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# Iodine-catalyzed Aromatization of Tetrahydrocarbazoles and their Utility in the Synthesis of Glycozoline and Murrayafoline A: A Combined Experimental and Computational Investigation

Vivek Humne,<sup>a</sup> Yuvraj Dangat,<sup>b</sup> Kumar Vanka,<sup>b</sup> Pradeep Lokhande\*<sup>a</sup>

<sup>a</sup>Center for Advance Studies, Department of Chemistry, University of Pune, Pune,

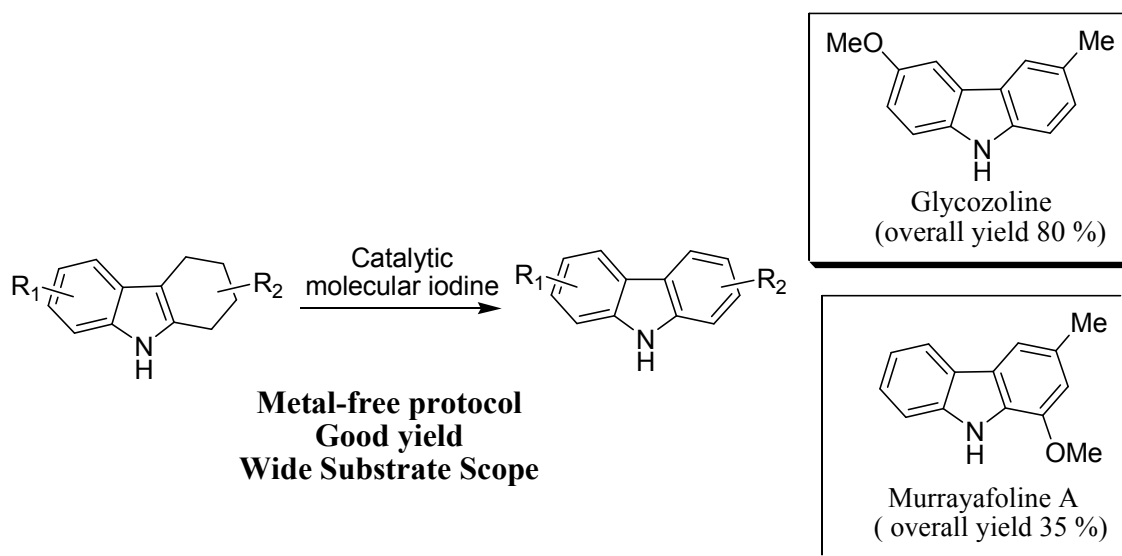
411007, india

<sup>b</sup>Division of Physical Chemistry, CSIR-National Chemical Laboratory, Pune, 411008, India

E-mail: [vivekhumne@rediffmail.com](mailto:vivekhumne@rediffmail.com); [pdlokhande@chem.unichem.ac.in](mailto:pdlokhande@chem.unichem.ac.in)

## Abstract

A new protocol for the aromatization of tetrahydrocarbazoles has been achieved using a catalytic amount of iodine, giving high yields. The role of iodine in aromatization has been explained by DFT and their wide scope is extended to the total synthesis of glycozoline and murrayafoline A. This method has proven to be tolerant of a broad range of functional groups.



Carbazole is a well-known alkaloid that shows a broad range of biological and medicinal properties. Moreover, their derivatives are widely used in organic materials for thermal, electrical, optical and exhibit light-emitting properties.<sup>1</sup> The carbazole scaffold has a significant feature therefore they paid an attractive attention in organic synthesis. Fischer-Borsche synthesis is the most common practical method used for the preparation of carbazole intermediates and their biologically active compounds.<sup>2</sup> In general, this involves condensation of phenylhydrazine with cyclohexanone, followed by aromatization. In final step, the aromatization of tetrahydrocarbazole is the challenging task. To the best of our knowledge, a very few reagents are documented for aromatization process in the literature (Scheme 1).

