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Single-step synthesis of 3-hydroxycarbazoles by annulation of electron-rich anilines and quinones

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ABSTRACT

A single-step synthesis of 3-hydroxycarbazoles has been achieved via annulation of electron-rich anilines and quinones in PhMe/AcOH (4:1) at room temperature. This chemistry tolerates various substituted benzoquinones and naphthoquinones, however, is sensitive to both the electronic and steric properties of the anilines. The desired 3-hydroxycarbazole derivatives are generally produced in moderate yield.

Introduction

Carbazole and its derivatives have attracted tremendous attention in the literature due to their intriguing structural features and promising photophysical and biological activities.[1] There are numerous pharmacologically active natural alkaloids which possess a unique 3-hydroxycarbazole motif (Scheme 1).[1] For example, glycozolidol shows activity against both Gram-positive and Gram-negative bacteria[2]; sansoakamine is an anti-malarial agent[3]; glybomine C displays significant antitumor-promoting activity[4]; and carazostatin is a strong anti-oxidant and exhibits a strong inhibitory activity against the free-radical induced lipid peroxidation in liposomal membranes.[5]

Various synthetic methods have thus been developed for the synthesis of 3-hydroxycarbazoles.[1] For example, Fischer-Borsche carbazole synthesis involves the formation of 3-oxygenated tetrahydrocarbazoles followed by dehydrogenation and deprotection (Scheme 2A)[6]; Tricarbonyl iron-coordinated cyclohexadienylium ions[7] undergo electrophilic aromatic substitution of electron-rich anilines, followed by oxidative cyclization, generating 3-hydroxycarbazoles (Scheme 2B)[8]; and palladium-catalyzed Buchwald-Hartwig amination[9] of anilines and aryl halides, followed by oxidative cyclization of functionalized diphenylamine products also leads to 3-hydroxycarbazoles after deprotection (Scheme 2C).[10] However, all these methods involve multi-step operations, the requirements of high reaction temperature or stoichiometric metal reagents, thus resulting in overall low yielding and atom-uneconomic transformations. Therefore, a more efficient synthesis of 3-hydroxycarbazoles under mild conditions is still highly desirable. Our own interest in this class of important heterocycles prompted us to develop and herein report a straightforward single-step synthesis of 3-hydroxycarbazoles by acetic acid promoted annulation of electron-rich anilines and quinones (Scheme 2D).

Results and discussion

Intrigued by the Nenitzescu indole synthesis[11] in which an enamine derivative reacts with benzoquinone to produce 5-hydroxyindole product, we hypothesized that electron-rich anilines could replace the enamine and react with benzoquinone to afford 3-hydroxycarbazoles (Scheme 3). Our investigation commenced with the optimization of reaction between *N*-benzyl-3,5-dimethoxyaniline (**1a**) and benzoquinone (**2a**) to form *N*-benzyl 3-hydroxycarbazole (**3a**). In a mixture of alcoholic solvent and acetic acid (4:1, v/v), the aniline starting material **1a** was quickly consumed at room temperature. However, multiple impurities

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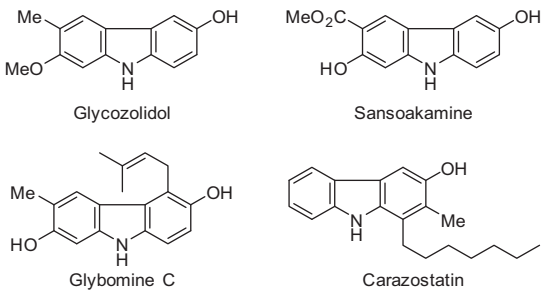
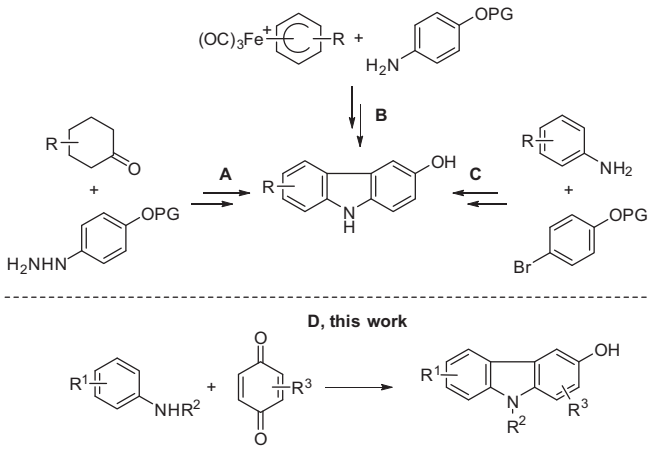
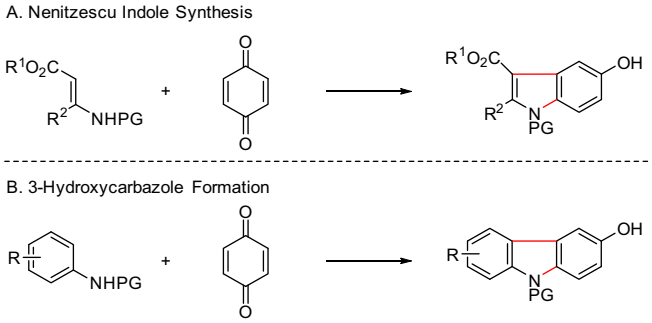


