Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 4832

Received 25th March 2014,
Accepted 24th April 2014

DOI: 10.1039/c4ob00635f

www.rsc.org/obc

Iodine-catalyzed aromatization of tetrahydrocarbazoles and its utility in the synthesis of glycozoline and murrayafoline A: a combined experimental and computational investigation†

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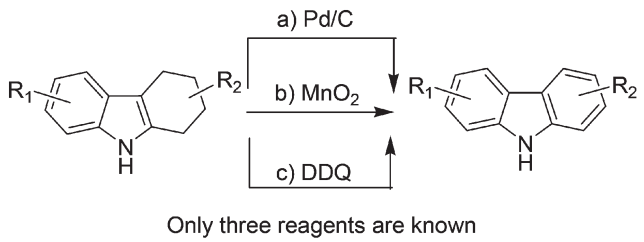
A new protocol for the aromatization of tetrahydrocarbazoles has been achieved using a catalytic amount of iodine, giving high yields. The role of iodine in the aromatization has been explained by DFT, and its wide scope is extended to the total synthesis of glycozoline and murrayafoline A. This method 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. Various carbazole derivatives are widely used in organic materials of thermal, electrical, optical and visible light-emitting applications.[1] The carbazole scaffold's significant features mean that it attracts great attention in the field of organic synthesis. Fischer–Borsche synthesis is the most common practical method used for the preparation of carbazole intermediates and their biologically active compounds.[2] In general, this involves the condensation of phenylhydrazine with cyclohexanone, followed by aromatization. The final step, aromatization of tetrahydrocarbazole, is the most challenging task. To the best of our knowledge, very few reagents are documented for use in this aromatization process in the literature (Scheme 1).



Scheme 1 Different reagents used for the aromatization of tetrahydrocarbazole.

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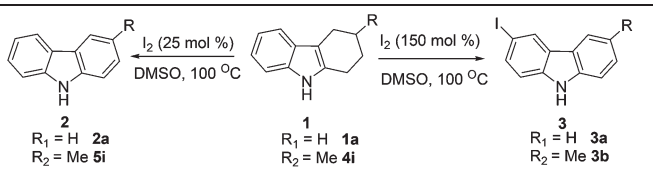
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c4ob00635f

The following drawbacks are observed in the aromatization process; (a) Pd/C is often used in a solvent with a high boiling point,[3] (b) tetrahydrocarbazoles containing carbonyl and cyclohexanyl groups at the C-1 position show a reduced ability for aromatization, and possibly produce various side products with Pd/C,[4] (c) MnO_2 requires high temperatures and high stoichiometric proportions,[5] (d) chloranil and DDQ are organically derived reagents capable of effecting the aromatization process, which require N-protection of the tetrahydrocarbazoles.[6] In order to avoid the use of these reagents, most research groups have prepared starting substrates that can rearrange into the corresponding aromatic products.[7] 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