The following drawbacks are observed in aromatization process; (a) Pd/C is often used in a high boiling point solvents,<sup>3</sup> (b) Tetrahydrocarbazoles containing carbonyl and cyclohexanyl groups at the C-1 position shows a reduced ability of aromatization and possibly gives various side products by Pd/C,<sup>4</sup> (c) MnO<sub>2</sub> requires high temperatures and high stoichiometric proportions,<sup>5</sup> (d) Chloranil and DDQ are the organic derived reagents capable of effecting the aromatization process required the N-protection of tetrahydrocarbazoles.<sup>6</sup> In order to avoid the used of these reagents, most of the research groups have prepared starting substrates that can rearrange into their corresponding aromatic products.<sup>7</sup> These materials are, however, unstable and commercially unavailable. Therefore, the development of easy, efficient and conventional methods for the aromatization of tetrahydrocarbazole is exceedingly desirable.

Over the last few decades, molecular iodine has been employed in pharmaceutical and organic syntheses owing to its inexpensive, non-toxic, and environmentally benign nature.<sup>8</sup> As a part of our continuing efforts to study the iodine mediated transformations,<sup>9</sup> we are interested to develop a novel and efficient protocol for the aromatization of tetrahydrocarbazoles using a catalytic

amount of iodine. The present method is extended to the synthesis of natural products such as glycozoline and murrayafoline A.

We started our experimental strategy by condensation of commercially available phenyl hydrazine and cyclohexanone, which were readily converted to tetrahydrocarbazole by Fischer indolization. We wish to study the efficacy of the aromatization of tetrahydrocarbazole by molecular iodine. First, when 10 mol% of iodine was added to substrate **1a**, no remarkable effect was observed at room temperature (Table 1). The process of aromatization was started by subsequent increase in proportional of iodine (25 mol%) at 100 °C, the corresponding carbazole was isolated with excellent yield (Table 1, entry f). The addition of 75 mol% of iodine gave the mixture of the aromatic product **2** and the iodinated products **3a,b** (Table 1, entry g). Moreover, when the amount of iodine was increased to 150 mol%, **3** was obtained as a sole product (Table 1, entry h). Several solvents such as MeOH, AcCN, DCM, DMF and diphenyl ether were examined for the reaction medium. Dimethyl sulfoxide was found to be an efficient solvent for aromatic process.

Under the optimal condition, the attention was shifted to explore the scope of aromatic process with a variety of tetrahydrocarbazoles (Scheme 2). In this context, both electron-donating and electron-withdrawing substituents were well tolerated. The reaction was clean and smooth, with cyano group, the corresponding aromatic product isolated in excellent yields (Scheme 2, entry 5a). However, substrate **5b** required a higher amount of iodine and high temperature along with a longer reaction time. This may be due to the interaction of iodine with the carboxylic group. On the other hand, 3-methyltetrahydrocarbazole has an important role in the aromatization process (Scheme 2, entry 4g-i). Interestingly, a shorter reaction time and low temperature were enough for the complete aromatization of 3-methyltetrahydrocarbazoles by a catalytic amount of

molecular iodine (Scheme 2, entry 5g-i).

To exemplify the power of iodine-catalyzed aromatization, we carried out a short synthesis of the antibiotic and antifungal natural product glycozoline.<sup>10</sup> A catalytic amount of iodine was employed to tetrahydrocarbazole **4h** afforded the glycozoline in good yield (Scheme 2, entry 5h). The functional group compatibility of the developed method is particularly noteworthy and is not limited to methoxy, carboxylic acid, halogen and cyano groups. Additionally, we constructed a variety of N-substituted carbazoles using a catalytic amount of iodine (Scheme 2, entry 5j-n). Gratifyingly, all the corresponding aromatic carbazoles were obtained in good to excellent yields, while the N-allyl group was found to remain intact throughout the whole procedure under optimal conditions.

The insight of mechanism for the aromatization of tetrahydrocarbazole (**1a**) using molecular iodine was studied by density functional theory (DFT). The PBE/B3LYP/TZVP<sup>11,12</sup> approach was employed for this purpose, with the Turbomole 6.4 suite<sup>13</sup> of programs. For other information regarding the calculations, please see the Supporting Information file. The results obtained are shown in Figure 1. The mechanism has been found to be an ionic, leading to the formation of [I-H-I] and the cationic complex “c” (see Figure 1). The barrier for this step has been calculated to be 13.0 kcal/mol. This is followed by the abstraction of another proton by [I-H-I], leading to the formation of two HI molecules and the species “d”, which is exergonically converted to e. This is further converted, with the aid of I<sub>2</sub>, to the final species **2a** through two steps having barriers below 10.0 kcal/mol (see Figure 1). The slowest step for this process is found to have a barrier ( $\Delta G$ ) of 24.7 kcal/mol, indicating that the reaction would be highly facile at elevated temperatures, as observed experimentally (100 °C, as discussed earlier). It is to be noted that the ionic mechanism was found to be preferred over the homolytic dissociation of I<sub>2</sub>.

