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An efficient, solvent-free approach to heteroarylcarbazoles: synthesis of 3-chromenylcarbazoles, 3,6-bis-(chromenyl)-carbazoles and 3-quinolylcarbazoles

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Abstract—An easy and efficient synthesis of 3-chromenylcarbazoles, 3,6-bis-(chromenyl)carbazoles and 3-quinolylcarbazoles is reported under solvent-free conditions.

There is strong interest in the synthesis of carbazole derivatives due to their intriguing structural features and promising biological activities.[1] Various hetero-annulated carbazole derivatives have gained considerable attention because of their natural occurrence and the broad spectrum of biological activity associated with these compounds.[2] Of particular interest have been natural products containing common heterocyclic rings such as furocarbazoles, pyranocarbazoles, pyrrolocarbazoles, indolocarbazoles, pyridocarbazoles and synthetic analogues thereof. A number of synthetic methodologies have emerged for their preparation.[1–3] On the other hand, there are very few reports on the synthesis of heteroaryl substituted carbazoles,[4] and hence a practical method for the synthesis of such compounds is desirable. In continuation of our interest on the synthesis of heteroaryl and diheteroarylcarbazoles[4c] of biological importance, we herein report a new method for the synthesis of 3-chromenylcarbazoles, 3,6-bis-(chromenyl)carbazoles and 3-quinolylcarbazoles.

The synthesis[5] and biological activity[6] of 3-nitrochromenes have been reported because of their potential as precursors to a variety of medically important 2*H*-benzopyran derivatives such as flavonols,[7] amines[8] and other important targets.[9] We have synthesized novel 3-nitrochromenylcarbazoles by the reaction of salicylaldehydes and β-nitrovinylcarbazole with DABCO.

β-Nitrovinylcarbazole[10] **1**, 2-hydroxybenzaldehyde **2a–e** and DABCO (50 mol %) were heated at 70 °C for 30 min to furnish chromenylcarbazoles **3a–e** in good yields (Scheme 1). The reaction proceeds via Michael addition of 2-hydroxybenzaldehyde to β-nitrovinylcarbazole followed by aldol condensation. The intermediate 4-hydroxyflavone was not observed, indicating its immediate dehydration to the corresponding 3-nitrochromenylcarbazoles. We carried out the same reaction using different bases such as sodium methoxide, triethylamine and piperidine but observed faster and cleaner reactions with DABCO.

Chromene formation[11] was confirmed by ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectrum of **3a**, the chromenyl 2*H* proton was observed as a sharp singlet at δ 6.8 and the 4*H* proton appeared as a singlet at δ 8.16. The ^{13}C NMR spectrum of **3a** showed the chromenyl C-2 carbon at 150 ppm indicating that it was attached to the electronegative oxygen atom. The structure of product **3d** was further confirmed by single crystal X-ray analysis (Fig. 1).[12] All new compounds were thoroughly characterized by mass and elemental analysis.

Extending the methodology, we have synthesized bis-(3-nitrochromenyl)carbazoles by reaction of salicylaldehydes with bis-(β-nitrovinyl)carbazole **4** using DABCO. Bis-(chromenyl)carbazole derivatives **5a–e** were

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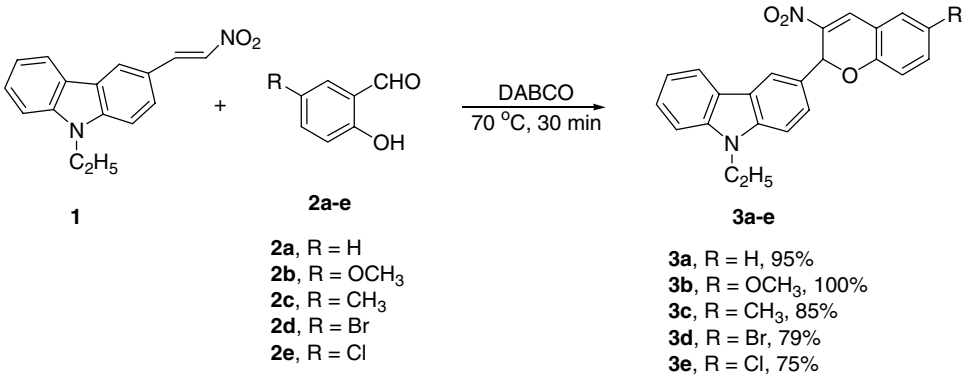


Scheme 1. Synthesis of 3-(3-nitrochromenyl)carbazoles.

