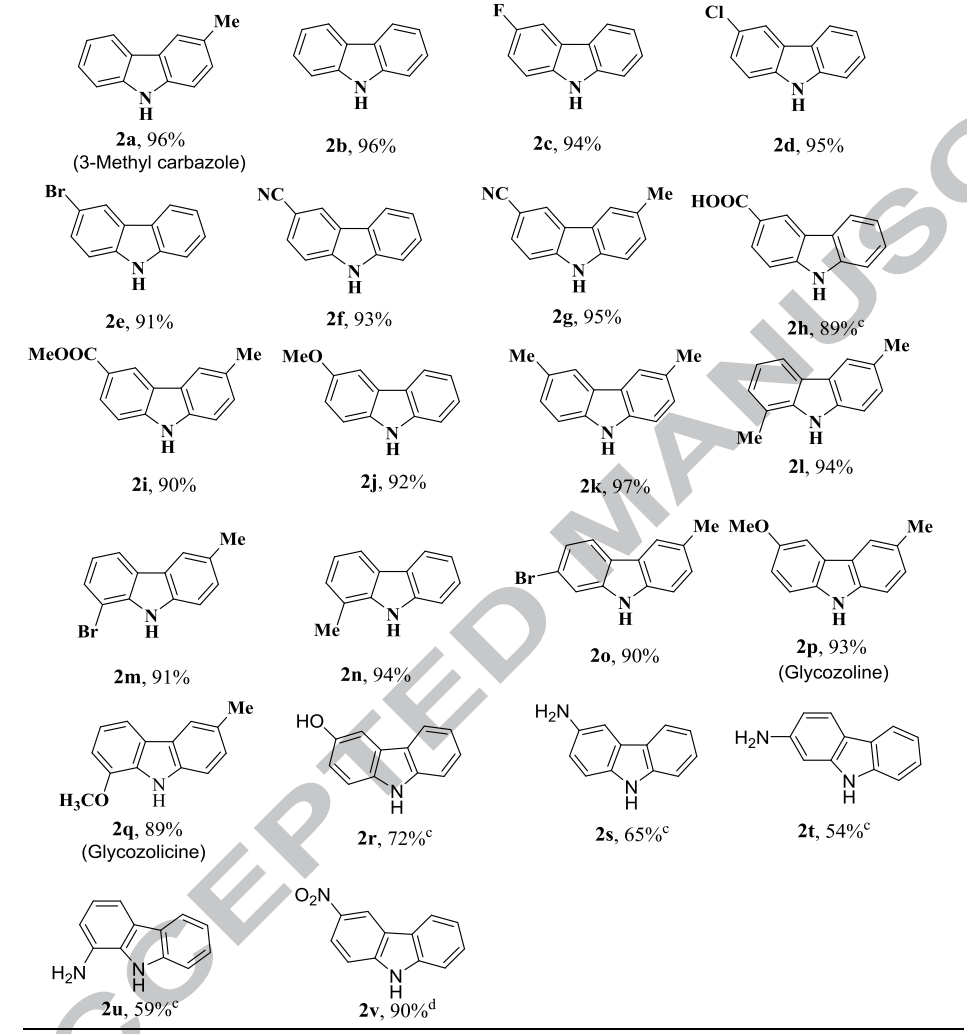
[a]The reactions were carried out using compound **1a** (2.70 mmol), cat. $CuCl_2.2H_2O$, solvent (5mL).
[b]Isolated product.
[c]Reaction carried at 80 °C.
ND: Not Detected

With the optimized condition in hand, we decided to explore the scope of this newly established methodology for the aromatization of substituted tetrahydrocarbazoles. The starting material substituted tetrahydrocarbazoles were prepared via Fischer-Borsche synthesis,[8a-c] which involves the treatment of substituted phenylhydrazines with cyclohexanone or 4-methyl cyclohexanone in acetic acid under the reflux condition for 8 h. Accordingly, a range of substituted tetrahydrocarbazoles were treated with $CuCl_2.2H_2O$ (0.10 equiv) in DMSO at 100 °C and the results are summarized in Table 2.

Table 2. Screening of the substituted tetrahydrocarbazole[a, b].



R=H, Me
R_1=H, F, Cl, Br, CN, COOH, COOMe,OMe, Me, NH_2, NO_2.
R_2=H, Me, Br, OMe, NH_2, NO_2.



