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Divergent Synthesis of Pyrano[3,2-c]- and Furo[3,2-c]-carbazoles

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Research Article

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ABSTRACT

A series of novel pyrano[3,2-*c*]- and furo[3,2-*c*]-carbazoles have been synthesized through diversity oriented synthesis, by adopting different methodologies using microwave condition and using different catalysts such as trifluoroacetic acid, $ZnCl_2/POCl_3$, $P_2O_5/POCl_3$, triphenylphosphine by the efficient reaction of 4-hydroxy carbazole (**1**) with phenylpropiolic acid, dimethyl acrylic acid, malonic acid, cinnamic acid, dimethylacetylene dicarboxylate, ethylacetoacetate, malic acid and ethylcyanoacetate as suitable co-reactants.

INTRODUCTION

The diversity oriented synthesis of small molecules is a challenge to synthetic chemists, requiring new strategies to generate appendage and skeletal diversity. Divergent reaction pathways are a very efficient way of generating structural diversity, particularly, diverse molecular frameworks and functional groups. Skeletal diversity is generated by using different reagents to change a common substrate into a collection of products having varied molecular skeletons.

Carbazoles display a wide range of biological activities [1], making them attractive compounds to synthetic and medicinal chemists [2-6]. Naturally occurring carbazoles and synthetic carbazole analogues are known to exhibit promising biological applications. Among these, oxygenated carbazoles like pyranocarbazole and furo carbazole alkaloids have spared in the natural product synthesis due to their wide isolation from various plants.

Pyranocarbazole alkaloids such as girinimbine, mupamine, mahanimbine, murrayanol and mahanine, which have been isolated from plants of the Rutaceae family [7], possess mosquitocidal, antimicrobial, anti-inflammatory and antioxidant activities. Girinimbine **(Figure 1)** and isomahanine have been reported to possess significant cytotoxicity against lung cancer (NCI-522) [8-10], whereas koenimbine showed rapid scavenging activities against the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical [11]. Furo carbazole alkaloids such as furostifoline and furoclausine- A and eustifoline-D which also have been isolated from plants of the Rutaceae family [12], widely used in Chinese folk medicine and reported to possess wide range of pharmacological activities [13]. Some of the important pyrano and furo carbazole alkaloids are shown in **Figure 1.**

In naturally occurring pyrano and furocarbazole derivatives isolated heretofore, the hetero atom oxygen of the pyran and furan ring is attached to carbon-2 of the carbazole nucleus to form pyrano[3,2-*a*]carbazoles such as grinimbine, heptazolicine, cis-dihydroxygirinimbine, clausine-T and furo[3,2-*a*]-carbazoles such as furostifoline and furoclausine- A respectively. Recently the synthesis of pyrano[2,3-c]carbazole alkaloids (Euchrestifoline-A and Euchrestifoline-B) had been demonstrated by Lebold and Kerr [14] and the synthesis of furo[2,3-*c*]carbazole alkaloids had been reported by Hans J. Knolker [15] in which the hetero atom oxygen of the pyran and furan ring is attached to carbon-3 of the carbazole nucleus.

In continuation of our ongoing interest in the development of diversity oriented synthetic routes to potentially bioactive

oxygenated carbazoles, we recently focused our attention on a relatively less studied class of pyrano[3,2-*c*]- and furo[3,2-*c*]-carbazoles in which the hetero atom oxygen of the pyran and furan ring is attached on carbon-4 of the carbazole nucleus. The aforementioned compounds are synthesized by adopting different methodologies using microwave condition and using different catalysts such as trifluoroacetic acid, $ZnCl_2/POCl_3$, $P_2O_5/POCl_3$, triphenylphosphine by the efficient reaction of 4-hydroxy carbazole with phenylpropiolic acid, dimethyl acrylic acid, malonic acid, cinnamic acid, dimethylacetylene dicarboxylate, ethylacetoacetate, malic acid and ethylcyanoacetate as suitable co-reactants.

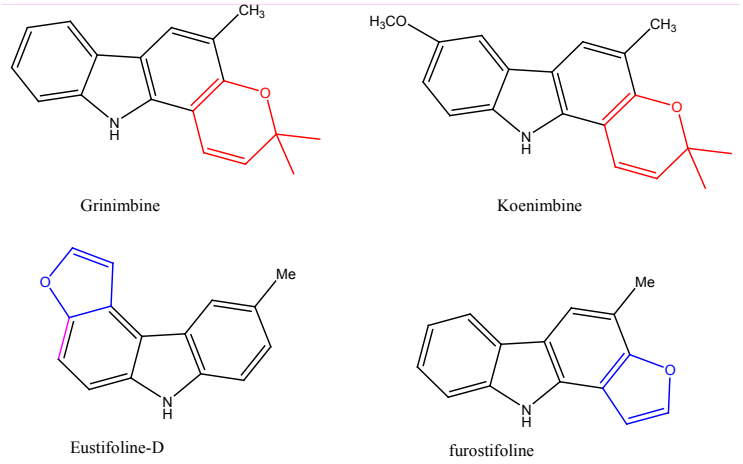


Figure 1. Naurally occurring bio active pyrano[3,2-*c*]- and furo[3,2-*c*]-carbazoles.