Scheme 1. 3-Hydroxycarbazole-containing natural alkaloids



Scheme 2. Synthetic strategies to 3-hydroxycarbazoles



Scheme 3. Nenitzescu indole synthesis and 3-hydroxycarbazole formation

were observed and the yield of carbazole **3a** based on HPLC quantitative analysis is relatively low (Table 1, entries 1–4). One of the major by-products observed is hydroquinone arising from the reduction of benzoquinone, which indicates possible over-oxidation of aniline **2a** and/or carbazole **3a** by benzoquinone. To our delight, among the aprotic solvents we screened, toluene generated the highest HPLC yield in 76% and carbazole **3a** was isolated in 66% yield (Table 1, entries 5–8). Interestingly, without acetic acid, the reaction proceeded very slowly even at an elevated temperature (100 °C), which indicates that acetic acid plays an important role in facilitating the carbazole formation reaction (Table 1, entry 9).

With a set of optimal conditions available, we then set out to investigate the scope and limitations of this 3-hydroxycarbazole formation reaction. As shown in Table 2, the protecting group on 3,5-dimethoxyaniline was first examined. Both benzyl (Bn) and *para*-methoxybenzyl (PMB) protected 3,5-dimethoxyanilines **1a** and **1b** underwent the annulation with benzoquinone (**2a**), generating moderate yields of the desired 3-hydroxycarbazoles **3a** and **3b** (Table 2, entries 1–2). Allyl and *n*-propyl proved to be better protecting group as protected anilines **1c** and **1d** produced the desired carbazoles **3c** and **3d** in 72% and 89% respectively, presumably because the protected anilines and/or the carbazole products are less prone to oxidation (Table 2, entries 3–4). Interestingly, Phenyl protected aniline **1e** did not produce any desired product, even at an elevated temperature 100 °C (Table 2, entry 5). One possible explanation is that the lone-pair electron of the nitrogen is delocalized to the phenyl ring, thus causing the 3,5-dimethoxyphenyl moiety less nucleophilic. Boc-protected aniline **1f** did not afford the desired product at all, likely because the aniline is no longer nucleophilic enough to attack benzoquinone (Table 2, entry 6). Unfortunately, the reaction of unprotected 3,5-dimethoxyaniline (**1g**) and benzoquinone (**2a**) underwent predominantly decomposition with multiple unidentifiable impurities and only insignificant amount of carbazole **3g** observed (Table 2, entry 7). When a substituent was introduced at the 4-position of the aniline, the annulation reaction gave messy reaction and relatively low yield of the desired carbazole product. For example, anilines **1h** and **1i** substituted with ethyl and benzyl group at the 4-position, only afforded 30% and 21% yield of the carbazole **3h** and **3i**, respectively (Table 2, entries 8–9). The less electron-rich aniline *N*-benzyl-3-methoxy-5-methylaniline (**1j**) reacted with benzoquinone (**2a**), producing 1:1 mixture of the desired carbazoles in only 25% yield (Table 2, entry 10). All of these results indicate that this annulation reaction is susceptible to both steric and electronic properties of the anilines.

Next, we focused on using *N*-benzyl-3,5-dimethoxyaniline (**1a**) to examine the scope of the quinones. Similar to Nenitzescu indole synthesis,[11b] 2-methylbenzoquinone **2b** generated two regioisomeric carbazoles **3k** and **3k′** in a combined 49% yield (Table 3, entry 1). Benzoquinone **2c** substituted with a bulky *tert*-butyl group took 20 h at 60 °C to reach high conversion and afforded carbazole **3l** in 43% yield (Table 3, entry 2). Both phenyl and methoxy substituted benzoquinones **2d** and **2e** reacted with aniline **1a**, generating the desired carbazoles **3m** and **3n** in 47% and 63% yield respectively (Table 3, entries 3–4). Similarly, when 2,3-disubstituted benzoquinones **2f** and **2g** were employed, the desired highly substituted carbazoles **3o** and **3p** were isolated in 55% and 53% yield, respectively (Table 3, entries 5–6). To our delight, naphthoquinones **2h**–**j** all generated the desired tetracyclic products **3q**–**s** in moderate yields (Table 3, entries 7–9). The steric effect of the quinones plays a significant role in this annulation chemistry. For example, sterically hindered benzoquinones **2k** and **2l**, and naphthoquinone **2m** unfortunately did not afford any detectable carbazole product even after the reactions were heated at 100 °C for prolonged time (Scheme 4).

We proposed a mechanism for this 3-hydroxycarbazole formation reaction, exemplified using aniline **1a** and benzoquinone **2a** (Scheme 5). Similarly to the Nenitzescu indole synthesis,[11b] it is believed that acetic acid activates benzoquinone **2a** and subsequently facilitates the carbon–carbon bond formation between the C_2-position of aniline **1a** and the C_2-position of quinone **2a** via a Michael addition, thus generating a highly reactive intermediate **4a**. Intermediate **4a** then quickly undergoes ring closure to afford tricyclic intermediate **5a** which then loses water to afford the desired carbazole **3a**.

It is worth noting that this annulation chemistry, consistent with Nenitzescu indole synthesis,[11b] generates multiple impurities in the reaction, thus resulting in relatively low yield of the desired 3-hydroxycarbazole. We were able to isolate impurity **6** in 17% yield besides 45% yield of **3q** when the annulation reaction employs aniline **1a** and naphthoquinone **2h**. The formation of impurity **6** could be rationalized by a