[a]Reaction condition: Substituted tetrahydrocarbazole (2.69 mmol), $CuCl_2.2H_2O$ (0.10 equiv.), DMSO (5 mL), 100 °C.

[b]Yields are of pure isolated products.

[c]The reaction was carried out in presence of $CuCl_2.2H_2O$ (0.50 equiv.), DMSO (5 mL), 100 °C in 18 h.

[d]The reaction was carried out $CuCl_2.2H_2O$ (1.5 equiv.), DMSO (5 mL), 100 °C in 24 h.

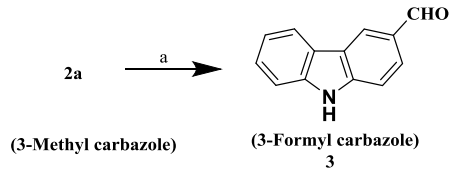
Tetrahydrocarbazole containing fluoro, chloro, bromo and methyl groups in the phenyl ring were employed successfully to afford the desired products in excellent yields. The carboxylate ester group in the phenyl ring of tetrahydrocarbazole reacted smoothly under the standard reaction condition to generate the corresponding product (Table 2, **2i)** in very good yield. However, tetrahydrocarbazoles containing substituent such as COOH, NO_2, OH, NH_2 required a higher amount of

$CuCl_2.2H_2O$ with a longer reaction time (Table 2, **2h**, **2r-v**). This may be due to the interaction of copper (II) chloride with the respective group to form complex. Therefore, approximately all electron neutral, rich and deficient substituents in benzene ring of tetrahydrocarbazole were well acceptable in this aromatization reaction. The present protocol represented its application towards the synthesis of naturally occurring carbazole alkaloids such as 3-methylcarbazole **2a**, glycozoline **2p**, glycozolicine **2q,** 3-formylcarbazole **3**, and clauszoline-K **5** in appreciable yields.

There are many methods reported so far for the synthesis of 3-methylcarbazole,[5i, 9j] glycozoline **2p**,[9a-j] glycozolicine **2q**.[10a-e] But most of the methods suffered from limitations such as expensive catalyst, low product yield, and long reaction. Our method has reduced the time significantly, to afford the **2a, 2p, 2q** products in excellent yield (Table 2, **2a**, **2p-q**).

The preparation of 3-formyl carbazole **3**[4e] a synthetic target was readily achieved as shown in (Scheme 1). Methyl group of 3-methyl carbazole **1a** undergo oxidation when reacted with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol/water medium at room temperature, to afford the aldehyde **3** in 93% yield. The isolated product **3** was detected preliminary by 2, 4 DNP and then confirmed by spectroscopic data.

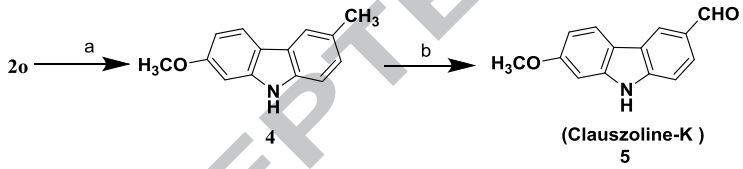
Scheme 1. Short synthesis of 3-formyl carbazole **3**.



Reagents and conditions: (a) **2a** (0.5517 mmol), DDQ (2.74 mmol), $MeOH/H_2O$ (16:1), rt, 16 h, 93%.

However, direct synthesis of 7-methoxy-3-methyl-carbazole **4** was unproductive through Fischer-Borsch route because of low yield of 7-methoxy-3-methyl terahydrocarbazole from the corresponding 3-methoxy phenyl hydrazine. HCl and 4-methyl cyclohexanone. Thus, we prepared carbazole **4** from carbazole **2o** through functional group interconversion.

Scheme 2. Short synthesis of Clauszoline-K **5**.



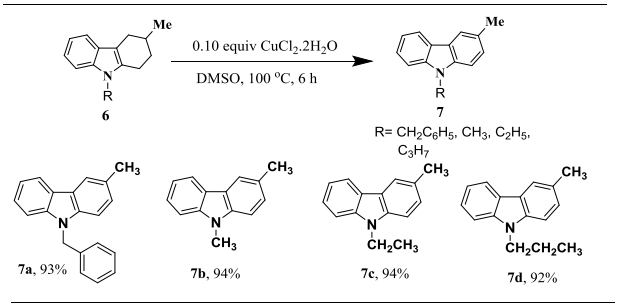
Reagents and conditions: (a) **2o** (0.38 mmol), NaOMe/DMF, CuI (0.76 mmol), 120 ^oC, 6 h, 88%. (b) **4** (0.5517 mmol), DDQ (2.743 mmol), $MeOH/H_2O$ (16:1), rt, 16 h, 87%.