EXPERIMENTAL

Procedure for the synthesis of phenylpyrano[3,2-c]carbazolones (2 & 3)

A mixture of 4-hydroxycarbazole (1, 0.001 mol), phenylpropiolic acid (0.001 mol) in trifluoroacetic acid (10 mL) was refluxed in a steam bath for 5 h. The reaction was monitored by TLC. After the completion of reaction the excess solvent was removed and the reaction mixture was poured onto ice cold water. The brown solid thus obtained was found to be a mixture of two products. The crude products were separated by column chromatography over silica gel using petroleum ether and ethyl acetate (97:3 for **2** and 90:10 for **3**) as eluents to yield the respective 2-phenylpyrano[3,2-*c*]carbazol-4-one (**2**) and 4-phenylpyrano[3,2-*c*]carbazole-2-one (**3**). The compounds were recrystallized from ethanol.

2-Phenylpyrano[3,2-c]carbazol-4-one (2): Pale yellow prisms; yield: 49% (0.152 g); m.p.283-285°C; IR (KBr, cm^{-1}) ν_{max}: 3306 (N-H), 1644 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 9.20 (b s, 1H, N_7-H), 7.70-7.00 (m, 11H, C_5, C_6, C_8, C_9, C_{10}, C_{11}, C_2', C_3', C_4', C_5' & C_6'-H), 6.87 (s, 1H, C_3-H); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 193.0 (C=O), 170.0 (C_2), 150.0 (C_1), 141.5 (C_{6a}), 133.8 (C_1'), 129.3 (C_3' & C_5'), 128.6 (C_4'), 127.4 (C_2' & C_6'), 126.0 (C_{7a}), 125.6 (C_{10}), 124.4 (C_5) 121.3 (C_{11}), 120.0 (C_9), 118.8 (C_{4a}), 115.4 (C_{11b}), 112.1 (C_8), 108.2 (C_6), 103.0 (C_{11a}), 92.1 (C_3); MS: *m/z* (M^+, 311); Anal. calc. for: $C_{21}H_{13}NO_2$: C, 81.01; H, 4.21; N, 4.50. Found: C, 81.09; H, 4.15; N, 4.56%.

4.1.2.4-Phenylpyrano[3,2-c]carbazol-2-one (3): Yellow prisms; yield: 36% (0.111 g); m.p.221-223°C; IR (KBr, cm^{-1}) ν_{max}: 3307 (N-H), 1730 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 8.53 (b s, 1H, N_7-H), 7.85-7.25 (m, 11H, C_5, C_6, C_8, C_9, C_{10}, C_{11}, C_2', C_3', C_4', C_5' & C_6'-H), 6.60 (s, 1H, C_3-H); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 171.9 (C=O), 161.8 (C_4), 146.7 (C_1), 134.6 (C_{6a}), 133.2 (C_1'), 130.0 (C_3' & C_5'), 129.0 (C_4'), 127.4 (C_2' & C_6'), 124.4 (C_{7a}), 121.5 (C_{10}), 120.9 (C_{4a}) 120.8 (C_{11}), 120.4 (C_{11b}), 119.2 (C_9), 115.6 (C_5), 110.9 (C_8), 108.2 (C_6), 105.5 (C_3), 102.8 (C_{11a}); MS *m/z* (M^+, 311); Anal. calc. for: $C_{21}H_{13}NO_2$: C, 81.01; H, 4.21; N, 4.50. Found: C, 80.93; H, 4.13; N, 4.42%.

Procedure for the reaction of 4-hydroxycarbazoles (1) and 3,3-dimethyl acrylic acid with trifluoroacetic acid

4-Hydroxycarbazole (**1**, 0.001 mol) dissolved in 10 ml of trifluoroacetic acid was stirred with 3,3-dimethylacrylic acid (0.001 mol) at room temperature for 48 h. After the completion of the reaction (as monitored by TLC), the excess trifluroacetic acid was removed using rotary evaporation. A solid precipitated out and the residue was poured onto ice water, then extracted using ethyl acetate and dried over anhydrous sodium sulphate. The residue was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (95:5) as eluent. Evaporation of the solvent afforded yellow crystals which were recrystallized from ethanol to yield 2,3-dihydro-2,2-dimethylpyrano[3,2-*c*]carbazol-4(7*H*)-one (**4**).

2,3-Dihydro-2,2-dimethylpyrano[3,2-c]carbazol-4(7H)-one (4): Yellow solid; yield: 84% (0.222 g); m.p.200-202°C; IR (KBr, cm^{-1}) ν_{max}: 3374 (N-H), 1678 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 9.30 (b s, 1H, N_7-H), 7.70-7.08 (m, 6H, C_5, C_6, C_8, C_9, C_{10} & C_{11}-H), 3.50 (s, 2H, C_3-H), 1.71 (s, 6H, C_2-two CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 200.0 (C=O), 152.2 (C_1), 143.1 (C_{6a}), 124.4 (C_{7a}), 122.6 (C_{10}), 121.8 (C_{11}), 120.3 (C_5), 118.9 (C_9), 117.0 (C_{4a}), 113.8 (C_{11b}), 111.3 (C_8), 103.7 (C_6 & C_{11a}), 69.2 (C_2), 58.4 (C_3), 28.7 (C_3-two CH_3); MS *m/z* (M^+, 265); Anal.calcd.for: $C_{17}H_{15}NO_2$: C, 76.96.; H, 5.70; N, 5.28. Found: C, 76.89; H, 5.77; N, 5.20%.

