A facile synthesis of 2-substituted pyrano[2,3-*a*]carbazoles

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The syntheses of 2-(3',3'-dimethylacryloyl)-1-hydroxycarbazoles (**2**), 2,2-dimethyl-2,3-dihydropyrano[2,3-*a*]carbazol-4(11*H*)-ones (**3**), 6-(3',3'-dimethylacryloyl)-2,2-dimethyl-2,3-dihydropyrano[2,3-*a*]carbazol-4(11*H*)-ones (**4**), and 2-phenyl- and 2-methyl-pyrano[2,3-*a*]carbazol-4(11*H*)-ones (**6** and **8**), from 1-hydroxycarbazoles in the presence of 3,3-dimethylacryloyl chloride, cinnamic acid and ethyl acetoacetate, are described.

Keywords: carbazoles, fused pyrans, cinnamic acid, fused chromones

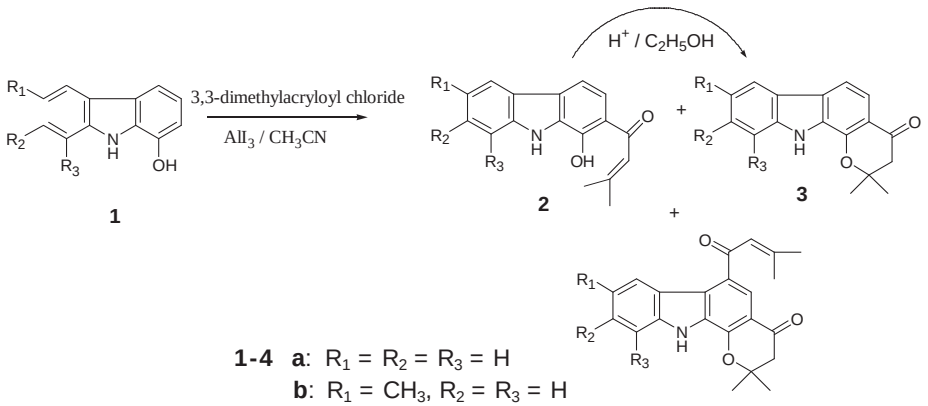
Pyrano[3,2-*a*]carbazoles such as girinimbine, mupamine, mahanimbine, murrayanol and mahanine have been isolated from plant species of the Rutaceae family.[1] It is noteworthy that the alkaloids mahanimbine, murrayanol and mahanine are reported to possess mosquitocidal, antimicrobial, anti-inflammatory and antioxidant activities.[1,2]

In this paper we describe a direct approach to pyrano[2,3-*a*]carbazol-4-one derivatives from 1-hydroxycarbazoles which proceeds in moderate to fair yields under mild conditions, and is relatively inexpensive. To our knowledge there is no report on the synthesis of 2-alkyl- or 2-aryl-pyrano[2,3-*a*]carbazol-4-ones. From the biogenetic point of view, there exists a possibility for the formation of these compounds in the plant body, although their isolation has not been reported. Hence, it needs further extensive search in the plant material for their presence. Based on the above facts, it was felt necessary to devise a simple synthetic method for 2-alkyl- and 2-aryl-pyrano[2,3-*a*]carbazol-4(11*H*)-ones with a view to the possible future isolation of these compounds from natural sources.

In the event, treatment of 1-hydroxycarbazoles[3,4] **1** with 3,3-dimethylacryloyl chloride in presence of aluminium iodide in acetonitrile,[5] resulted in the formation of three products detected by TLC, which were separated by column chromatography using petroleum ether – ethyl acetate as eluant. The two products obtained from 99 : 1 and 85 : 15 petroleum ether – ethyl acetate fractions were found to be identical in all respects with the known[4] 2-(3',3'-dimethylacryloyl)-1-hydroxycarbazoles (**2**) and 2,2-dimethyl-2,3-dihydropyrano [2,3-*a*]carbazol-4(11*H*)-ones (**3**), respectively (m.p. mixed mp, ^{1}H NMR and superimposable IR spectra). Acid catalysed cyclisation of **2** resulted in the formation of **3**. This confirmed the structure 2-(3',3'-dimethylacryloyl)-1-hydroxycarbazoles **2** for the compound realised. The product obtained from the 97 : 3 petroleum ether – ethyl acetate fraction in each case was found to be a new product and identified as the 6-(3',3'-dimethylacryloyl)-2,2-dimethyl-2,3-dihydropyrano[2,3-*a*]carbazol-4(11*H*)-one (**4**) on the basis of IR and ^{1}H NMR and mass spectral analyses (Scheme 1).

When a 1-hydroxycarbazole (**1**) was reacted with cinnamic acid using freshly fused finely powdered zinc chloride and phosphorus oxychloride,[6] after work up the reaction mixture showed only one spot on TLC and was found to be the 2-cinnamoyl-1-hydroxycarbazole (**5**) from spectral and analytical data. 2-Cinnamoyl-1-hydroxycarbazoles **5** on oxidative cyclisation with dimethyl sulfoxide in presence of a catalytic amount of iodine for 10 min[7-10] yielded 2-phenylpyrano[2,3-*a*]carbazol-4(11*H*)-ones (**6**) (Scheme 2).

