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Synthesis of New Precursors for the Carbazole Alkaloids

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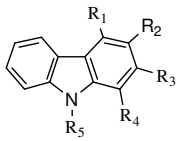
In this study, the synthesis of 3-substituted tetrahydrocarbazole-4-one derivatives was described. These derivatives (**4a-c** and **5b-c**) can be used as key intermediates in the synthesis of new carbazole alkaloids due to the carbonyl functionality at C-4.

Key Words: Tetrahydrocarbazole-4-one, Carbazole alkaloids.

INTRODUCTION

Most of the carbazole alkaloids such as 3-methylcarbazole and its several oxidized derivatives have been isolated from taxonomically related higher plants of the genera *Glycosmis*, *Clausena* and *Murraya* (family *Rutaceae*)[1-4]. The structure of these alkaloids can vary from simple substituted carbazoles to molecules containing complex terpene moieties.

Non-oxygenated derivatives of carbazole alkaloids have been isolated from the roots of different *Clausena* species, such as *Clausena heptaphylla*, *Clausena indica* and *Clausena anisata*[5-7]. One of the non-oxygenated derivatives, 9-formyl-3-methylcarbazole has showed weak cytotoxicity against both mouse melanoma B16 and adriamycin-resistant P388 mouse leukemia cell lines[8].



R_1, R_3, R_4, R_5=H; **R_2**=CH_3 3-methylcarbazole

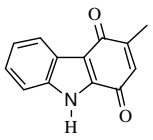
R_1, R_3, R_5=H; **R_2**=CH_3; **R_5**:CHO 9-formyl 3-methylcarbazole

R_1, R_3, R_5=H; **R_2**=CH_3; **R_4**:OCH_3 Murrayofoline A

R_1, R_3, R_5=H; **R_2**=CH_2OH; **R_4**:OCH_3 Koenoline

R_1, R_3, R_5=H; **R_2**=CHO; **R_4**:OCH_3 Murrayanine

R_1, R_3, R_5=H; **R_2**=CO_2CH_3; **R_4**:OCH_3 Mukonine

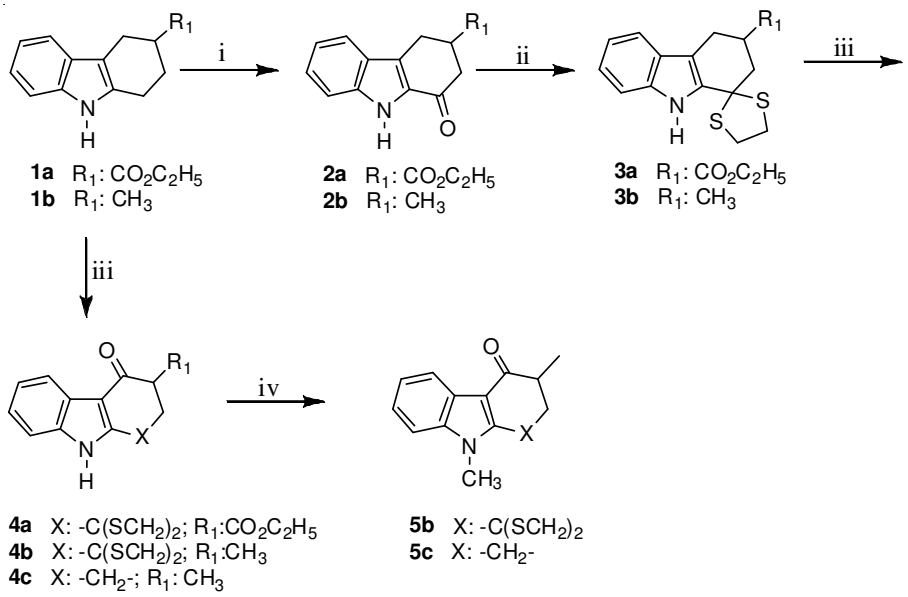


Murrayaquinone A

The higher plants of the genus *Murraya*, which are trees growing in southern Asia, are the major source of 1-oxygenated carbazole alkaloids. Extracts of the leaves and bark of this tree have been used in traditional medicine for analgesia and local anesthesia and for the treatment of eczema, bronchitis, malaria, rheumatism

and dropsy[9]. Some of oxygenated carbazole derivatives for instance, koenoline showed cytotoxic activity and murrayanine showed antimicrobial properties against human pathogenic fungi[10,11].