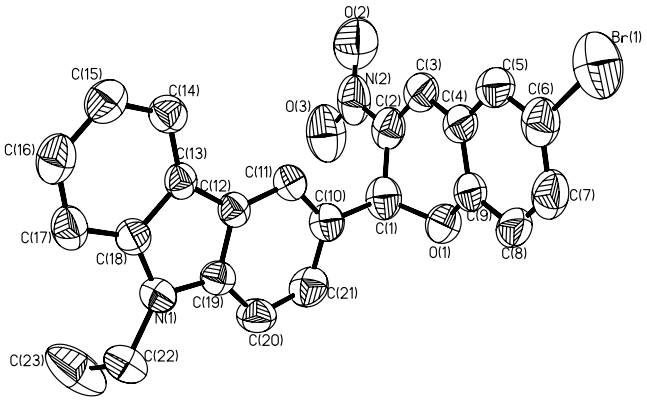


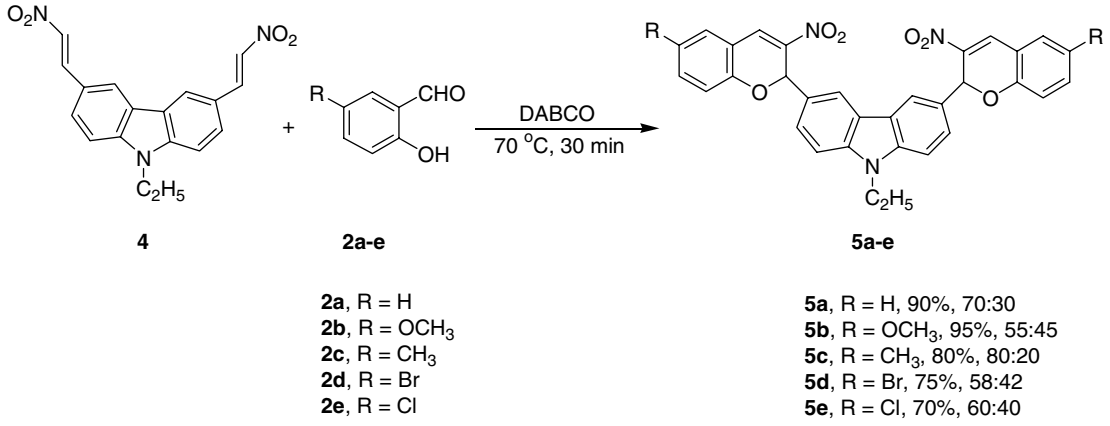
Figure 1. ORTEP diagram of 9-ethyl-3-(6-bromo-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole **3d**. Hydrogen atoms are omitted for clarity.

obtained[13] as a mixture of two diastereomers in good yields (Scheme 2). The structures were confirmed by ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR of **5a**, the 2*H* and 4*H* protons were observed at δ 6.84 and δ 8.17, similar to monochromenyl derivatives **3a**–**e**. The diastereomeric ratio was calculated from ^{1}H NMR spectra. At higher temperatures polymerization of 3,6-bis-β-nitrovinylcarbazole was observed.

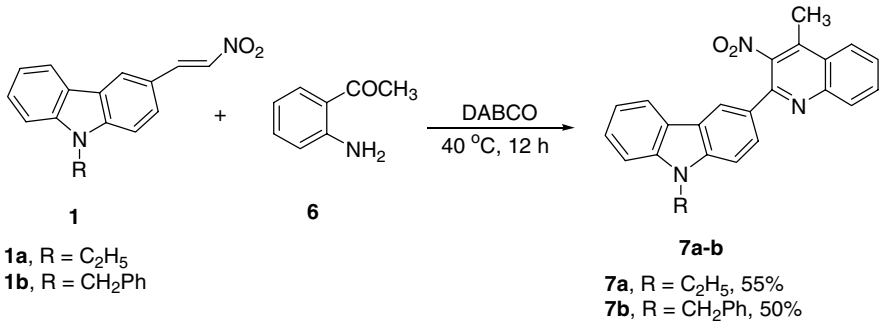
Quinolines[14] are important and widely used heterocyclic compounds in organic chemistry, and a variety of methods for the preparation of nitroquinolines have been reported.[15] Direct nitration of quinolines leads to several regioisomers.[16] We have synthesized carbazole-substituted 3-nitroquinolines using our methodology.