The interaction of I<sub>2</sub> with **1a** was found to lead to a significantly endothermic (by 52 kcal/mol: ΔE value) product when I<sub>2</sub> split homolytically, as opposed to the heterolytic splitting of I<sub>2</sub> upon interaction with **1a**, where the ionic product was found to be endothermic by only 1.0 kcal/mol (ΔE value). This is illustrated in Figure 12.1 of the Supporting Information file. The regeneration from HI of I<sub>2</sub> during the reaction (after the formation of **d** – see Figure 1) is seen to be a facile process, having a barrier of only 0.9 kcal/mol (see Figure 12.3 in the Supporting Information file).

Encouraged by the findings discussed above, we attempted the total synthesis of murrayafoline A (Scheme 3).<sup>14</sup> The phenyl hydrazine was added to the boiling solution of 4-methylcyclohexanone in acetic acid in order to furnish the tetrahydrocarbazole **4i**. Our next endeavor was to obtain 1-oxotetrahydrocarbazole **6** from substrate **4i**. The reaction was not proceeding at all with a variety of oxidants. However, periodic acid was found to be a befitting oxidant, leading to the desired product **6** in 69% yield.<sup>15</sup> Substrate **6** was reduced by sodium borohydride in methanol to yield **7**. Thereafter, we were interested in illustrating the synthetic utility of iodine on tetrahydrocarbazole **7**. The results were quite interesting: product **5i** was formed significantly after 5 h, suggesting that dehydration could be preferable to dehydrogenation in this case. However, the protection of the hydroxyl motif of **7** by the alkyl group could not establish compatible conditions. Sissouma<sup>16</sup> proposed the total synthesis of Calothrixin B without protection of the indole nitrogen by using enolate formation, followed by dehydrogenation. We thought that enolation of substrate **6** followed by oxidative dehydrogenation by molecular iodine could achieve the product **8**. In order to avoid the use of an expensive catalyst, we decided to employ readily available salts such as KI and NaI, but these salts did not afford the desired product, while LiBr with molecular iodine gave the expected product **8** in good yield. Phenol **8**

on methylation with diazomethane in the presence of methanol furnished murrayafoline A (**9**).<sup>17</sup>

The spectroscopic data of murrayafoline A is in agreement with that reported in the literature.

The overall yield of the product **9**, obtained in 3 steps, was found to be 35% (Scheme 3).

To summarize, we have explored a simple and efficient metal-free method for the aromatization of tetrahydrocarbazoles using a catalytic amount of iodine. The current method has been successfully applied to the synthesis of glycozoline and murrayafoline A, and the overall yields have been found to be 80% and 35% respectively. Overall, the operational simplicity and the economic viability of this method have definitely broadened the scope for the further study of aromatization.

