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Novel synthesis of benzo[*b*]carbazoles

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ABSTRACT

A new method was adopted for the synthesis of benzo[*b*]carbazoles by Claisen condensation followed by Fischer indole cyclization. Newly synthesized benzo[*b*]carbazoles were treated with ethanol amine in the presence of polyphosphoric acid which leads to the formation of pyrazino carbazoles. All the synthesized compounds were characterized by all spectral means.

Carbazoles are important class of indole alkaloids exhibiting a variety of biological activities,[1] and their analogues are also widely used in the construction of optoelectronic devices.[2] Benzo-annulated carbazole ring systems are found only rarely in natural products. Even though they are rarely found in natural products, benzocarbazole derivatives display a wide range of biological functions. They exhibit anticancer activity against leukemia, renal, colon cancer cell line,[3] and anti-inflammatory activities,[4] and some of the benzocarbazoles are found to bind with estrogen receptors and inhibit the growth of mammary tumors in rats.[5] These analogues are widely used in photographic materials.[6] The skeleton of benzo[*b*]carbazoles, being isosteric with that of the antitumor pyrido[4,3-*b*]carbazole alkaloid, ellipticine, has led to the development of numerous approaches for the construction of benzo[*b*]carbazoles. There are numerous methods developed for the synthesis of benzo[*b*]carbazoles,[7] including Fischer indolization of phenylhydrazones,[8] reaction of *p*-benzoquinones with 2-aminomethylene-1-indanones,[7] benzannulation of indoles,[9] Diels–Alder reactions of pyrano[3,4-*b*]indol-3-ones,[10] 4*H*-furo[3,4-*b*]indoles,[11] and 2,4-dihydropyrrolo[3,4-*b*]indoles,[12] cycloaromatization of *N*-[2-(1-alkynyl)phenyl]ketenimines,[13] and intramolecular cyclization of substituted 3-(benzotriazol-1-ylmethyl)indole.[14] Examples of benzo[*b*]carbazoles are represented in Figure 1.

Even though numerous methods are available for the synthesis of benzo[*b*]carbazoles, there is still a considerable need for the development of more versatile and regioselective synthetic routes toward highly substituted benzo[*b*]carbazoles, especially with respect to tolerance of a wider variety of functional groups. Prompted by the biological value of benzo[*b*]carbazoles, we made an attempt to synthesize benzo[*b*]carbazoles by Claisen condensation and Fischer indole cyclization and then tested the synthetic utility of benzo[*b*]carbazoles by reacting it with ethanolamine.

Earlier 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones[15] were derived from the Japp–Klingemann reaction of hydroxymethylenecyclohexanone with diazotized anilines followed by cyclization.[15] In order to access the 5*H*-benzo[*b*]carbazole, a modified method was adopted instead of utilizing the conventional 2-hydroxylmethylene-1-tetralone. In this modified method (Scheme 1), 2-oxo-2-(1-oxo-1,2,3,4-tetrahydronaphthalene-2-yl)acetate (**3**) has been derived from Claisen condensation of α-tetralone (**1**) with diethyl oxalate (**2**) as per the literature.[16] The obtained 2-oxo-2-(1-oxo-1,2,3,4-tetrahydronaphthalene-2-yl)acetate was treated with diazotized anilines in the presence of sodium acetate trihydrate to yield the respective hydrazones. The above reaction yielded the expected hydrazones, which were cyclized through Fischer-indole

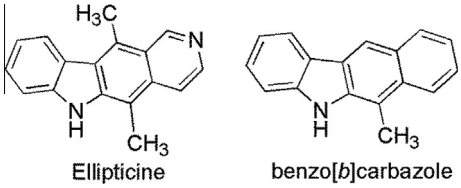

Figure 1. Examples of benzo[*b*]carbazoles.

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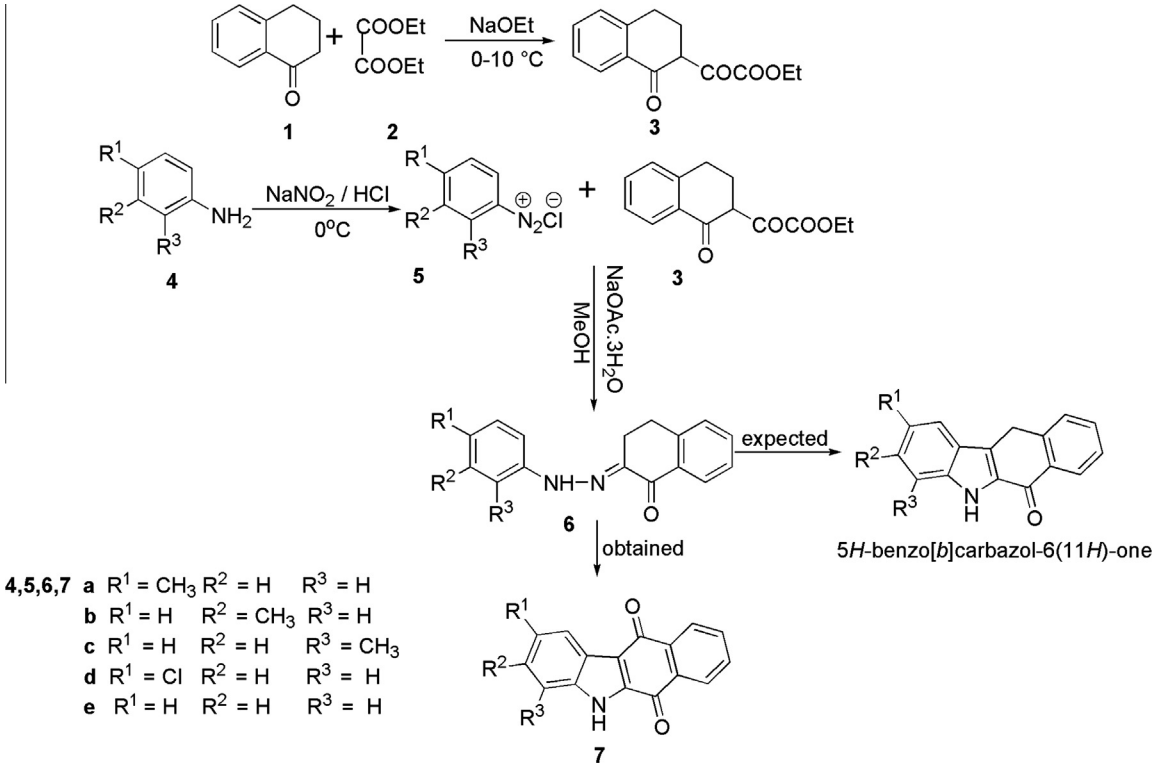