In this study, the synthesis of 3-substituted tetrahydrocarbazole-4-one derivatives was described. These derivatives can be used as key intermediates in the synthesis of new carbazole alkaloids due to the carbonyl functionality at **C-4**.



Scheme-I

(i) H_5IO_6, methanol:water, stirred, 0 °C; (ii) $ZnCl_2$, ethane dithiol, CH_2Cl_2, reflux; (iii) DDQ, THF (90 %), stirred, 0 °C; (iv) TBAHS, NaOH (50 %), CH_2Cl_2, CH_3I, stirred at 0 °C.

EXPERIMENTAL

All melting points were measured in sealed tubes using an electrothermal digital melting point apparatus (Gallenkamp) and are uncorrected. IR Spectra were recorded on a Hitachi 270-30 infrared spectrometer. ^{1}H NMR spectra were obtained on a high resolution furier transform Bruker WH-400 NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra were determined on the electron impact mode by direct insertion at 70 eV with a Micromass UK Platform II LC-MS spectrometer. Combustion analysis of compounds was obtained on a CHNS-932-LECO. Analytical and preparative thin layer chromatography (TLC) was carried out using silica gel 60 HF-254 (Merck). Column chromatography was carried out by using 70-230 mesh silica gel (0.063-0.2 mm, Merck) and aluminum oxide 90 active neutral (Merck).

Ethyl 2,3,4,9-tetrahydrospiro[carbazole-1,2'-[1,3]dithiolane]-3-carboxylate (3a): To a solution of 2.3 g (9 mmol) of **2a** in 50 mL of dichloromethane was added 1.48 g (10.8 mmol) of zinc chloride and 1.02 g (10.8 mmol) of 1,2-ethanedithiol. The mixture was refluxed for 11 h and then the reaction mixture was washed with 50 mL of 10 % potassium hydroxide. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. Recrystallization of the product from cyclohexane-diethyl ether yielded 2.20 g (74 %) of **3a**, TLC: R_f 0.87 [ethyl acetate-hexane (1:1)], m.p. 132 °C; IR (KBr, ν_{max}, cm^{-1}): 3314 (NH), 2970 (CH), 1692 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 2.58 (t, 1H, *J* = 12.5 Hz, CH), 2.81-2.91 (m, 2H, CH_2), 3.15-3.20 (m, 2H, CH_2), 3.42-3.67 (m, 4H, SCH_2CH_2S), 4.26 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 7.11 (t, 1H, *J* = 7.2 Hz, aromatic proton), 7.21 (t, 1H, *J* = 7.1 Hz, aromatic proton), 7.33 (d, 1H, *J* = 8.1 Hz, aromatic proton), 7.48 (d, 1H, *J* = 7.8 Hz, aromatic proton), 8.26 (s, 1H, NH); LC-MS (70 eV): m/z % 335 (22.7), 334 (100), 274 (22.7), 240 (4.3), 196 (1.5), 168 (1.4). Anal. calcd. for $C_{17}H_{19}NO_2S_2$: C, 61.23; H, 5.74; N, 4.20; S, 19.23. Found: C, 61.39; H, 5.86; N, 4.09; S, 19.17.