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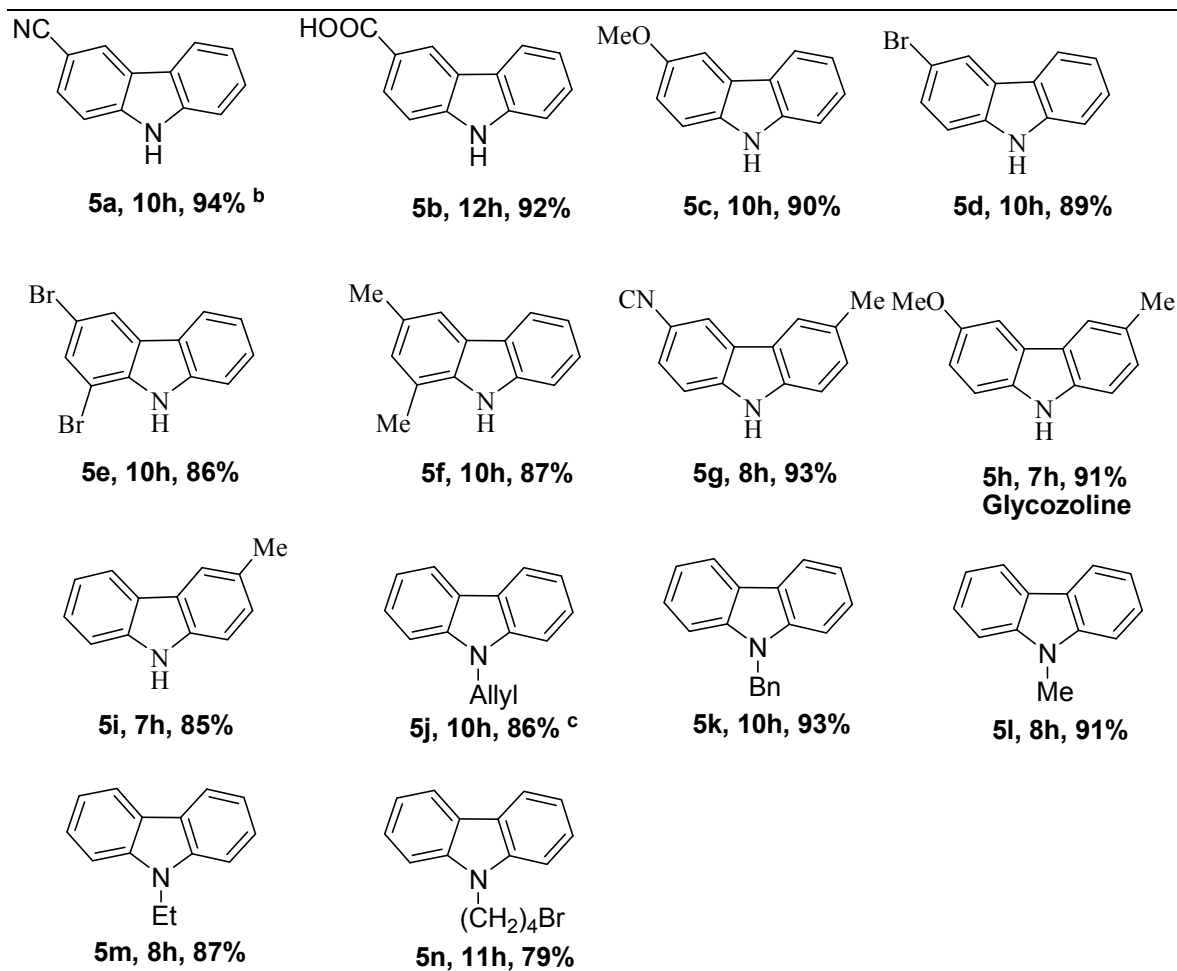
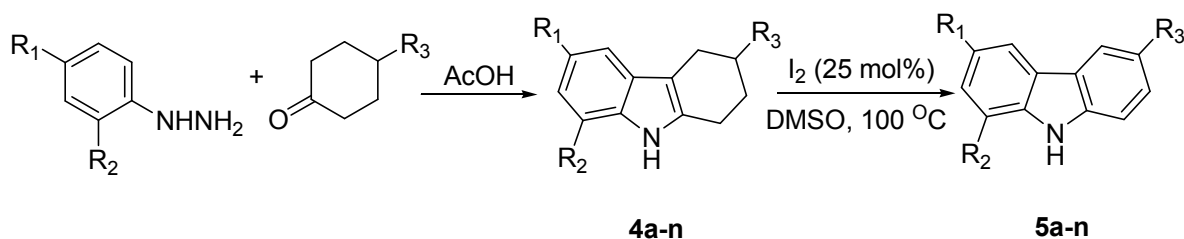
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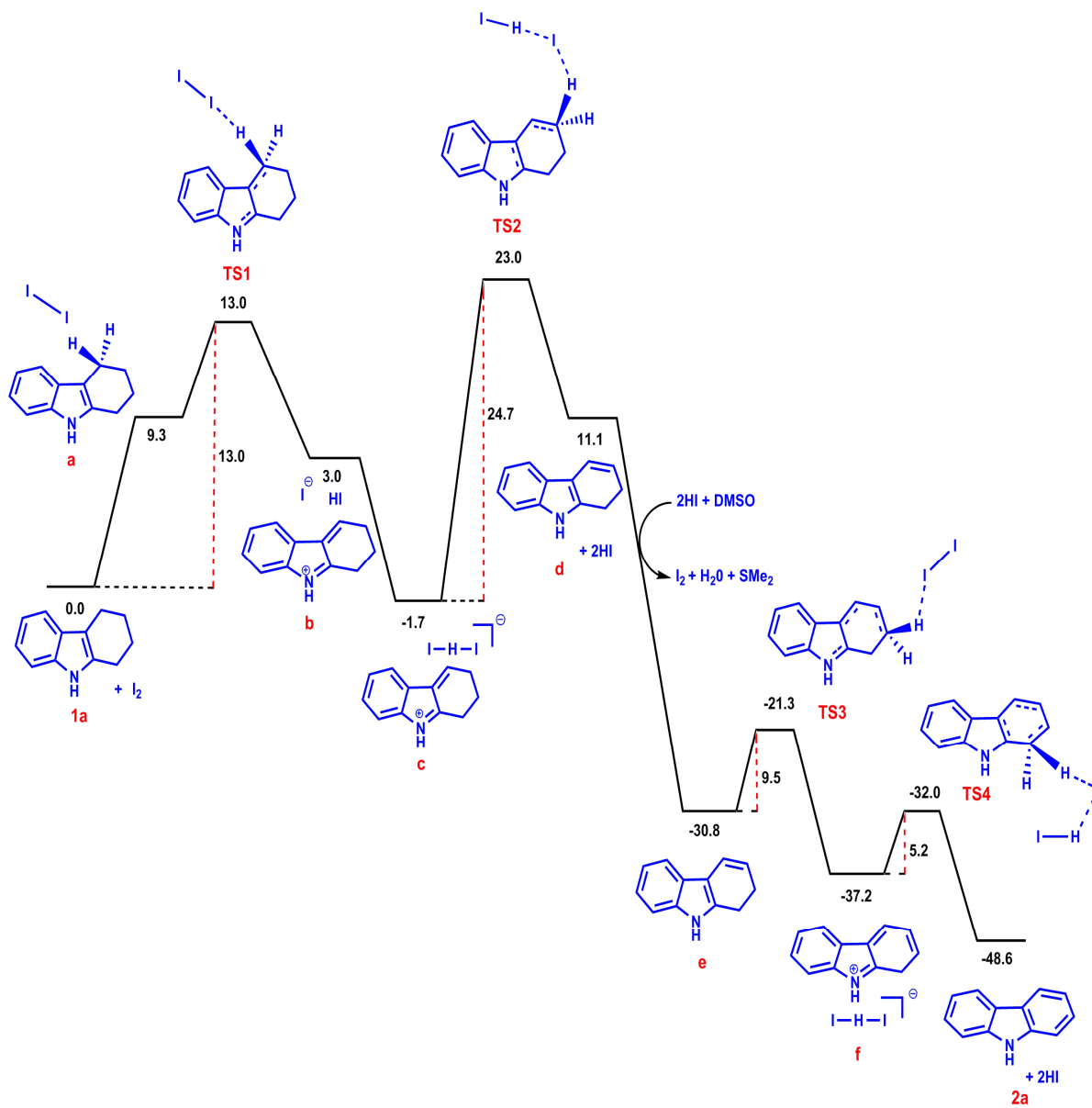


Scheme 2. Aromatization of Tetrahydrocarbazoles by Molecular Iodine<sup>a</sup>

<sup>a</sup>Reaction condition: **4** (2.4 mmol) and I<sub>2</sub> (25 mol%) in DMSO (5 mL) at 100 °C.

<sup>b</sup>Isolated yield. <sup>c</sup>Preparation of substrate **4j-n** is given in supporting information

Figure 1. The free-energy profile for the conversion of 1a to 2a



## Scheme 3. A Short Synthesis of Murrayafoline A