Procedure for the synthesis of 3,7-dihydropyrano[3,2-c]carbazol-2,4-dione (5).

A mixture of 4-hydroxy carbazole (**1**, 0.005 mol), malonic acid (0.005 mol), freshly fused zinc chloride (3 g) and phosphorus oxy chloride(4 mL) was kept at room temperature for 24 h, with occasional shaking. The reaction mixture was then poured into crushed ice and the precipitate obtained was filtered and washed with water, dried and purified by column chromatography over silica gel eluting with petroleum ether:ethyl acetate mixture (98:2) to get yellow crystals of 3,7-dihydropyrano[3,2-*c*]carbazol-2,4-dione (**5**).

3,7-Dihydropyrano[3,2-c]carbazol-2,4-dione (5): Yellow solid; yield: 56% (0.140 g); m.p.103-105°C; IR (KBr, cm^{-1}) ν_{max}: 3384 (N-H), 1698 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 11.00 (b s, 1H, C_4-OH), 8.35 (b s, 1H, N_7-H), 7.87-7.07 (m, 6H, C_5, C_6, C_8, C_9, C_{10} & C_{11}-H), 6.55 (s, 1H, C_3-H), 3.00 (s, 2H, C_3-H_2) (The ratio of 4-oxo- and 4-hydroxy forms, 3:1); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 184.3 (C_4), 160.0 (C_2), 145.2 (C_1), 140.6 (C_{6a}), 129.4 (C_{7a}), 128.2 (C_{10}), 127.0 (C_{4a}), 124.1 (C_{11}), 122.9 (C_{11b}), 120.0 (C_5), 118.4 (C_9), 110.6 (C_8), 105.5 (C_6), 101.7 (C_{11a}), 50.2 (C_3); MS *m/z* (M^+, 251); Anal.calcd.for: $C_{15}H_9NO_3$: C, 71.71; H, 3.61; N, 5.58. Found: C, 71.77; H, 3.56; N, 5.49%.

Procedure for the synthesis of methyl2-oxo-2,7-dihydropyrano[3,2-c]carbazole-4-carboxylate (7)

To a solution of 4-hydroxy carbazole (**1**, 2.5 mmol) and triphenyl phosphine (2.5 mmol) in dichloromethane, dimethyl acetylene dicarboxylate (2.5 mmol) was added at -5°C. Then, the reaction mixture was stirred for 24 h at room temperature. After completion of the reaction, the excess solvent was removed and the reaction mixture was poured into ice cold water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulphate evaporated and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (97:3) afforded a single product methyl2-oxo-2,7-dihydropyrano[3,2-*c*]carbazole-4-carboxylate (**7**).

Methyl2-oxo-2,7-dihydropyrano[3,2-c]carbazole-4-carboxylate (7): Yellow solid; yield: 95% (0.278 g); m.p.295-297°C; IR (KBr, cm^{-1}) ν_{max}: 3258 (N-H), 1706 (**COO**CH_3), 1630 (O**C=O**); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 8.68 (b s, 1H, N_7-H), 7.60-7.30 (m, 6H, C_5, C_6, C_8, C_9, C_{10} & C_{11}-H), 6.86 (s, 1H, C_3-H), 3.98 (s, 3H, COO**CH_3**); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 170.0 (C_4-**CO**O-CH_3), 160.0 (C_2-C=O), 153.7 (C_4), 145.8. (C_1), 136.3 (C_{6a}), 124.6 (C_{7a}), 123.5 (C_3), 122.7 (C_{10}), 121.3 (C_{4a}), 120.8 (C_{11}), 120.4 (C_{11b}), 119.5 (C_9), 116.4 (C_5), 111.0 (C_8), 107.8 (C_6), 102.4 (C_{11a}), 52.7 (COO**CH_3**); MS *m/z* (M^+, 293); Anal.calcd.for: $C_{17}H_{11}NO_4$: C, 69.62.; H, 3.78; N, 4.78. Found: C, 69.55; H, 3.86; N, 4.85%.

Procedure for the synthesis of 4-methylpyrano[3,2-c]carbazole-2(7H)-one (8)

To a mixture of 4-hydroxy carbazole (**1**, 1 mmol) and ethylacetoacetate (1 mmol), catalytic amount of con.H_2SO_4 was added and the reaction mixture was subjected to microwave irradiation for 5 min. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was poured into ice cold water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulphate evaporated and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (98:2). A single product 4-methylpyrano[3,2-*c*]carbazole-2(7*H*)-one (**8**) was obtained. The compound thus obtained was recrystallized from ethanol to yield white crystals.

4-Methylpyrano[3,2-c]carbazole-2(7H)-one (8): White solid; yield: 90% (0.224 g); m.p.260-262°C; IR (KBr, cm^{-1}) ν_{max}: 3259 (N-H), 1704 (lactone C=O); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 9.15 (b s, 1H, N_7-H), 7.67-7.07 (m, 6H, C_5, C_6, C_8, C_9, C_{10} & C_{11}-H), 6.72 (s, 1H, C_3-H), 2.10 (s, 3H, C_4-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 164.2 (C_2-C=O), 157.6 (C_4), 144.3 (C_1), 137.8 (C_{6a}), 125.0 (C_{7a}), 124.1 (C_{10}), 123.0 (C_{4a}), 120.6 (C_{11}), 120.2 (C_{11b}), 118.5 (C_9), 117.8 (C_5), 111.3 (C_8), 108.4 (C_3), 105.8. (C_6), 101.9 (C_{11a}), 29.9 (C_4-CH_3); MS *m/z* (M^+, 249); Anal. calcd. for: $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.00; H, 4.37; N, 5.55%.