A short synthesis of clauszoline-K, practiced by others[11a-e, 9j] was accomplished by taking substrate **4** obtained from substrate **2o** using NaOMe/CuI in DMF at 120 ^oC in 88 % yield. Aromatization of **1o** using $CuCl_2.2H_2O$ (0.10 equiv) in DMSO at 100 ^oC afforded **2o** as a key compound in 89% yield. Finally the target molecule clauszoline-K was obtained in 87% yield, when reacted with (DDQ) in methanol/water medium at room temperature which was confirmed by spectroscopic data.

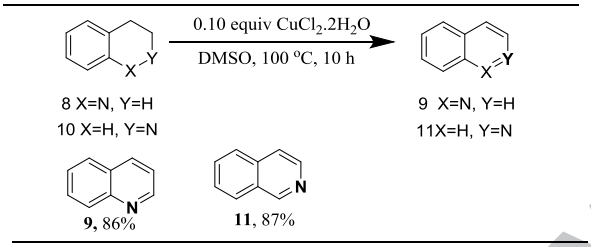
The generality of this methodology was further confirmed by employing *N*-protected terahydrocarbazoles and other tetrahydroheterocyclic compounds. When *N*-substituted terahydrocarbazoles treated under the standard reaction condition (Table 3, entry **7a-d**), the products were isolated in excellent yield. Thus it is evident that, this protocol is unaffected by the *N*-protection and can be employed for the synthesis of various natural products. Similarly, quinoline, isoquinoline and *β*-carboline were also synthesized in excellent yield (Scheme 3, **9**, **11**; Scheme 4, **13**) using $CuCl_2.2H_2O$ (0.10 equiv.) in

DMSO at 100 °C. Overall, 32 compounds were prepared and characterized by spectral (IR, NMR, MS) and HRMS data analysis.

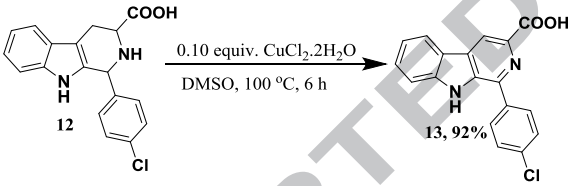
Table 3. Aromatization of *N*-substituted tetrahydrocarbazole.



Scheme 3. Aromatization of tetrahydroquinoline and tetrahydroisoquinoline.

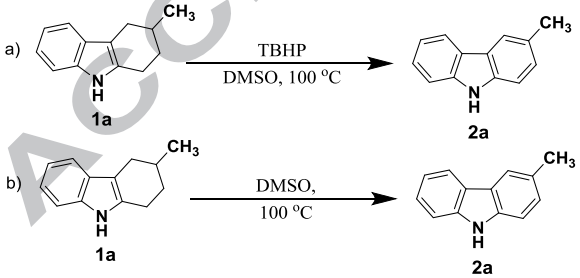


Scheme 4 Aromatization of substituted tetrahydro-β-carboline.



This methodology is easily scalable. When we applied our set condition for the aromatization of **1a** (1.0 g) in the presence of $CuCl_2.2H_2O$ (0.10 equiv.) catalyst in DMSO afforded the corresponding 3-methyl carbazole **2a** in 92% isolated yield.

Scheme 5 Primary mechanism studies.



To study the reaction mechanism, aromatization of **1a** was performed in the presence of 2 mol% TBHP in DMSO, afforded 39% of **2a**. However, when aromatization of **1a** was carried out in presence of 30 equiv. of DMSO solvent, 36% of **2a** was isolated with the recovery 57% of 1a. Similar yields were observed in both the experiments (Scheme 5, **a** and **b**). Instead, to check the role of oxygen, the aromatization reaction was also performed under N_2 conditions. Under this condition, **2a** was isolated in 95% yield.

