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Synthesis of substituted carbazoles and β-carbolines by cyclization of diketoindole derivatives ☆

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Abstract—A new route to substituted β-carbolines and carbazoles is described. Diketoindole intermediates, prepared by Friedel–Crafts acylations of 3-substituted indoles, have been converted to 3-hydroxycarbazoles and β-carbolines in good yields, 51–96% and 82–97%, respectively. This method also allows for the formation of 4-substituted β-carbolines. The application of this methodology to the synthesis of the natural products hyellazole and 6-chlorohyellazole is also described.

β-carbolines and carbazoles are found in many natural products, such as lavendamycin[1] (**1**), hyellazole[2] (**2**), 6-chlorohyellazole (**3**), carazostatin[3] (**4**) and carbazomadurin A[4] (**5**) (Fig. 1). Many of these natural products possess interesting biological activities. These properties have spurred the development of many synthetic methodologies for the assembly of β-carbolines and carbazoles.[5] Classical methods of constructing the β-carboline core include the Pictet–Spengler[6] and Bishler–Napieralski syntheses. More recently, several transition-metal mediated methods have been described for carbazoles[7,8] and β-carbolines.[9]

To our knowledge, the use of diketoindoles in the synthesis of carbazoles and β-carbolines has not been described. Dulenko et al. have used pyrilium salts to synthesize a limited set of benzo[4,5]thieno[2,3-*c*]pyridines and dibenzothiophenes,[10] as well as some β-carbolines.[11] In addition, other recent works have described the base-mediated conversion of diketophenyl compounds into naphthol derivatives.[12]

Our interest in carbazoles was initially kindled by the reported anti-oxidant and neuroprotective activities of compounds such as carazostatin (**4**) and carbazomadurin A (**5**), whose synthesis has recently been described.[13] In the course of our work, a convergent route to carbazoles via the cyclization of diketoindoles was devised. These versatile intermediates also allowed for the formation of functionalized β-carbolines. We report herein the results of these studies.

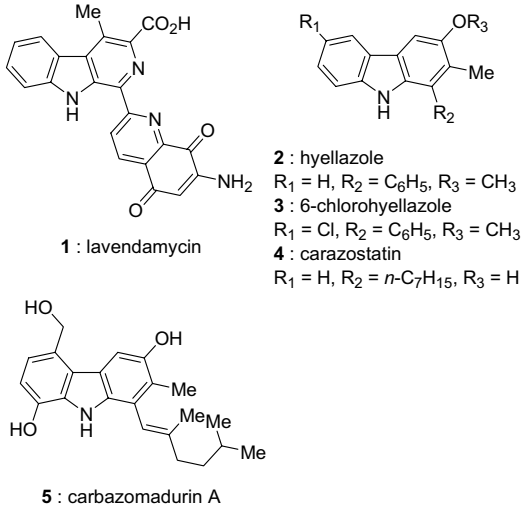

Figure 1. Several naturally occurring carbazoles and β-carbolines.

The diketoindoles were prepared in three steps from indol-3-yl acetic acids (Scheme 1).[14,15] The acids **6** were converted into Weinreb amides and then allowed to

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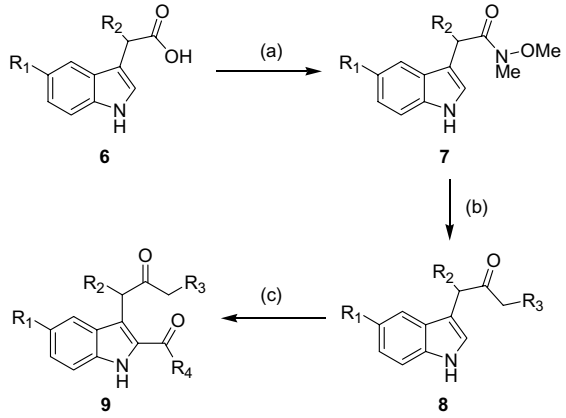


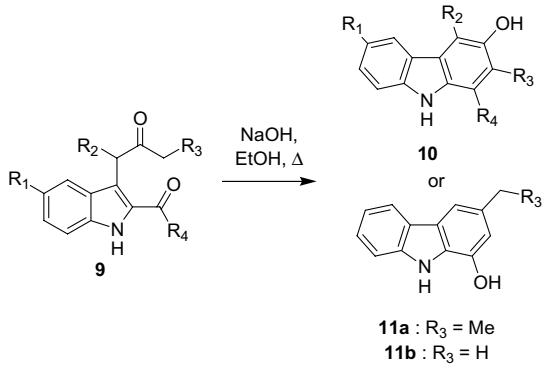
Scheme 1. Synthesis of diketones **9**. Reagents and conditions: (a) $ClCO_2i$-Pr, NMM, THF, −20 °C, then MeNH(OMe)·HCl, Et_3N, DMF, 0 °C, 84–92%; (b) MeMgCl or EtMgBr, THF, 0 °C/rt, 71–88%; (c) acylating agent, $ZnCl_2$, Et_2O, see Table 1.

react with methyl or ethyl Grignard reagents to afford indol-3-yl ketones **8** in good yields (71–88%). In order to introduce the second carbonyl moiety, the 3-substituted indoles **8** were subjected to Friedel–Crafts acylations.[16] The reaction of **8** with acid chlorides or anhydrides was efficiently promoted by the addition of excess zinc chloride to give a variety of diketoindoles **9** in acceptable yields (35–75%, Table 1). The acylation occurred selectively at the 2-position of the indole, as expected. However, no general reaction conditions could be discovered. In each case, the amounts of zinc chloride and acylating agent had to be optimized.