3-(3-Nitroquinolyl)carbazoles were synthesized[17] in good yields under solvent-free conditions in one-pot by the reaction of β-nitrovinylcarbazole **1** with 2-amino acetophenone **6** at 40 °C (Scheme 3). The intermediate dihydroquinoline was not observed, and this indicates immediate aromatization to quinolines. At higher temperatures (>50 °C) lower yields were obtained due to the self-condensation of 2-aminoacetophenone and partial polymerization of β-nitrovinylcarbazole. In the ^{1}H NMR spectrum of **7a**, the C-4 methyl group of the quinoline was observed as a sharp singlet at δ 2.76. The carbazole 4*H* proton was observed downfield resonating at δ 8.47 because of the –NO_2 space effect. The absence of –N*H* and 2*H* proton resonances of the quinoline indicates complete aromatization. The structure was also confirmed by single crystal X-ray analysis (Fig. 2).[18] Attempts to synthesize bis-quinolyl derivatives failed due to the polymerization of bis-β-nitrovinylcarbazole.

In conclusion, we have reported a new, easy and efficient synthesis of 3-(3-nitrochromenyl)carbazoles, 3,6-bis-(3-nitrochromenyl)carbazoles and 3-(3-nitroquinolyl)carbazoles under solvent-free conditions in moderate to



Scheme 2. Synthesis of 3,6-bis-(3-nitrochromenyl)carbazoles.



Scheme 3. Synthesis of 3-(3-nitroquinolyl)carbazoles.

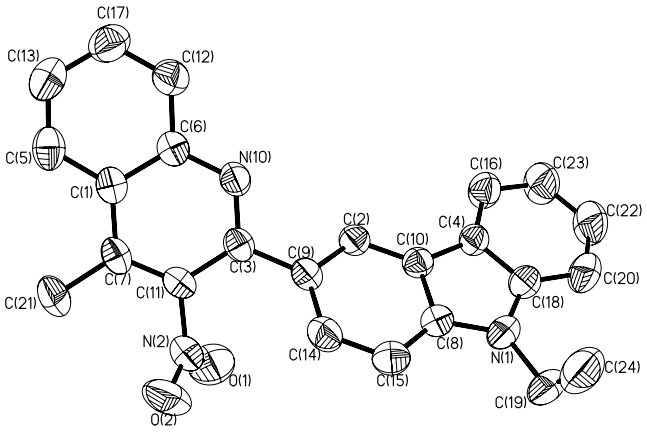


Figure 2. ORTEP diagram of 9-ethyl-3-(4-methyl-3-nitroquinolin-2-yl)-9*H*-carbazole **7a**. Hydrogen atoms are omitted for clarity.

excellent yields. The procedures benefit from short reaction times and one-pot reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.02.031.

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11. *General procedure*: 9-Ethyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole **1** (0.27 g, 1 mmol), salicylaldehyde **2a**–**e** (0.60 g, 3 mmol) and DABCO (0.06 g, 0.5 mmol) were stirred and heated at 70 °C for 30 min. After the reaction was complete (TLC), the residue was diluted with dichloromethane (5 mL), adsorbed on silica gel and subjected to column chromatography with 5% ethyl acetate in hexane to obtain the chromenes in good yields. 9-Ethyl-3-(6-bromo-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole **3d**: Red solid; mp: 182–184 °C; IR (KBr): 3074, 2972, 1645, 1251, 1234, 1195, 1165, 1128, 1060, 954 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, $J = 7.05$ Hz, 3H), 4.32 (q, $J = 7.3$ Hz, 2H), 6.72 (d, $J = 8.9$ Hz, 1H), 6.76 (s, 1H), 7.22 (t, $J = 7.1$ Hz, 1H), 7.25 (s, 1H), 7.34 (d, $J = 2.4$ Hz, 1H), 7.36 (t, $J = 2.2$ Hz, 1H), 7.39 (s, 1H), 7.44 (d, $J = 2$ Hz, 1H), 7.46 (d, $J = 1.2$ Hz, 1H), 7.49 (d, $J = 2.3$ Hz, 1H), 8.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 37.6, 75.3, 108.7, 108.9, 114.0, 119.2, 119.3, 119.5, 119.9, 120.6, 122.6, 123.1, 124.8, 126.2, 126.5, 127.6, 132.2, 136.5, 140.3, 140.6, 142.4, 152.5; LC–MS: *m/z* 450 ($M+H^+$), 452 ([M+2]+H^+); positive mode. Anal. Calcd for $C_{23}H_{17}BrN_2O_3$: C, 61.48; H, 3.81; N, 6.23. Found: C, 61.40; H, 3.83; N, 6.26.