Among the carbazole derivatives, pyridocarbazoles such as ellipticine, 9-hydroxyellipticine[11] and olivacine show good antitumor properties. Recently, a pyrido[4,3-*a*]carbazole has been reported to show anti-HIV activity.[12] We therefore felt it worthwhile to devise a method for the synthesis of pyrido[2,3-*a*]carbazole derivatives and to evaluate their pharmacological activities. 1-Hydroxy-6-methylcarbazole **1b** upon condensation with ethyl acetoacetate in the presence of conc. sulfuric acid afforded the fused coumarin (α-pyrone) ring system 4,8-dimethylpyrano[2,3-*a*]carbazol-2(11*H*)-one **7b** in low yield.[13] In this connection, 6-methyl-1-hydroxycarbazole **1b** were condensed with ethyl acetoacetate in presence of zinc chloride and phosphorus oxychloride or with polyphosphoric acid with an expectation to afford α-pyrone fused ring system **7b** from which 4,8-dimethyl-1,11-dihydro-2*H*-pyrido[2,3-*a*]carbazol-2-one can be obtained by passing ammonia gas in alcoholic medium.[14,15]



1-4 **a**: $R_1 = R_2 = R_3 = H$
b: $R_1 = CH_3$, $R_2 = R_3 = H$
c: $R_2 = CH_3$, $R_1 = R_3 = H$
d: $R_3 = CH_3$, $R_1 = R_2 = H$

Scheme 1

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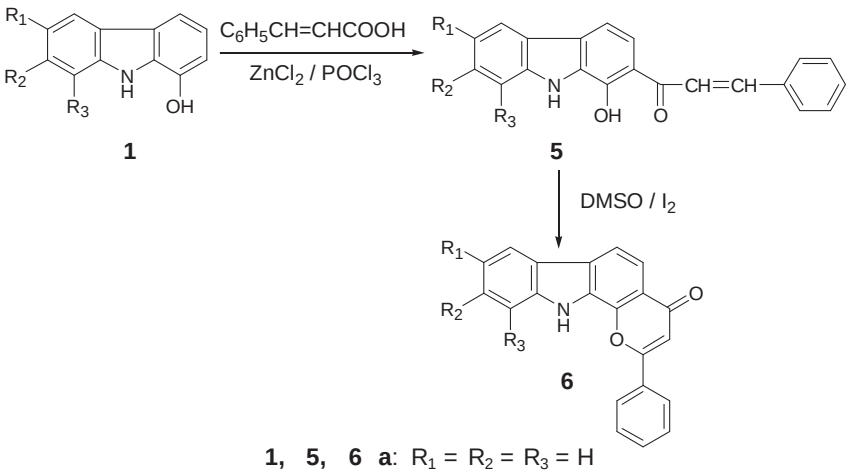
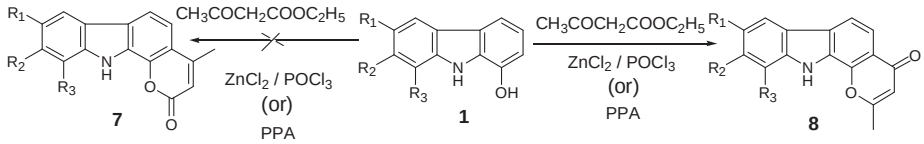


1, 5, 6 **a**: $R_1 = R_2 = R_3 = H$
b: $R_1 = CH_3$, $R_2 = R_3 = H$
c: $R_2 = CH_3$, $R_1 = R_3 = H$
d: $R_3 = CH_3$, $R_1 = R_2 = H$

Scheme 2



1, 7, 8 **a**: $R_1 = R_2 = R_3 = H$
b: $R_1 = CH_3$, $R_2 = R_3 = H$
c: $R_2 = CH_3$, $R_1 = R_3 = H$
d: $R_3 = CH_3$, $R_1 = R_2 = H$

Scheme 3

Thus, 1-hydroxycarbazole (**1b**) was condensed with ethyl acetoacetate in presence of freshly fused finely powdered zinc chloride and phosphorus oxychloride or with polyphosphoric acid. It yielded a single product of m.p. 220°C. It did not give an alcoholic ferric chloride test, which confirmed the absence of phenolic OH. The IR spectrum also revealed the absence of a hydroxyl group, lacking absorption around 3495 cm^{-1}, and the absence of lactone carbonyl around 1740 cm^{-1} (α-pyrone)[13] but showed the formation of the C–O–C group in a strong band at 1258 cm^{-1} and α,β-unsaturated C=O stretching vibration at 1646 cm^{-1}, and from the ^{1}H NMR and mass spectral data the structure of the product was assigned as 2,8-dimethylpyrano[2,3-*a*]carbazol-4(11*H*)-one (**8b**) and not the isomeric 4,8-dimethyl-pyrano[2,3-*a*]carbazol-2(11*H*)-one (4,8-dimethyl-2*H*,11*H*-indolo[3,2-*h*]coumarin) (**7b**). Similar treatment of other 1-hydroxycarbazoles **1a**, **1c** and **1d** gave the corresponding 2-methyl-4-oxopyrano[2,3-*a*]carbazoles **8a**, **8c** and **8d** (Scheme 3).

These reactions provide short synthetic pathways to prepare biogenetically possible 2-methyl-4-oxopyrano[2,3-*a*]carbazoles of potential pharmaceutical interest.

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Techniques used: FTIR, ^{1}H NMR and mass spectrometry

References: 15

Schemes: 3

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