Procedure for the synthesis of pyrano[3,2-c]carbazole-2(7H)-one (9).

To a mixture of 4-hydroxy carbazole (**1**, 1 mmol) and malic acid (1 mmol), catalytic amount of conc. H_2SO_4 was added and the reaction mixture was subjected to microwave irradiation for 5 min. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was poured into ice cold water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulphate evaporated and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (97:3). A single product pyrano[3,2-*c*]carbazole-2(7*H*)-one (**9**) was obtained. The compound thus obtained was recrystallized from ethanol to yield pale white crystals.

Pyrano[3,2-c]carbazole-2(7H)-one (9): Pale white solid; yield: 86% (0.202 g); m.p.276-278°C; IR (KBr, cm^{-1}) ν_{max}:3253 (N-H), 1726 (lactone C=O) ;^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 8.95 (b s, 1H, N_7-H), 7.78 (d, 1H, C_4-H, *J*=9.50 Hz), 7.62-7.02 (m, 6H, C_5, C_6, C_8, C_9, C_{10} & C_{11}-H), 6.70 (d, 1H, C_3-H, *J*=9.50 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 168.2 (C_2-C=O), 148.9 (C_4), 143.8 (C_1), 134.7 (C_{6a}), 125.6 (C_{7a}), 123.7 (C_{10}), 122.9 (C_{4a}), 120.9 (C_{11}), 120.1 (C_{11b}), 118.4 (C_9), 116.9 (C_5), 115.2 (C_3), 112.7. (C_8), 107.3. (C_6), 103.4 (C_{11a}); MS *m/z* (M^+, 235); Anal.calcd.for: $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95. Found: C, 76.67; H, 3.77; N, 5.87%.

Procedure for the synthesis of 4-hydroxypyrano[3,2-c]carbazole-2(7H)-one (10)

The reaction of 4-hydroxy carbazole (**1**, 1 mmol) with ethylcyanoacetate (**5**, 1 mmol) in the presence of fused zinc chloride

and catalytic amount of conc. H_2SO_4 under microwave irradiation (5 min) yielded **10**. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was poured into ice cold water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulphate evaporated and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (98:2). A single product 4-hydroxypyrano[3,2-*c*]carbazole-2(7*H*)-one (**10**) was obtained. The compound thus obtained was recrystallized from ethanol to yield white crystals.

4-Hydroxypyrano[3,2-c]carbazole-2(7H)-one (10): White solid; yield: 93% (0.233 g); m.p.276-278°C; IR (KBr, cm^{-1}) ν_{max}: 3343 (O-H), 3048 (N-H), 1642 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 13.05 (b s, 1H, C_4-OH), 9.52 (b s, 1H, N_7-H), 7.71-7.20 (m, 6H, C_5, C_6, C_8, C_9, C_{10} & C_{11}-H), 6.57 (s, 1H, C_3-H); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 179.0 (C_4-OH), 166.2 (C_2-C=O) 147.5 (C_1), 140.5 (C_{6a}), 125.7 (C_{7a}), 124.9 (C_{4a}), 122.8 (C_{10}) 121.4 (C_{11}), 120.1 (C_{11b}), 119.2 (C_9), 117.1 (C_5), 112.7 (C_8), 109.6 (C_6), 101.1 (C_{11a}), 83.7 (C_3); MS *m/z* (M^+, 251); Anal.calcd. for: $C_{15}H_9NO_3$: C, 71.71; H, 3.61; N, 5.58. Found: C, 71.66; H, 3.53; N, 5.50%.

Procedure for the synthesis of 3-cinnamoyl-4-hydroxy carbazole (11)

A mixture of 4-hydroxy carbazole (**1**, 0.005 mol), cinnamic acid (0.005 mol), freshly fused zinc chloride (3 g) and phosphorus oxy chloride (4 mL) was kept at room temperature for 24 h, with occasional shaking. The reaction mixture was then poured into crushed ice and the precipitate obtained was filtered and washed with water, dried and subjected to silica gel chromatography eluting with petroleum ether:ethyl acetate (98:2) to afford dark brown crystals of 3-cinnamoyl-4-hydroxy carbazole (**11**).

3-Cinnamoyl-4-hydroxy carbazole (11): Brown yellow solid; yield: 58% (0.181 g); m.p.231-233°C; IR (KBr, cm^{-1}) ν_{max}: 3409 (O-H), 3198 (N-H), 1733 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 11.50 (b s, 1H, C_4-OH), 9.23 (b s, 1H, N_9-H), 7.87-7.07 (m, 13H, C_1, C_2, C_5, C_6, C_7, C_8, C_2", C_3", C_4", C_5", C_6" & two olefinic protons (C_2' & C_3')); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 190.0 (C=O), 158.9 (C_4-OH), 148.0 (C_3'), 139.3 (C_{9a}), 132.8 (C_1"), 129.6 (C_3" & C_5") 128.3 (C_4"), 127.9 (C_2" & C_6"), 126.2 (C_{8a}), 125.3 (C_2'), 124.2 (C_2), 123.7 (C_6), 121.9 (C_5), 119.7 (C_7), 117.8 (C_3), 115.5 (C_{4a}), 111.6 (C_8), 102.0 (C_1), 101.8 (C_{4b}); MS *m/z* (M^+, 313); Anal.calcd. for: $C_{21}H_{15}NO_2$: C, 80.49; H, 4.82; N, 4.47. Found: C, 80.40; H, 4.89; N, 4.40%.