Ethyl 4-oxo-2,3,4,9-tetrahydrospiro[carbazole-1,2'-[1,3]dithiolane]-3-carboxylate (4a): To a solution of 850 mg (2.54 mmol) **3a** in 10 mL of tetrahydrofuran (90 %) was added dropwise 1.16 g (5.08 mmol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in tetrahydrofuran at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then 5 h at room temperature. The solution was poured into 500 mL of 10 % solution of sodium hydroxide and extracted twice with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. Recrystallization of the product from methanol yielded 75 mg (8.5 %) of **4a**, TLC: R_f 0.61 [ethyl acetate-hexane (1:1)]; m.p.: 206 °C; IR (KBr, ν_{max}, cm^{-1}): 3262 (NH), 2977 (CH), 1720 (C=O), 1650 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 2.82 (dd, 1H, *J* = 13.7 and 4.2 Hz, CH), 3.24 (t, 1H, *J* = 13.6 Hz, CH), 3.47-3.49 (m, 1H, $SHCHCH_2S$), 3.60-3.65 (m, 2H, SCH_2CH_2S), 3.67-3.72 (m, 1H, $SHCHCH_2S$), 4.02 (d, 1H, *J* = 12.2 and 4.2 Hz, CH), 4.32 (q, 2H, OCH_2CH_3), 7.23-7.33 (m, 2H, aromatic proton), 7.37-7.41 (m, 1H, aromatic proton), 8.20 (d, 1H, *J* = 7.4 Hz, aromatic proton), 8.96 (s, 1H, NH); LC-MS (70 eV): m/z % 350 (12.4), 349 (19.9), 348 (100), 315 (1.6), 314 (7.4), 302 (9.6), 286 (7.8), 256 (10.3). Anal. calcd. for $C_{17}H_{17}NO_3S_2$: C, 58.77; H, 4.93; N, 4.03; S, 18.46. Found: C, 58.62; H, 4.84; N, 4.07; S, 18.49.

3-Methyl-1,2,3,4-tetrahydro-9*H*-carbazole-1-one (2b): To a solution of 2.46 g (10.8 mmol) periodic acid in 25 mL of methanol-water (1:1) was added dropwise 1 g (5.4 mmol) of **1b** in 15 mL methanol-THF (2:1) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then stirring was continued for 2 h at room temperature. The solvent was evaporated then the residue was dissolved in ethyl acetate and washed with 50 mL of 10 % sodium bisulfide and then with brine. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. Recrystallization of the residue from cyclohexane yielded 830 mg (77 %) of **2b**[14],

TLC: R_f 0.85 [ethyl acetate-hexane (1:1)], m.p.: 191 °C; IR (KBr, ν_{max}, cm^{-1}): 3263 (NH), 2947 (CH), 1645 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.13 (d, 3H, *J* = 5.6 Hz, CH_3CH), 2.37 (d, 2H, *J* = 10.4 Hz, CH_2) , 2.51 (d, 1H, *J* = 5.2 Hz, CH), 2.54-2.58 (m, 1H, CH), 3.05-3.10 (dd, 1H, *J* = 9.6 and 6.4 Hz, CH), 7.05 (t, 1H, *J* = 7.6 Hz, aromatic proton), 7.27 (t, 1H, *J* = 7.4 Hz, aromatic proton), 7.37 (d, 1H, *J* = 8.8 Hz, aromatic proton), 7.63 (d, 1H, *J* = 8.0 Hz, aromatic proton), 11.53 (s, 1H, NH); LC-MS (70 eV): m/z % 201 (15.2), 200 (100), 73 (5.1), 55 (4.0). Anal. calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.19; H, 6.51; N, 7.18.