Table 1 Optimization of the reaction conditions



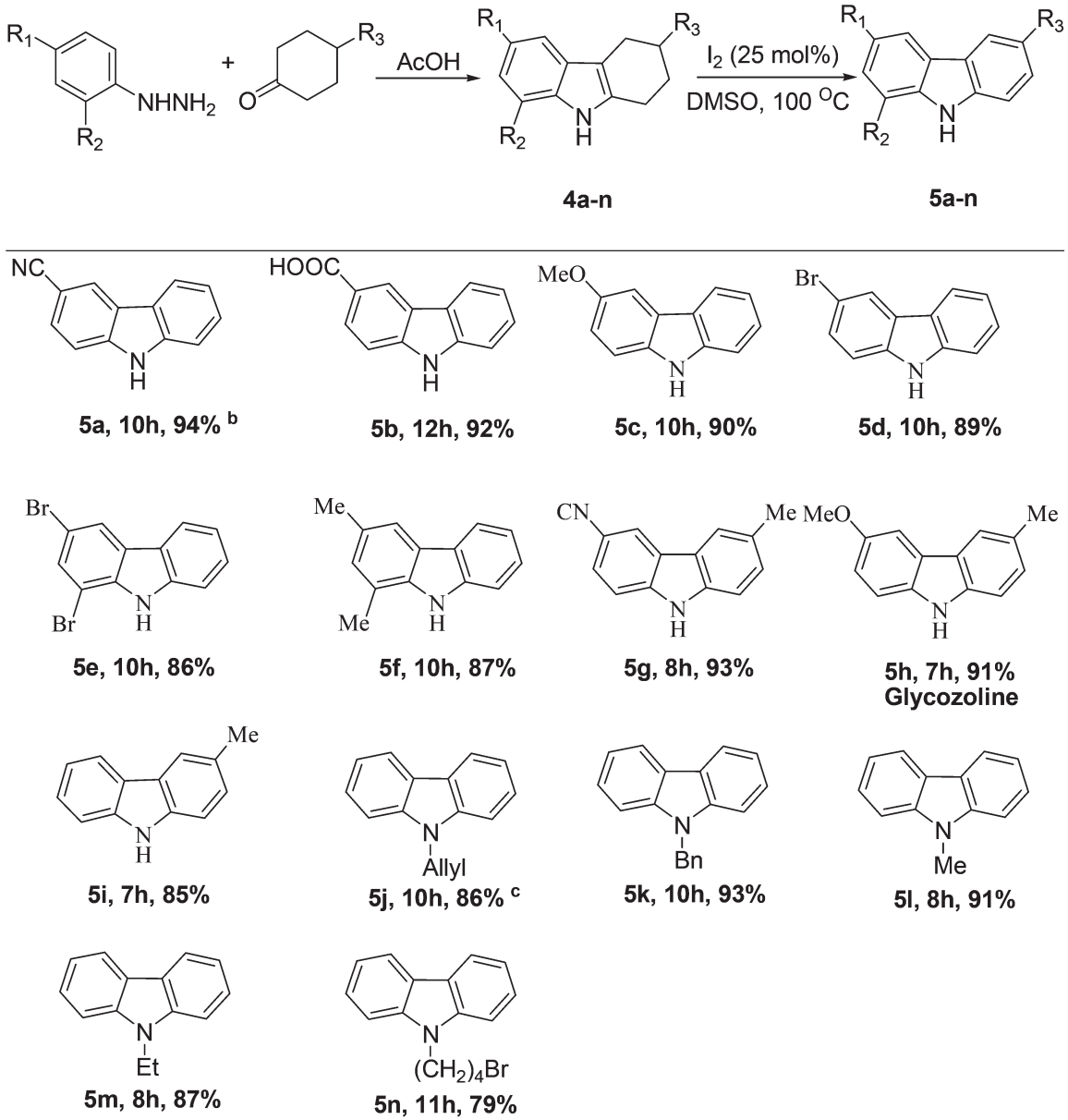
Entry	I_2 (mol%)	Temp (°C)	Time (h)	Yield % (2)[a]	Yield % (3)[b]
a	10	Rt	48	NR	NR
b	25	Rt	48	NR	NR
c	100	Rt	48	NR	NR
d	10	50	48	NR	NR
e	10	100	48	53[c]	NR
f	25	100	7	93	NR
g	75	100	10	73	28
h	150	100	10	NR	89[d]

[a,b] Isolated products. [c] Starting substrate was recovered with the product. [d] Product was confirmed by NMR and GCMS.

nature.[8] As part of our continuing efforts to study iodine-mediated transformations,[9] we are interested in developing a novel and efficient protocol for the aromatization of tetrahydrocarbazoles using a catalytic amount of iodine. The method we have developed is extended to the synthesis of natural products such as glycozoline and murrayafoline A.

We started our experimental strategy with the condensation of commercially available phenyl hydrazine and cyclohexanone, which were readily converted to tetrahydrocarbazole by Fischer indolization. We wished 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 a subsequent increase in the proportional amount of iodine (25 mol%) at 100 °C, and the corresponding carbazole was isolated with an excellent yield (Table 1, entry f). The addition of 75 mol% of iodine gave a mixture of the aromatic product **2** and the iodinated products **3a and b** (Table 1, entry g). Moreover, when the amount of iodine was increased to 150 mol%, **3** was obtained as the sole product (Table 1, entry h). Several solvents, such as MeOH, AcCN, DCM, DMF and diphenyl ether, were examined as the reaction medium. Dimethyl sulfoxide was found to be an efficient solvent for the aromatic process.

Under the optimal conditions, our attention shifted to exploring the scope of the aromatic process with a variety of tetrahydrocarbazoles (Scheme 2). In this context, both electron-donating and electron-withdrawing substituents were well



Scheme 2 Aromatization of tetrahydrocarbazoles by molecular iodine. [a]Reaction conditions: **4** (2.4 mmol) and I_2 (25 mol%) in DMSO (5 mL) at 100 °C. [b]Isolated yield. [c]Preparation of substrate **4j–n** is given in the ESI.†

tolerated. The reaction was clean and smooth, with a cyano group-containing aromatic product isolated in an excellent yield (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 carboxyl group. On the other hand, 3-methyltetrahydrocarbazole had 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.[10] A catalytic amount of iodine was added to tetrahydrocarbazole **4h**, which afforded glycozoline in a good yield (Scheme 2, entry **5h**). The functional group compatibility of the developed method is particularly noteworthy, and is not limited to methoxyl, 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 the optimal conditions.

