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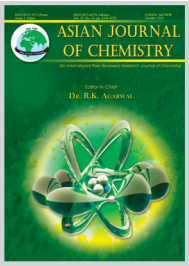

Synthesis of Tetrahydrocarbazole Derivatives of the Indol Alkaloids

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The synthesis of the tetrahydrocarbazole derivatives **6** and **11** which can give rise to synthesize indole or carbazole alkaloids were described. Many new tetrahydrocarbazole derivatives have also been synthesized.

Key Words: Indol alkaloids, Condyfoline, Tetrahydrocarbazolones.

INTRODUCTION

Although 1-oxo and 4-oxo-tetrahydrocarbazoles rarely occur in nature, they have been increasingly important intermediates in the synthesis of indole or carbazole alkaloids and various biologically active heterocyclic compounds because of their unique structures. For instance, 4-oxo-tetrahydrocarbazole was used in the synthesis of antiemetic drugs, central nervous system active drugs and NPY-1 antagonists[1-4]. 4-Oxo-tetrahydrocarbazole derivatives have also been used in the synthesis of indole alkaloids[5,6]. Tetrahydrocarbazolone based antitumor active compounds and inhibitors of HIV integrase were synthesized from 1-oxo-tetrahydydrocarbazoles[7,8]. 1-Oxo-tetrahydydrocarbazoles have also been used in the synthesis of indole based alkaloids[9,10].

EXPERIMENTAL

All melting points were measured in sealed tubes using an electro thermal 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 fourier 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).

Metyl cyano(4-ethylcyclohexanone-3yl)acetate (2): To a solution of a catalytic amount of sodium methoxide in methanol (prepared by adding 1 g of metallic sodium to 250 mL of absolute methanol at 0 ºC) were added 8.9 g (89 mmoles) of methyl cyanoacetate and the solution was stirred for 15 min at 0 ºC. To this solution were added dropwise 10 g (81 mmol) of 4-ethyl 2-cyclohexenone (**1**) at the same temperature. The reaction mixture was stirred for 16 h at room temperature. The solution was acidified with acetic acid and then diluted with water. The compound was extracted with diethyl ether and the extract was dried with anhydrous magnesium sulfate. The solvent was removed and the residue was purified by chromatography using silica gel and ethyl acetate-hexane (1:1). After the solvent was evaporated, the product was yielded 16.5 g (92 %) of **2** as oil, TLC: R_f 0.43 (ethyl acetate-hexane). IR (KBr, ν_{max}, cm^{-1}): 2962 (CH), 2250 (CN), 1747 (C=O, ester), 1714 (C=O, ketone). ^{1}H NMR ($CDCl_3$): δ 0.96 (t, 3H, J = 7.14 Hz, CH_2CH_3), 1.24-1.40 (m, 1H, CH), 1.43-1.60 (m, 1H, CH), 1.65-1.77 (m, 1H, CH), 1.82-1.95 (m, 1H, CH), 2.10-2.38 (m, 3H, CH and CH_2), 2.42-2.56 (m, 2H, CH_2CH_3), 3.85 (s, 3H, OCH_3), 3.95 (d, 1H, J = 3.57 Hz, CHCN). MS (70 eV): m/z % 224 (M^+ + 1, 4.3), 125(9), 100(1.4), 89(6.8), 75(100). Anal. calcd. (%) for C_{12} $H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found (%): C, 64.45; H, 7.70; N, 6.32.

Methyl cyano-(3-ethyl-1,2,3,4-tetrahydrocarbazole-2yl)acetate (3): A solution of 5 g (22.4 mmol) of **2** and 2.54 g (23.5 mmol) of phenyl hydrazine in 250 mL of acetic acid was refluxed for 6 h under nitrogen and then cooled to room temperature. The reaction mixture was poured into 250 mL of cold water and extracted with ether. The extract was washed with 100 mL of 10 % hydrochloric acid and then 100 mL of 10 % sodium bicarbonate. The organic layer was dried with anhydrous magnesium sulfate and the solvent was evaporated. The crude product was chromatographed using silica gel and