Scheme 1.

cyclization using Kent's reagent to yield an unexpected product (**7**) instead of the expected 5*H*-benzo[*b*]carbazol-6(11*H*)-one.

The IR spectrum of **7a** showed absorption bands at 3224 cm^{-1} (NH) and 1651 cm^{-1} (C=O). In its ^1H NMR spectrum the indole NH group appeared as singlet at δ 13.5. The C_8 & C_9 protons appeared as multiplet between δ 8.19 and 8.17. The C_1 proton appeared as singlet at δ 8.07. The C_7 & C_{10} protons appeared as multiplet between δ 7.92 and 7.90. The C_4 proton appeared as doublet at δ 7.56 (J = 8.40 Hz). The C_3 proton appeared as doublet of doublet at δ 7.32 (J_o = 8.40 Hz, J_m = 1.60 Hz). The methyl protons appeared as a singlet at δ 2.51. The total number of protons matched perfectly with its structure. The ^{13}C NMR spectrum revealed the presence of 17 carbons with two carbonyl groups. The C_6 carbonyl group resonated at δ 177.4 and the C_{11}-carbonyl group resonated at δ 180.3 and the elemental analysis agrees well with the molecular formula $C_{17}H_{11}NO_2$. Based on the above data the structure of the product was assigned as 2-methyl-5*H*-benzo[*b*]carbazol-6,11-dione (**7a**). The X-ray crystal structure of **7a** is shown in Figure 2. The universal validity of the reaction was tested with other substituted hydrazones **6**(**b**–**e**) which afforded the corresponding diones **7**(**b**–**e**).

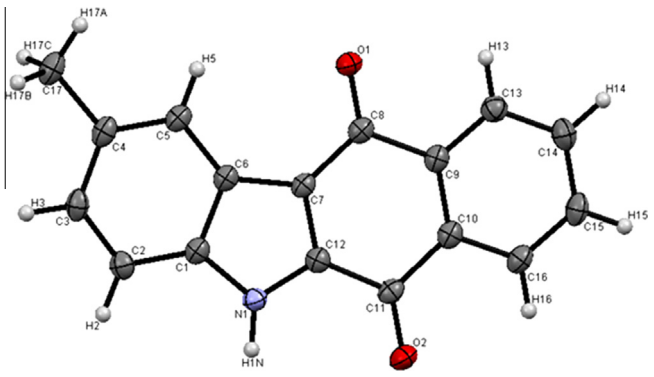

Figure 2. X-ray crystal structure and atom numbering scheme for **7a** as thermal ellipsoids at 50% probability level.

The mechanism for the formation of compound (**7**) is, hydrazone **6** when subjected to cyclization using Kent's reagent leads to the formation of the intermediate (**II**) in situ which cannot be isolated. The intermediate (**II**) undergoes prototrophic shift cum aromatization to afford the intermediate (**IV**). Then the intermediate (**IV**) undergoes aerial oxidation to give intermediate (**V**). Further the elimination of water molecule from the intermediate (**V**) leads to the formation of compound (**7**) (Scheme 2). The same reaction when carried out under inert atmosphere did not proceed further and it retained the starting material. This indicates the mechanism for the transformation from **6** to **7** involves aerial oxidation.

In order to explore the synthetic utility of the obtained 5*H*-benzo[*b*]carbazol-6,11-dione (**7**), an effort was made by attempting a condensation reaction of 5*H*-benzo[*b*]carbazol-6,11-dione with ethanolamine in different reaction conditions. The attempt failed and no reaction proceeded in 5*H*-benzo[*b*]carbazol-6,11-dione. This may be due to the deactivating nature of the C_{11} carbonyl group. In reaction condition due to polarization the C_6 carbonyl group gets converted into C–OH which prevents the condensation reaction to proceed further. It is represented in Figure 3.

Since the reaction attempt failed due to the presence of the C_{11} carbonyl group, we reduced the C_{11}—C=O using stannous chloride. 2-Methyl-5*H*-benzo[*b*]carbazol-6,11-dione (**7**) was subjected to reduction using stannous chloride (Scheme 3). Its IR spectrum showed absorption bands at 3413 cm^{-1} (NH) and 1659 cm^{-1} (C=O). In its ^1H NMR spectrum the indole NH group appeared as singlet at δ 9.31. The C_8 & C_9 protons appeared as multiplet between δ 8.22 and 8.20. The C_7 & C_{10} protons appeared as multiplet between δ 7.87 and 7.85. The C_1, C_3, & C_4 protons appeared as