Procedure for the synthesis of 2-benzoyl-3-styrylfuro[3,2-c]carbazole (12)

A mixture of the 3-cinnamoyl-4-hydroxycarbazole (**11**, 0.001 mol), phenacyl bromide (200 mg, 0.001 mol) and ignited potassium carbonate (276 mg, 0.002 mol) in dry acetone (15 mL) was refluxed in a steam bath for 4 h. The reaction was monitored by TLC. After the completion of reaction the excess solvent was removed and the reaction mixture was poured onto ice cold water. The solid separated out was filtered, dried, and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (95:5) as eluent to get 2-benzoyl-3-styryl-furo[3,2-*c*]carbazole (**12**). The compound thus obtained was recrystallized from ethanol.

2-benzoyl-3-styrylfuro[3,2-c]carbazole (12): Yellow prisms; yield: 72% (0.297 g); m.p.248-250°C; IR (KBr, cm^{-1}) ν_{max}: 3386 (N-H), 1686 (C=O) ; ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 8.92 (b s, 1H, N_6-H), 7.85-6.95 (m, 17H, C_4, C_5, C_6, C_7, C_8, C_9-H, C_3-(styryl-β-H), C_2-(C_2', C_3', C_4', C_5' & C_6'-H) & C_3-(C_2", C_3", C_4", C_5", C_6"-H), 6.38 (d, 1H, C_3-styryl-α-H, *J*=15.20 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 180.1 (C_2-C=O), 160.2 (C_{1a}), 149.8 (C_2), 146.8 (C_3-C_1"), 142.6 (C_2-C_1'), 139.4 (C_3), 137.3 (C_3-β-C), 136.8 (C_2-C_4'), 133.6 (C_3-C_4"), 132.3 (C_3-α-C), 129.8 (C_2-C_2' & C_2-C_6'), 129.2 (C_2-C_3' & C_2-C_5'), 128.6 (C_3-C_2" & C_3-C_6"), 127.7 (C_3-C_3" & C_3-C_5"), 126.8 (C_{3a}), 125.4 (C_{5a}), 124.6 (C_{6a}), 123.9 (C_5), 123.2 (C_9), 122.1 (C_4), 121.5 (C_{10}), 118.2 (C_8), 113.0 (C_{10b}), 110.1 (C_7), 104.6 (C_{10a}); MS *m/z* (M^+, 413); Anal.calc. for: $C_{29}H_{19}NO_2$: C, 84.24; H, 4.63; N, 3.39. Found: C, 84.16; H, 4.56; N, 3.31%.

Procedure for the synthesis of 2-benzylidene-furo[3,2-c]carbazol-3(6H)-one (13)

3-Cinnamoyl-4-hydroxycarbazole (**11**, 0.001 mol) was dissolved in dimethylsulfoxide (6 mL) and after adding mercuric acetate (0.48 g, 0.0015 mol) the contents were refluxed for 6 h. The reaction was monitored by TLC. After the completion, the mixture was poured into ice cold water. A yellow colored solid separated out, which was filtered, washed well with water, dried and recrystallized from methanol to yield 2-benzylidene-furo[3,2-*c*]carbazol-3(6*H*)-one (**13**) as yellow prisms.

2-Benzylidene-furo[3,2-c]carbazol-3(6H)-one (13): Yellow prisms; yield: 72% (0.223); m.p.266-268°C; IR (KBr, cm^{-1}) ν_{max}: 3304 (N-H), 1644 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 8.89 (b s, 1H, N_6-H), 7.90-7.07 (m, 11H, C_4, C_5, C_7, C_8, C_9 & C_{10}-H, C_2-(C_2', C_3', C_4', C_5' & C_6'-H), 6.96 (s, 1H, C_2-olefinic-H); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 192.4 (C=O), 155.6 (C_1), 152.7 (C_2), 144.9 (C_{5a}), 139.0 (C_1'), 129.5 (C_3' & C_5') 127.6 (C_4'), 125.2 (C_2' & C_6'), 124.7 (C_{6a}), 123.4 (C_9), 121.9 (C_4), 121.4 (C_{10}), 119.6 (C_8), 117.4 (C_3), 114.6 (C_{10b}), 113.5 (olefinic C), 109.6 (C_7), 107.8 (C_5), 102.8 (C_{10a}); MS *m/z* (M^+,311); Anal.calc.for: $C_{21}H_{13}NO_2$: C, 81.01; H, 4.21; N, 4.50. Found: C, 81.11; H, 4.13; N, 4.41%.