ethyl acetate. The solvent was evaporated and the residue was recrystallized from methanol-water to yield 4.25 g (64 %) of **3**, m.p. 98 ºC. TLC: R_f 0.56 (ethyl acetate-hexane (1:1)). IR (KBr, n_{max}, cm^{-1}): 3410 (NH), 2960 (CH), 2250 (CN), 1746 (C=O, ester). ^1H NMR ($CDCl_3$): δ 1.05 (t, 3H, *J* = 7.25 Hz, CH_2CH_3), 1.35-1.50 (m, 1H, CH), 1.65-1.76 (m, 1H, CH), 1.80-1.97 (m, 1H, CH), 2.52-2.73 (m, 3H, CH and CH_2), 2.80-3.07 (m, 3H, CH and CH_2), 3.86 (s, 3H, OCH_3), 7.09-7.23 (m, 2H, ArH), 7.25-7-32 (m, 1H, ArH), 7.47 (d, 1H, *J* = 7.57 Hz, ArH), 7.75 (s, 1H, NH). MS (70 eV): m/z % 298 (M^+ + 2, 6.2), 297(M^+ + 1, 23.6), 296 (M^+, 83.4), 198 (42.1), 168 (56.7), 143 (100). Anal. calcd. (%) for $C_{18}H_2ON_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found (%): C, 73.10; H, 6.64; N, 9.32.

(3-Ethyl-1,2,3,4-tetrahydrocarbazole-2-yl)-acetonitrile (4): A solution of 2.5 g (8.4 mmol) of **3**, 1.48 g (25.3 mmol) of sodium chloride and 0.46 g (25.3 mmol) of water in 25 mL of dimethyl sulfoxide was stirred for 16 h at 160 ºC. Then the mixture was poured into 50 mL of cold water and extracted with ether. The organic layer was dried with anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate. After the solvent was evaporated, the product was recrystallized from methanol to yield 1.10 g (55 %) of **4**, mp: 121 ºC. TLC: R_f 0.63 (ethyl acetate). IR (KBr, ν_{max}, cm^{-1}): 3350 (NH), 2962 (CH), 2254 (C=N). ^1H NMR ($CDCl_3$): δ 1.01 (t, 3H, *J* = 7.40 Hz, CH_2CH_3), 1.36-1.41 (m, 1H, $HCHCH_3$), 1.54-1.60 (m, 1H, $HCHCH_3$), 1.84-1.88 (m, 1H, C_3H), 2.25-2.30 (m, 1H, C_2H), 2.46-2.50 (m, 2H, C_1H_2), 2.54 (dd, 1H, *J* = 16.53 and 5.85 Hz, C_4H), 2.68 (dd, 1H, *J* = 11.60 and 5.85 Hz, C_4H), 2.83 (dd, 1H, *J* = 16.18 and 5.45 Hz, HCHCN), 2.94 (dd, 1H, *J* = 11.22 and 5.28 Hz, HCHCN), 7.11-7.24 (m, 2H, ArH), 7.30 (t, 1H, *J* = 7.99 Hz, ArH), 7.45 (d, 1H, *J* = 7.57 Hz, ArH), 7.70 (s, 1H, NH). MS (70 eV): m/z % 239 (M^+ + 1, 5.5), 238 (M^+, 23), 168 (21), 143 (100). Anal. calcd. (%) for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found (%): C, 80.59; H, 7.56; N, 11.82.