3-Methyl-2,3,4,9-tetrahydrospiro[1*H*-carbazole-1,2'-(1,3)-dithiolane] (3b): To a solution of 1.8 g (9 mmol) of **2b** in 50 mL of dichloromethane was added 1.48 g (10.8 mmol) of $ZnCl_2$ and 1.02 g (10.8 mmol) of 1,2-ethanedithiol. The mixture was refluxed for 11 h and then the reaction mixture was washed with 50 mL of 10 % potassium hydroxide. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. Recrystallization of the product from cyclohexane yielded 1.7 g (68 %) of **3b**, TLC: R_f 0.90 [ethyl acetate-hexane (1:1)], m.p.: 136 °C; IR (KBr, ν_{max}, cm^{-1}): 3399 (NH), 2953 (CH); ^{1}H NMR ($CDCl_3$): δ 1.18 (d, 3H, *J* = 6.0 Hz, CH_3CH), 2.17-2.32 (m, 3H, CH), 2.44 (dd, 1H, *J* = 11.2 and 1.2 Hz, CH), 2.86 (d, 1H, *J* = 10.4 Hz, CH), 3.34-3.65 (m, 4H, SCH_2CH_2S), 7.04-7.08 (m, 1H, aromatic proton), 7.14-7.18 (m, 1H, aromatic proton), 7.29 (d, 1H, *J* = 8.0 Hz, aromatic proton), 7.43 (d, 1H, *J* = 7.6 Hz, aromatic proton), 8.18 (s, 1H, NH); LC-MS (70 eV): m/z % 277 (16.1), 276 (100), 261 (2.0), 234 (4.0), 216 (15.9), 199 (12.5), 198 (93.6), 145 (20.8). Anal. calcd. for $C_{15}H_{17}NS_2$: C, 65.41; H, 6.22; N, 5.09; S, 23.28. Found: C, 65.29; H, 6.27; N, 5.14; S, 23.29.

3-Methyl-2,3-dihydrospiro [1*H*-carbazole-1,2'-(1,3)-dithiolane]-4-one (4b): To a solution of 700 mg (2.54 mmol) **3b** in 10 mL of tetrahydrofuran (90 %) was added dropwise 1.16 g (5.08 mmol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in tetrahydrofuran at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then 5 h at room temperature. The solution was poured into 50 mL of 10 % solution of sodium hydroxide and extracted twice with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. Recrystallization of the product from methanol yielded 480 mg (65 %) of **4b**, TLC: R_f 0.69 [ethyl acetate-hexane (1:1)]; m.p.: 246 °C; IR (KBr, ν_{max}, cm^{-1}): 3220 (NH), 2924 (CH), 1610 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.17 (d, 3H, *J* = 6.4 Hz, CH_3CH), 2.48 (m, 1H, CH), 2.61 (m, 1H, CH), 2.75-2.81 (m, 1H, CH), 3.43-3.78 (m, 4H, SCH_2CH_2S), 7.15 (t, 1H, *J* = 7.6 Hz, aromatic proton), 7.21 (d, 1H, *J* = 7.6 Hz, aromatic proton), 7.44 (d, 1H, *J* = 7.6 Hz, aromatic proton), 7.96 (d, 1H, *J* = 7.6 Hz, aromatic proton), 11.9 (s, 1H, NH); LC-MS (70 eV): m/z % 292 (9.7), 291 (18.6), 290 (100), 73 (7.3), 55 (6.6). Anal. calcd. for $C_{15}H_{15}NOS_2$: C, 62.25; H, 5.22; N, 4.84; S, 22.16. Found: C, 62.10; H, 5.27; N, 4.82; S, 22.19.

3,9-Dimethyl-2,3-dihydrospiro[1*H*-carbazole-1,2'-(1,3)-dithiolane]-4-one (5b): A solution of 1.5 g (5.2 mmol) of **4b** in 40 mL of dichloromethane was cooled

to 0 °C. After that, 1.5 mL of 50 % sodium hydroxide, 100 mg tetrabutylammonium hydrogen sulfate and 0.75 g (5.3 mmol) of methyl iodide were added. The mixture was stirred for 1 h at 0 °C then stirring was continued for 2 h at room temperature, washed with 50 mL 10 % hydrochloric acid and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was recrystallized from ethyl acetate to afford 1.5 g (96 %) of **5b**, TLC: R_f 0.74 [ethyl acetate-hexane (1:1)]; m.p.: 174 °C; IR (KBr, ν_{max}, cm^{-1}): 2925 (CH), 1652 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.29 (d, 3H, *J* = 6.4Hz, CH_3CH), 2.64-2.65 (m, 2H, CH_2), 2.96-3.00 (m, 1H, CH), 3.39-3.70 (m, 4H, SCH_2CH_2S), 4.01 (s, 3H, NCH_3), 7.26-7.36 (m, 3H, aromatic protons), 8.30-8.33 (m, 1H, aromatic proton); LC-MS (70 eV): m/z % 305 (17.6), 304 (100), 212 (1.1), 211 (9.5), 210 (5.2). Anal. calcd. for $C_{16}H_{17}NOS_2$: C, 63.33; H, 5.65; N, 4.62; S, 21.13. Found: C, 63.18; H, 5.59; N, 4.76; S, 21.17.