Procedure for the synthesis of 3-hydroxy-2-phenylpyrano[3,2-c]carbazol-4(7H)-one (14)

A solution of 3-cinnamoyl-4-hydroxycarbazole (**11**, 0.001 mol) in 20 mL of a 10% alcoholic sodium hydroxide kept at 0°C, hydrogen peroxide (2 mL) was added in drops, and the mixture was stirred for 5 h. The reaction was monitored by TLC. After the completion of the reaction, the solvent was removed and the residue was poured onto ice cold water. The separated solid was filtered, dried and purified by column chromatography over silica gel using petroleum ether:ethyl acetate (85:15) as eluent to get 3-hydroxy-2-phenylpyrano[3,2-*c*]carbazol-4(7*H*)-one (**14**). The compound thus obtained was recrystallized from ethanol to yield pale yellow crystals.

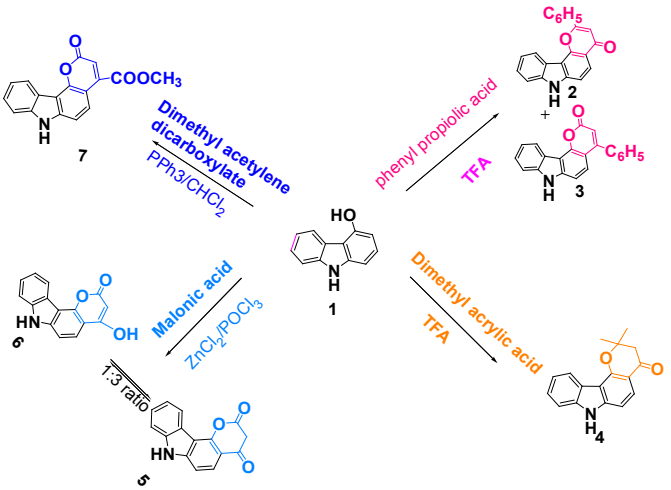
3-Hydroxy-2-phenylpyrano[3,2-c]carbazol-4(7H)-one (14): Yellow crystal; yield: 81% (0.264 g); m.p.269-271°C; IR (KBr, cm^{-1}) ν_{max}: 3426 (O-H), 3280 (N-H), 1615 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) (ppm) δ_H: 12.07 (b s, 1H, C_3-OH), 9.09 (b s, 1H, N_7-H), 7.60-7.00 (m, 11H, C_5, C_6, C_8, C_9, C_{10}, C_{11}, C_2-[C_2', C_3', C_4', C_5' & C_6'-H]); ^{13}C NMR (125 MHz, $CDCl_3$) (ppm) δ_C: 191.8 (C=O), 150.8 (C_1), 143.4 (C_{6a}), 139.0 (C_1'), 137.5 (C_2), 129.0 (C_3' & C_5'), 128.9 (C_4'), 127.5 (C_2' & C_6'), 125.7 (C_{7a}), 123.5 (C_3), 122.8 (C_{10}), 121.5 (C_5), 120.5 (C_{11}), 118.8 (C_9), 115.9 (C_{4a}), 114.6 (C_{11b}), 111.7 (C_8), 105.7 (C_6), 102.0 (C_{11a}); MS *m/z* (M^+, 327); Anal. calc. for $C_{21}H_{13}NO_3$: C, 77.05; H, 4.00; N, 4.28. Found: C, 77.13; H, 3.89; N, 4.21%.

RESULTS AND DISCUSSION

Synthesis of substituted pyrano[3,2-c]carbazoles using catalysts

As part of our ongoing studies on the development of facile methods for the synthesis of pyrano[3,2-*c*]carbazoles, 4-hydroxy carbazole which was bought commercially from Sigma Aldrich chemicals was used as potential precursor, which has opened new avenues for the synthesis of highly functionalized pyrano[3,2-*c*]- and furo[3,2-*c*]-carbazoles in excellent yields.

In an attempt to get substituted pyrano[3,2-*c*]carbazoles, first 4-hydroxy carbazole (**1**) was reacted with phenylpropiolic acid in the presence of trifluoroacetic acid, a mixture of two products (**2** & **3**) was obtained which were separated by column chromatography using petroleum ether and ethyl acetate (97:3 and 90:10) as eluent **(Scheme 1).** The structures of the products were substantiated on the basis of IR, ^{1}H NMR, ^{13}C NMR data and elemental analysis.



Scheme 1. Synthesis of pyrano[3,2-*c*]-carbazoles.

The IR spectrum of first product **2** displayed absorption bands at 3306 cm^{-1} for the N-H stretching and at 1644 cm^{-1} for the C=O vibrations. In its ^{1}H NMR spectrum the indole NH proton appeared as a broad singlet at δ 9.20. The aromatic protons appeared as a multiplet between the region δ.7.70-7.00. One olefinic proton at C_3 appeared as a singlet at δ 6.87. The total number of protons matched perfectly with its structure. The ^{13}C NMR spectrum of **2** revealed the presence of 21 carbons. The molecular ion peak in the mass spectrum at *m/z* 311 and the elemental analysis data agree well with the molecular formula $C_{21}H_{13}NO_2$.

The IR spectrum of the second product (**3**), displayed absorption bands at 3307 cm^{-1} for the N-H stretching and at 1730 cm^{-1} for the lactone carbonyl (α-pyrone) vibrations. In its ^{1}H NMR spectrum the indole NH proton appeared as a broad singlet at δ 8.53. The aromatic protons appeared as a multiplet between the region δ 7.85-7.25. One olefinic proton at C_3 appeared as a singlet at δ 6.60. The total number of protons matched perfectly with its structure. Analytical data are in accordance with the proposed structure for compound **3**.