(3-Ethyl-4-oxo-1,2,3,4-tetrahydrocarbazole-2-yl)acetonitrile (5): To a solution of 2.5 g (10.50 mmol) of **4** in 50 mL of tetrahydrofuran (90 %) were added dropwise 4.78 g (21.0 mmol) of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone in 20 mL of tetrahydrofuran at 0 ºC. The reaction mixture was stirred for 4 h at room temperature then the solution was poured into 250 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 purified by chromatography using silica gel and ethyl acetate. After the evaporation of the solvent, the product was recrystallized from ether to afford 1.40 g (53 %) of **5**, m.p. 193 ºC. TLC: R_f 0.60 (ethyl acetate). IR (KBr, ν_{max}, cm^{-1}): 3220 (NH), 2246 (C=N), 1621 (C=O). ^1H NMR ($CDCl_3$): δ 1.03 (t, 3H, *J* = 7.16 Hz, CH_2CH_3), 1.74-1.78 (m, 1H, $HCHCH_3$), 1.93-2.05 (m, 1H, $HCHCH_3$), 2.36-2.41 (m, 1H, C_2H), 2.56-2.59 (d, 2H, *J* = 7.17 Hz, C_1H_2), 2.73-2.77 (m, 1H, C_3H), 3.06 (dd, 1H, *J* = 17.20 and 5.33 Hz, HCHCN), 3.35 (dd, 1H, *J* = 17.19 and 5.01 Hz, HCHCN), 7.22-7.33 (m, 2H, ArH), 7.36-7.40 (m, 1H, ArH), 8.20 (d, 1H, *J* = 8.10 Hz, ArH), 8.53 (s, 1H, NH). MS(70 eV): m/z % 253(M^+ + 1, 1.8), 252 (M^+, 8.5), 184 (61), 157 (67.8), 129 (100), 102 (44), 83(57). Anal. calcd. (%) for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found (%): C, 76.26; H, 6.28; N, 11.05.

(3-Ethyl-4-oxo-1,2,3,4-tetrahydro-9-benzene sulfonyl-carbazole-2-yl)-acetonitrile (6): A solution of 1.5 g (6 mmol) of **5** in 50 mL of dichloromethane was cooled to 0 ºC. After that 5 mL of 20 % sodium hydroxide and 100 mg of tetrabutyl ammonium hydrogen sulfate were added. The reaction mixture was stirred for 0.5 h at 0 ºC and then 1.16 g (6.5 mmol) of benzenesulfonyl chloride was added. The mixture which was let to come to room temperature stirred for 2 h. Then it was washed with 50 mL of 10 % hydrochloric acid and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was chromatographed using silica gel and ethyl acetate-hexane (1:1). The solvent was removed and then the product was recrystallized from ethanol to afford 2.10 g (90 %) of **6**, m.p. 141 ºC. IR (KBr, ν_{max}, cm^{-1}): 2241 (CN), 1619 (C=O); ^1H NMR ($CDCl_3$): δ 1.04 (t, 3H, *J* = 7.25 Hz, CH_2CH_3), 1.25-1.36 (m, 2H, CH_2), 1.66-1.78 (m, 2H, CH_2), 1.85-1.92 (m, 1H, CH), 2.15-2.27 (m, 1H, CH), 2.90 (dd, 1H, *J* = 13.54 and 3.52 Hz, HCHCN), 3.51 (dd, 1H, *J* = 13.89 and 5.31 Hz, HCHCN), 7.01-7.10 (m, 1H, ArH), 7.17-7.34 (m, 3H, ArH), 7.41-7.49 (m, 2H, ArH), 7.56 (d, 1H, *J* = 8.01 Hz, ArH), 7.80-7.89 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$): δ 12.4, 17.3, 19.5, 28.6, 30.2, 49.3, 114.6, 115.7, 119.4, 122.3, 124.5, 125.2, 127.7, 131.3, 132.5, 134.1, 136.3, 137.6, 138.7, 141.2, 149.3, 184.2. MS (70 eV): m/z % 393 (M^+ + 1, 1.3), 392 (M^+, 3.1), 363 (26), 323 (28.7), 295 (62), 255 (100). Anal. calcd. (%) for $C_{22}H_{20}N_2SO_3$: C, 67.32; H, 5.14; N, 7.14. Found (%): C, 67.42; H, 5.17; N, 7.11.