An insight into the mechanism for the aromatization of tetrahydrocarbazole (**1a**) using molecular iodine was obtained using density functional theory (DFT). The PBE/B3LYP/TZVP[11,12] approach was employed for this purpose, with the Turbomole 6.4 suite[13] of programs. For other information regarding the calculations, please see the ESI.† The results obtained are shown in Fig. 1. The mechanism has been found

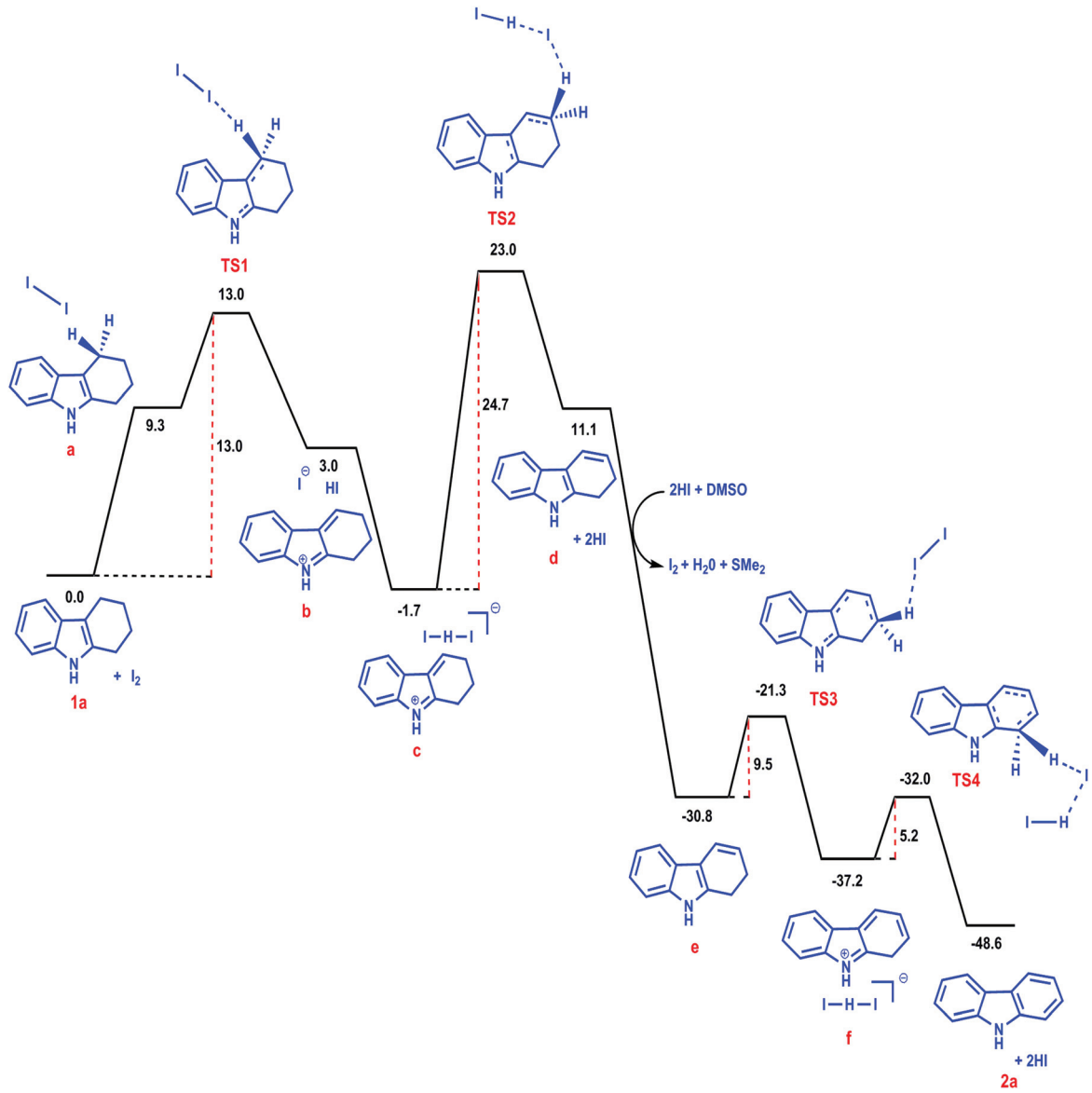
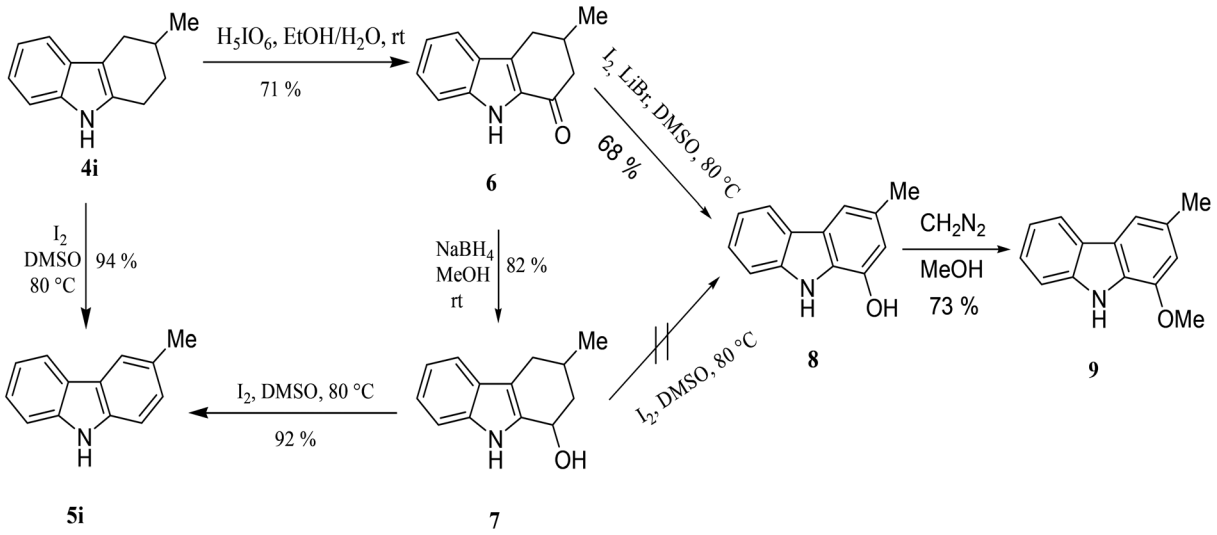