In an anticipation to derive substituted pyrano[3,2-*c*]carbazoles, the reaction of 4-hydroxy carbazole (**1**) with 3,3-dimethylacrylic acid in trifluoroacetic acid at room temperature for 48 h, was carried out that yield a single product (**4**) in excellent yield. A singlet at δ 3.50 for the C_3 methylene proton and another six proton singlet at δ 1.71 corresponding the two methyl groups at C_2 further confirms the formation of the product (**4**) **(Scheme 1).**

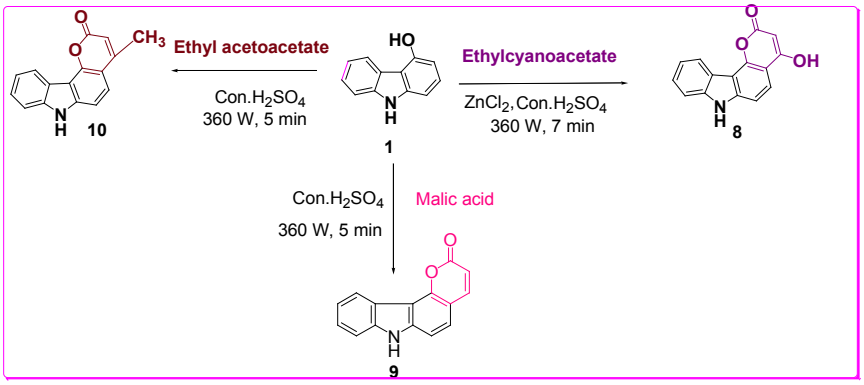
Inorder to get substituted pyrano[3,2-*c*]carbazoles, 4-hydroxy carbazole (**1**) was reacted with malonic acid in the presence of fused zinc chloride and phosphorus oxychloride at room temperature which afforded a single product (**5**) **(Scheme 1).** The IR spectrum of **5** displayed strong absorption band at 3384 cm^{-1} for the N-H stretching and at 1698 cm^{-1} for C=O vibrations. In its ^{1}H NMR spectrum a sharp singlet at δ 11.00 was due to C_4-OH proton. The indole NH proton appeared as a broad singlet at δ 8.35. The aromatic protons of the carbazole ring appeared as multiplet between the region δ 7.87-7.07. A singlet at δ 6.55 was due to the C_3 proton (enol form). The C_3-H_2 proton appeared as singlet at δ 3.00 (keto form). From the proton integration of C_3-H_2 of oxo form **5** and that of C_3-H and C_4-OH of hydroxy form **6**, the ratio of keto and enol forms was found to be in the ratio 3:1. Its ^{13}C NMR spectrum revealed the presence of 15 carbons further confirms the formation of the desired product.

In an aim to get pyrano[3,2-*c*]carbazoles, the reaction of 4-hydroxy carbazole (**1**) with dimethyl acetylene dicarboxylate in the presence of triphenylphosphine in CH_2Cl_2 was carried out which yielded a yellow coloured solid (7). A stretching vibration at 1630 cm^{-1} in the IR spectrum and a three proton singlet at δ 3.98 in the ^1H NMR spectrum correspond for $COOCH_3$ group which further confirms the product **(Scheme 1).**

Synthesis of substituted pyrano[3,2-c]carbazoles using microwave

Being triggered by the biological importance of pyranocarbazoles, various methods have been reported for their construction [16,17]. However those methods suffer from limitations such as prolonged reaction time, use of toxic solvents and requirement of excess of reagents, laborious work up procedure or harsh reaction condition. Thus the development of an alternate clean procedure is highly demanding for the synthesis of pyanocarbazole, which excels those limitations, we herein disclose a convenient and one pot synthesis of simple and substituted pyranocarbazoles from 4-hydroxy carbazole and ethylacetoacetate/malic acid/ ethylcyanoacetate in the presence of catalytic amount of conc. H_2SO_4 under microwave condition.

When 4-hydroxy carbazole (**1**) and ethylacetoacetate were subjected to microwave irradiation in the presence of catalytic amount of concentrated H_2SO_4, a single product was (**8**) obtained via Pechmann condensation as outlined in **Scheme 2.** Absorption at 1704 cm^{-1} for lactone C=O group in the IR and a three proton singlet at δ 2.10 for C_4-CH_3 in the ^1H NMR spectrum are in accordance with the proposed structure of the compound (**8**).



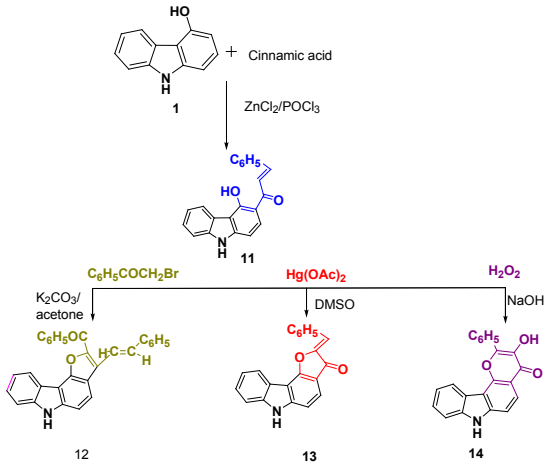
Scheme 2. Microwave assisted synthesis of pyrano[3,2-*c*]carbazoles.