12. Crystallographic data for structure **3d** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 627871. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]; 9-ethyl-3-(6-bromo-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole; formula: $C_{23}H_{17}N_2O_3Br$; unit cell parameters: *a* 15.154(4), *b* 12.088(3), *c* 11.316(3); space group *P*2/*c*.
13. 9-Ethyl-3,6-bis-[(*E*)-2-nitrovinyl]-9*H*-carbazole (0.34 g, 1 mmol), 5-methoxysalicylaldehyde (0.75 g, 5 mmol) and DABCO (0.12 g, 1 mmol) were stirred and heated at 70 °C for 30 min. After completion, the reaction mass was dissolved in CH_2Cl_2 (5 mL), adsorbed on silica gel and subjected to column chromatography with 7% ethyl acetate in hexane to obtain the 3,6-bis-(3-nitro-chromen-2-yl)carbazoles in good yields. 9-Ethyl-3,6-bis-(6-methoxy-3-nitro-2*H*-chromen-2-yl)-9*H*-carbazole **5b**: Yellow solid; mp: 228–230 °C; IR (KBr): 3059, 2959, 2829, 1874, 1730, 1643, 1244, 1201, 1157, 1068, 1030, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, $J = 7.1$ Hz, 3H), 3.81 (s, 6H), 4.14 (q, $J = 7.0$ Hz, 2H), 6.73 (s, 2H), 6.77 (d, $J = 8.9$ Hz, 2H), 6.86–6.91 (m, 4H), 7.25 (d, $J = 8.4$ Hz, 2H), 7.44–7.47 (m, 2H), 8.01 (d, $J = 5.2$ Hz, 2H), 8.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 37.6, 56.0, 74.3, 110.1, 115.02, 118.1, 119.3, 120.4, 120.9, 122.3, 125.4, 127.7, 130.7, 140.7, 141.8, 147.1, 154.6; LC–MS: *m*/*z* 606 ($M+H^+$), positive mode. Anal. Calcd for $C_{34}H_{27}N_3O_8$: C, 67.43; H, 4.49; N, 6.94. Found: C, 67.59; H, 4.48; N, 6.92.
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17. 9-Ethyl-3-[(*E*)-2-nitrovinyl]-9*H*-carbazole (0.27 g, 1 mmol), 2′-aminoacetophenone (0.68 g, 5 mmol) and DABCO (0.06 g, 0.5 mmol) were stirred at 40 °C for 12 h. After completion, the residue was diluted with CH_2Cl_2 (5 mL), adsorbed on silica gel and subjected to column chromatography with 7% ethyl acetate in hexane to obtain nitroquinolines **7a**–**b** in good yields. 9-Ethyl-3-(4-methyl-3-nitroquinolin-2-yl)-9*H*-carbazole **7a**: mp: 186–188 °C; IR (KBr): 3414, 3057, 1728, 1589, 1520, 1471, 1344, 1232, 1153, 1120, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (t, $J = 7.3$ Hz, 3H), 2.76 (s, 3H), 4.39 (q, $J = 7.3$ Hz, 2H), 7.23–7.27 (m, 1H), 7.42 (d, $J = 7.6$ Hz, 1H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.63–7.70 (m, 1H), 7.79–8.85 (m, 2H), 8.08 (d, $J = 8.1$ Hz, 1H), 8.14 (d, $J = 7.6$ Hz, 1H), 8.23 (d, $J = 8.3$ Hz, 1H), 8.47 (d, $J = 1.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 27.8, 37.7, 56.7, 108.8, 115.7, 117.2, 118.4, 119.3, 120.7, 123.4, 124.6, 125.5, 126.1, 127.7, 130.4, 131.2, 132.0, 134.4, 136.5, 140.8, 146.0, 147.1, 151.1; LC–MS: *m*/*z* 380 ($M-H^+$), negative mode. Anal. Calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.54; H, 5.04; N, 11.04.
18. Crystallographic data for structure **7a** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 627870. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]; 9-ethyl-3-(4-methyl-3-nitroquinolin-2-yl)-9*H*-carbazole; formula: $C_{24}H_{19}N_3O_2$; unit cell parameters: *a* 26.834(3), *b* 9.3498(11), *c* 15.3302(18); space group *C*2/*c*.