From the above observations we found that inclusion of TBHP or atmospheric O_2 has no any significant role in the aromatization process.Therefore, we conclude that the aromatization of tetrahydrocarbazole can be achieved without using TBHP or atmospheric O_2 in an excellent yield.

Based on the literature as well as experimental precedents we carried, copper (II) chloride dihydrate has unusual strong tendency to form dimethyl sulphoxide complex or $CuCl_2$.2DMSO solvates, which is presumably driving force for this unique aromatization reaction.[12a-c] On further increasing the temperature promotes the copper dissolution reaction to generate CuCl as the self-catalytic intermediate species in DMSO. This self-catalytic intermediate species (CuCl) is key factor responsible for the aromatization reaction to proceed smoothly.

Conclusion: In summary, we have successfully developed catalytic $CuCl_2.2H_2O$ in DMSO as an aromatization protocol for tetrahydrocarbazole. we have efficiently utilize this protocol, for the synthesis 32 compounds including substituted carbazoles, bioactive carbazole alkaloids such as 3-methylcarbazole **2a**, glycozoline **2p**, glycozolicine **2q,** 3-formyl carbazole **3** and clauszoline-K **5,** *N*- substituted carbazole **7a-d**, quinoline **9**, isoquinoline **11** and *β*-carboline **13** in excellent yield. The present methodology is operationally simple and does not require expensive reagent. It accepts approximately all electron neutral (**2c-f**), rich (**2a**, **2j-u**) and deficient substrates (**2h**, **2i**, **2v**) in benzene ring of tetrahydrocarbazole. In addition, considering the importance of its impurity biscarbazole,[13a-d] our future studies will be focused on the development of methodology for the synthesis of biscarbazole obtained during optimization of aromatization reaction.

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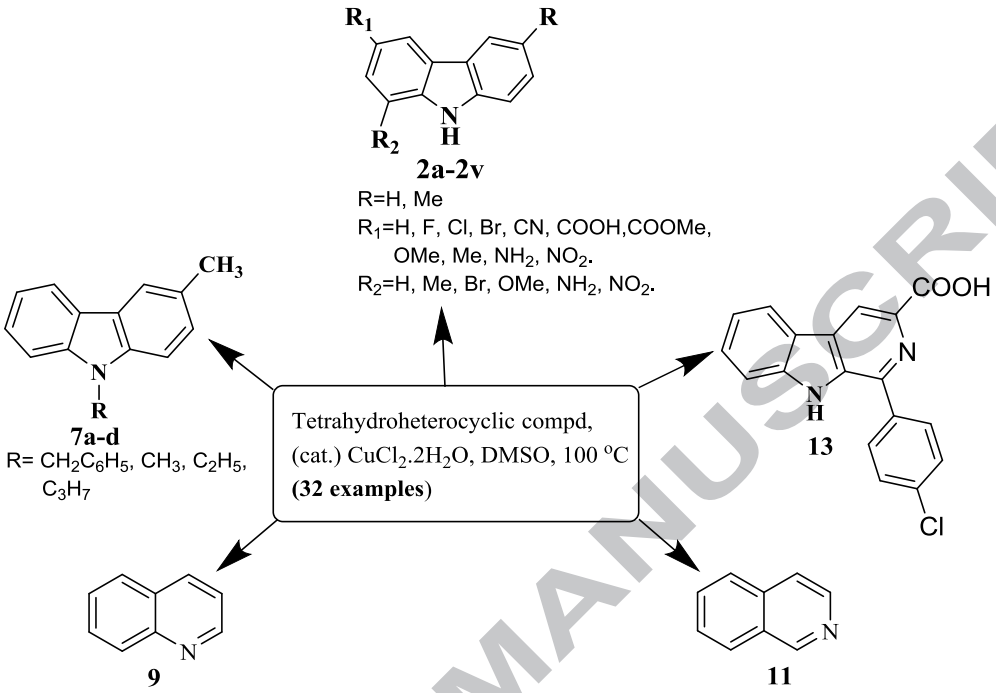
Copper (II) catalyzed aromatization of tetrahydrocarbazole: An unprecedented protocol and its utility towards the synthesis of carbazole alkaloids



Highlights

- 32 Examples.
- Simple work up, short reaction time and economically stable.
- It's application represented in the synthesis of five naturally occurring carbazole alkaloids.
- Generalized for the synthesis of *N*- substituted carbazoles, quinoline, isoquinoline and β-carboline.