In order to extend the above synthesis, simple pyrano[3,2-*c*]carbazole (**9**) can be synthesized by the Pechmann condensation of 4-hydroxy carbazole (**1**) with malic acid in the presence of concentrated sulphuric acid under microwave irradiation **(Scheme 2).** Two doublets at δ 7.78 (*J*=9.50 Hz) & 6.70 (*J*=9.50 Hz) due to the C_4 & C_3-H in the ^1H NMR spectrum gave strong evidence for the formation of the compound **9**.

Pechmann condensation of 4-hydroxy carbazole (**1**) with ethylcyanoacetate in the presence of fused $ZnCl_2$ and concentrated sulphuric acid under microwave irradiation yielded **10 (Scheme 2).** Its IR spectrum showed absorptions at 3343, 3048, and 1642 cm^{-1} due to the presence of -OH, N-H, and C=O groups respectively. The structure of **10** is fully supported by spectral and analytical data.

Synthesis of substituted furo[3,2-c]carbazoles

In order to attain the targeted furo[3,2-*c*]carbazoles, a putative synthon, 3-cinnamoyl-4-hydroxy carbazole (**11**) which can be obtained by the efficient reaction of 4-hydroxy carbazole (**1**) with cinnamic acid in the presence of fused zinc chloride and phosphorous oxychloride as reagent was carried out **(Scheme 3).**



Scheme 3. Synthesis of hydroxypyrano[3,2-*c*]carbazoles and furo[3,2-*c*]carbazoles.

The IR spectrum of **11** showed strong absorption bands at 3409, 3198 and 1733 cm^{-1} for the O-H stretching, N-H stretching and C=O stretchings respectively. In its ^{1}H NMR spectrum a sharp singlet at δ 11.50 was due to the C_4-OH proton. The indole NH proton appeared as a broad singlet at δ 9.23 and the aromatic cluster appeared between δ 7.87-7.07 accounting for 11 aromatic protons and two olefinic protons. The ^{13}C NMR spectrum revealed the presence of 21 carbons. The molecular ion peak in the mass spectrum at *m/z* 313 and the elemental analysis data agree well with the molecular formula $C_{21}H_{15}NO_2$. The compound thus generated was fully exploited for the synthesis of furocarbazole analogues.

For the synthesis of furocarbazole, we treated 3-cinnamoyl-4-hydroxycarbazole **11** with phenacyl bromide in the presence of ignited potassium carbonate in dry acetone **(Scheme 3).** Its IR spectrum showed absorptions at 3376 and 1686 cm^{-1} for N-H and C=O stretching respectively. In the ^{1}H NMR spectrum a one-proton broad singlet at δ 8.92 was accounted for the N-H proton. The aromatic cluster in the region δ 7.85-6.95 accounted for 17 aromatic protons including one styryl-*β*- proton. A doublet at δ 6.38 with *J*=15.20 Hz was due to the styryl-*α*-H present in the system at C_3 position. The ^{13}C NMR spectrum of **12** accounts for the presence of 29 carbons in the molecule. The elemental analysis and mass spectral data were compatible with the molecular formula $C_{29}H_{19}NO_2$ (**12**).

The reaction of 3-cinnamoyl-4-hydroxy carbazole (**11**) with mercuric acetate, (which is well known for highly regioselective and stereospecific oxymercuration of olefins), in the presence of dimethyl sulfoxide yielded a yellow colored product **13 (Scheme 3).**

The IR spectrum of **13** showed N-H stretching at 3304 cm^{-1} and carbonyl stretching at 1644 cm^{-1}. The ^{1}H NMR spectrum showed a broad singlet at δ 8.89 for the N-H proton. Eleven aromatic protons appeared as a multiplet in the region δ 7.90-7.07. A singlet at δ 6.96 accounted for olefinic proton. The presence of 21 carbons was inferred from its ^{13}C NMR spectrum. The elemental analysis data and the molecular ion peak at *m/z* 311 gave strong evidence for the formation of the compound **13**.

We also made an attempt to obtain 3- hydroxy-2-phenylpyrano[3,2-*c*]carbazole (**14**) from the precursor, 3-cinnamoyl-4-hydroxy carbazole (**11**) using alkaline hydrogen peroxide **(Scheme 3).**

Its IR spectrum showed absorptions at 3426, 3280 and 1615 cm^{-1} due to the presence of -OH, N-H, and C=O groups respectively. The carbonyl absorption was at low wave numbers due to the presence of a hydroxy group adjacent to the carbonyl group. The ^{1}H NMR spectrum showed two broad singlets at δ 12.07 and 9.09 due to the presence of OH and N-H protons. Further, the ^{1}H NMR gave strong evidence for the formation of compound **14**. Moreover, structure **14** was supported by mass spectrum and elemental analysis, which was compatible with assigned structure.

SUMMARY

In summary, we have developed a divergent synthetic route to potentially bio-active pyrano- and furo- carbazoles by the efficient reaction of 4-hydroxy carbazole with a variety of reagents and co-reactants using different methodologies. Products are well characterizd to establish the structure. The series of pyrano[3,2-*c*]carbazole and furo[3,2-*c*]carbazole were synthesized which may have wider scope in drug discovery.

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