Fig. 1 The free-energy profile for the conversion of **1a** to **2a**.



Scheme 3 A short synthesis of murrayafoline A.

to be ionic, leading to the formation of $[I–H–I]^-$ and the cationic complex "**c**" (see Fig. 1). The barrier for this step has been calculated to be 13.0 kcal mol^{-1}. 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_2, to the final species **2a**, through two steps which have barriers below 10.0 kcal mol^{-1} (see Fig. 1). The slowest step for this process was found to have a barrier (ΔG) of 24.7 kcal mol^{-1}, 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_2. The interaction of I_2 with **1a** was found to lead to a significantly endothermic (by 52 kcal mol^{-1}: ΔE value) product when I_2 split homolytically, as opposed to the heterolytic splitting of I_2 upon interaction with **1a**, where the ionic product was found to be endothermic by only 1.0 kcal mol^{-1} (ΔE value). This is illustrated in Fig. 12.1 of the ESI.† The regeneration from HI of I_2 during the reaction (after the formation of **d** – see Fig. 1) is seen to be a facile process, having a barrier of only 0.9 kcal mol^{-1} (see Fig. 12.3 in the ESI†).

Encouraged by the findings discussed above, we attempted the total synthesis of murrayafoline A (Scheme 3).[14] Phenyl hydrazine was added to a boiling solution of 4-methylcyclohexanone in acetic acid, in order to obtain the tetrahydrocarbazole **4i**. Our next endeavor was to obtain 1-oxotetrahydrocarbazole **6** from substrate **4i**. The reaction did not proceed at all with a variety of oxidants. However, periodic acid was found to be a befitting oxidant, leading to the desired product **6** in a 69% yield.[15] Substrate **6** was reduced by sodium borohydride in methanol to yield **7**. Thereafter, we were interested in illustrating the synthetic utility of iodine with 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, protection of the hydroxyl motif of **7** by the alkyl group meant that compatible conditions could not be established. Sissouma[16] proposed the total synthesis of Calothrixin B without protection of the indole nitrogen using enolate formation, followed by dehydrogenation. We thought that enolation of substrate **6** followed by oxidative dehydrogenation with molecular iodine could achieve 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 a good yield. Phenol **8**, upon methylation with diazomethane in the presence of methanol, afforded murrayafoline A (**9**).[17] The spectroscopic data of murrayafoline A is in agreement with that reported in the literature. The overall yield of 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.

Acknowledgements

VTH is thankful to CSIR, New Delhi, India, for the award of a senior research fellowship. KV and YD acknowledge the XIIth Five Year Plan project, MSM, for financial assistance.

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