The base mediated cyclization of diketoindoles **9** into carbazoles **10** proceeded in the presence of sodium hydroxide (0.5 equiv) generally with good yields (51–96%, Scheme 2 and Table 2). The reaction was usually complete within 30 min, even when the amount of sodium hydroxide was reduced to 0.1 equiv. For substrates where both ketones were enolizable, cyclization could lead to two isomeric carbazoles. However, the reaction showed a clear preference for the formation of 1-hydroxycarbazoles (Table 2, entries 4 and 5). The carbazoles described herein, although sensitive to degradation presumably by air oxidation when in solution,[17] could be stored as solids without noticeable decomposition.

Next, the diketoindoles **9a**–**g** were converted to β-carbolines **12a**–**g** in good yields (82–97%, Scheme 3) in the presence of ammonium acetate. In particular, the formation of derivative **12f** from diketone **9f** demonstrated that this approach could be utilized for the synthesis of 4-substituted β-carbolines. This strategy represents an advantage over other methods, such as the Pictet–Spengler synthesis, which requires the preparation of functionalized tryptamine derivatives (Scheme 4).

In order to illustrate the utility of the methodology described herein, several of the carbazole products were further transformed. For example, methylation of **10a** and **10g** afforded the natural products hyellazole (**2**) and 6-chlorohyellazole (**3**) (Scheme 3).[18c] The syntheses were

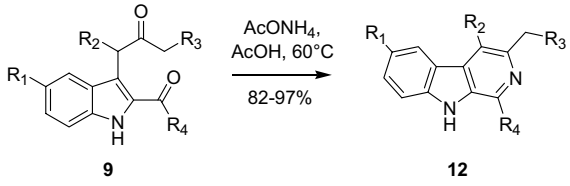


Scheme 2. Base-promoted cyclization of diketoindoles **9**.

Table 2. Synthesis of carbazoles **10** or **11**

Entry	Substrate	Product(s)	Yield (%)
1	**9a**	**10a**[19a]	85
2	**9b**	**10b**	96
3	**9c**	**10c**	51
4	**9d**	**10d**[19b]+**11a** (1:10)[a]	95
5	**9e**	**11b**[b,19c]	88
6	**9f**	**10f**	79
7	**9g**	**10g**	74

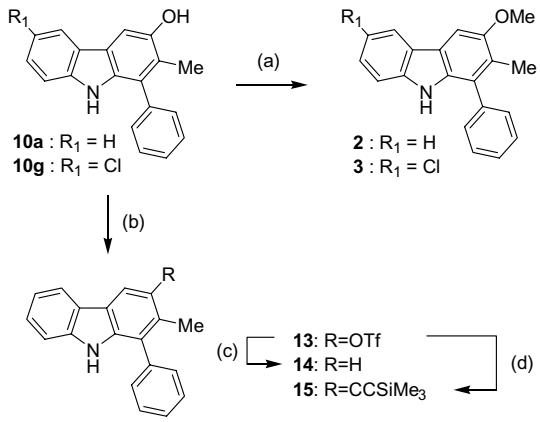
[a] Isolated as a mixture.
[b] Only product isolated.



Scheme 3. Conversion of diketoindoles **9a**–**g** into β-carbolines **12a**–**g**.

Table 1. Synthesis of **9** by Friedel–Crafts acylations of **8**

Entry	R_1	R_2	R_3	Acylating agent (equiv)	$ZnCl_2$ (equiv)	R_4	Product; yield (%)
1	H	H	CH_3	PhCOCl (5)	5	C_6H_6	**9a**; 75
2	H	H	CH_3	2-Naphthoyl chloride (5)	5	2-Naphthyl	**9b**; 71
3	H	H	CH_3	Cinnamoyl chloride (1.2)	2	(E)–CH=CH–C_6H_6	**9c**; 35
4	H	H	CH_3	AcCl (2)	1.5	CH_3	**9d**; 50
5	H	H	H	Ac_2O (2)	3	CH_3	**9e**; 43
6	H	CH_3	CH_3	PhCOCl (5)	5	C_6H_6	**9f**; 43
7	Cl	H	CH_3	PhCOCl (5)	5	C_6H_6	**9g**; 66



Scheme 4. Further transformations of 3-hydroxycarbazoles. Reagents and conditions: (a) MeI, K_2CO_3, acetone, reflux; (b) Tf_2O, 2,6-lutidine, CH_2Cl_2, 90%. (c) $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H, DMF, 86%; (d) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, HCCTMS, DMF, 87%.

thus completed in five steps from readily available indole-3-acetic acids.[18] Carbazole **10a** has also been converted into derivatives **14** and **15** utilizing palladium-catalyzed reactions.

In conclusion, a convergent route to highly substituted carbazoles and β-carbolines via diketoindoles **9** was devised. In addition, the application of this methodology to the synthesis of the natural products hyellazole and 6-chlorohyellazole was also presented. Further applications of this methodology for the synthesis of other highly substituted carbazole and β-carboline natural and non-natural compounds are underway.

Supplementary data

Detailed experimental procedures and compound characterizations provided.

Acknowledgements

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