3-Methyl-1,2,3,4- tetrahydro-9*H*-carbazole-4-one (4c): To a solution of 2 g (10.79 mmol) **1b** in 30 mL of tetrahydrofuran (90 %) was added dropwise 4.9 g 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (21.59 mmol) of in tetrahydrofurane at 0 °C. The reaction mixture was stirred 5 h at room temperature then the solution was poured into 500 mL of 10 % sodium hydroxide and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate and the solvent was removed. The residue was crystallized from methanol to yield 1.55 g (72 %) of **4c**, TLC: R_f 0.59 [ethyl acetate-hexane (1:1)]; m.p.: 228 °C; IR (KBr, ν_{max}, cm^{-1}): 3216 (NH), 2927 (CH), 1627 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.31 (d, 3H, *J* = 7.2 Hz, CH_3CH), 1.98-2.07 (m, 1H, CH), 2.28-2.35 (m, 1H, CH), 2.58-2.64 (m, 1H, CH), 3.00-3.04 (m, 2H, CH_2), 7.21-7.26 (m, 2H, aromatic protons), 7.32 (m, 1H, aromatic proton), 8.24 (m, 1H, aromatic proton), 8.32 (s, 1H, NH); LC-MS (70 eV): m/z % 201 (12.5), 200 (100), 130 (2.4), 73 (1.7). Anal. calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.24; H, 6.54; N, 7.08.

3,9-Dimethyl-1,2,3,4-tetrahydrocarbazole-4-one (5c): A solution of 1.55 g (7.79 mmol) of **4c** in 20 mL of dichloromethane was cooled to 0 °C. After that, 2 mL of 50 % sodium hydroxide, 100 mg of tetrabuthylammonium hydrogen sulfate and 1.14 g (8.02 mmol) of methyl iodide were added. The mixture was stirred for 1 h at 0 °C and then 2 h at room temperature, washed with 50 mL 10 % hydrochloric acid and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the residue was recrystallized from methanol to afford 1.5 g (90 %) of **5c**, TLC: R_f 0.61 [ethyl acetate-hexane (1:1)]; m.p.: 126 °C; IR (KBr, ν_{max}, cm^{-1}): 2924 (CH), 1634 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.28 (d, 3H, *J* = 6,8 Hz, CH_3CH) , 1.93-2.03 (m, 1H, CH), 2.27-2.35 (m, 1H, CH), 2.51-2.59 (m, 1H, CH), 2.85-3.01 (m, 2H, CH_2), 3.66 (s, 3H, CH_3), 7.25 (m, 3H, aromatic protons), 8.25 (m, 1H, aromatic proton); LC-MS (70 eV): m/z % 215 (13.8), 214 (100), 144 (1.7), 73 (0.6). Anal. calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.98; H, 7.03; N, 6.51.

RESULTS AND DISCUSSION

We selected two tetrahydrocarbazole derivatives **1a** and **1b** as the starting material which were synthesized previously[8,12]. Oxidation of compounds **1a** and **1b** at position 1 with periodic acid resulted in the formation of compound **2a**[13] and **2b**[14] which in the next step were protected with ethane dithiole to give **3a** and **3b**[15,16]. Compounds **3a**, **3b** and **1b** were selectively oxidized at position 4 with 2,3-dichloro-5,6-dicyano-*p*-benzo-quinone to yield respectively **4a**, **4b** and **4c**, but the yield was too low for **4a**[17]. Then indole nitrogen atom of **4b** and **4c** was protected using tetrabutyl-ammonium hydrogen sulphate and methyl iodide which resulted in compounds **5b** and **5c**[18].

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