N-(2,2-Dimethoxyethyl)-N-methyl-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxamide (8b): A mixture of 7.31 g (34 mmol) of **7**, 17 mL (121.88 mmol) of triethylamine and 4.2 mL (54 mmol) of ethylchloroformate in 150 mL of dichloromethane was stirred for 2 h at 0 ºC. Then 4.05 g (34 mmol) methyl aminoacetaldehyde dimethyl acetal in 20 mL of dichloromethane was added dropwise and the mixture was stirred for 18 h at room temperature. The organic layer was extracted with chloroform and washed with 100 mL of 10 % hydrochloric acid and then 100 mL of 10 % sodium carbonate. The organic layer dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was obtained as a pain red oil 4.94 g (47.5 %) of **8a**. IR (KBr, ν_{max}, cm^{-1}): 3302 (NH), 3000-2800 (CH), 1699 (C=O), 1629 (C=O). ^1H NMR ($CDCl_3$): δ 2.80-3.12 (m, 5H, CH, CH_2), 3.18 (s, 3H, NCH_3), 3.30-3.36 (m, 2H, CH_2), 3.38 (d, 2H, *J* = 3.6 Hz, NCH_2), 3.42 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 4.54 (t, 1H, *J* = 5.6 Hz, $CH(OCH_3)_2$), 7.01-7.11 (m, 2H, ArH), 7.23 (d, 1H, *J* = 7.6 Hz, ArH), 7.41 (d, 1H, *J* = 7.6 Hz, ArH), 7.94 (s, 1H, NH).

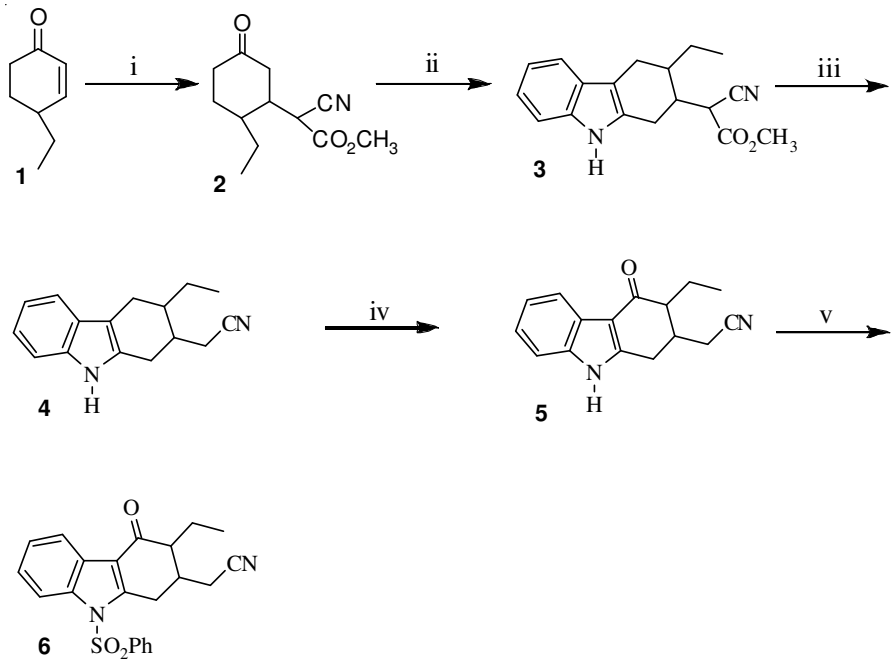
2,2-Dimethoxy-N-((2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)methyl)ethanamine (9a): A solution of 3 g (9.5 mmol) of **8a** in anhydrous tetrahydrofuran was added to a stirred solution of 4.3 g (113.3 mmol) of lithium aluminum hydride in 50 mL of tetrahydrofuran. The mixture was refluxed under nitrogen for 5 h and then cooled 0 ºC and the excess of lithium aluminum hydride destroyed with water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate

and the solvent was removed under reduced pressure and the resulting residue was obtained as an oil to yield 1.66 g (58 %) of **9b**. IR (KBr, ν_{max}, cm^{-1}): 3400 (NH), 3315 (NH), 3000-2800 (CH). ^1H NMR ($CDCl_3$): δ 1.80-1.87 (m, 1H, CH), 1.90-2.08 (m, 3H, NH, CH_2), 2.24-2.31 (m, 1H, CH), 2.61-2.68 (m, 3H, CH, CH_2), 2.70-2.76 (m, 1H, CH), 2.83 (dd, 1H, *J* = 4.4 and 14.8 Hz), 3.32 (d, 1H, *J* = 3.6 Hz, CH), 3.38 (s, 6H, 2xOCH_3), 3.70-3.74 (m, 1H, CH), 4.48 (t, 1H, *J* = 5.7 Hz, $CH(OCH_3)_2$), 6.98-7.06 (m, 2H, ArH), 7.14 (d, 1H, *J* = 7.3 Hz, ArH), 7.38 (d, 1H, *J* = 7.2 Hz, ArH), 8.13 (s, 1H, NH).

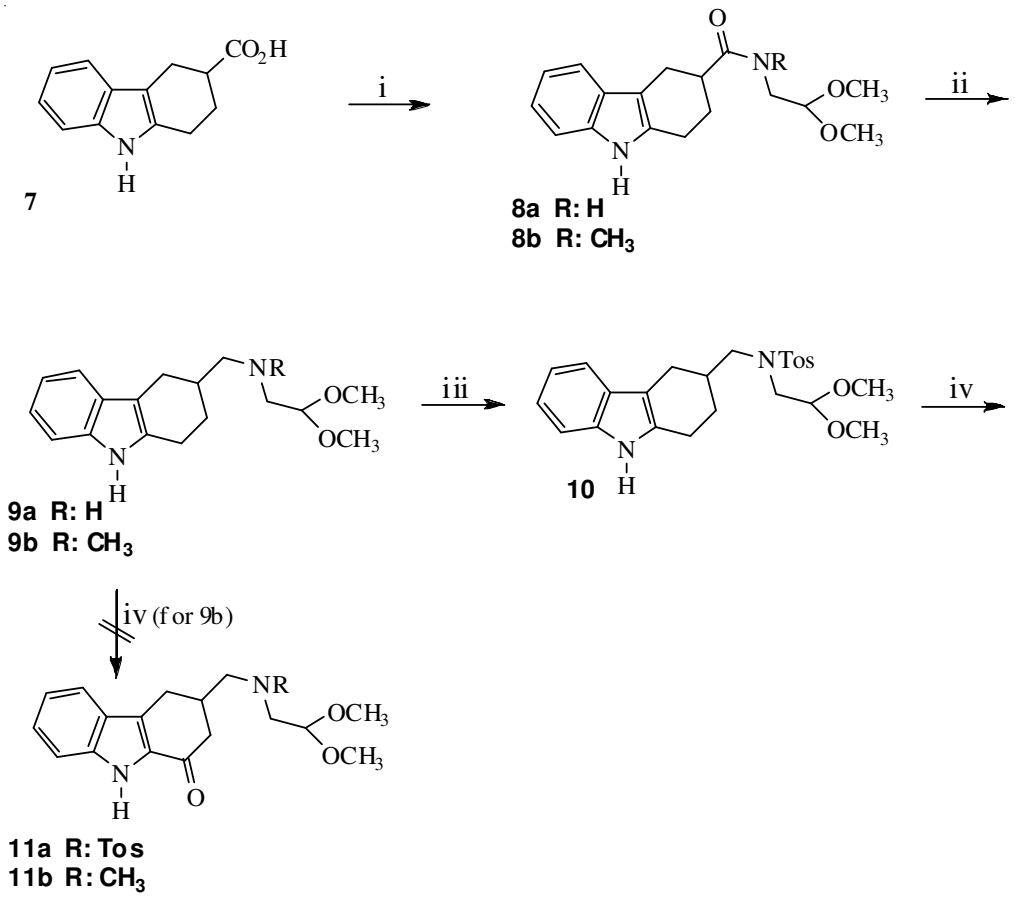
2,2-Dimethoxy-N-methyl-N-((2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)methyl)ethanamine (9b): A solution of 3 g (9.9 mmol) of **8b** in anhydrous tetrahydrofuran was added to a stirred solution of 4.3 g (113.3 mmol) of lithium aluminum hydride in 50 mL of tetrahydrofuran. The mixture was refluxed under nitrogen for 5 h and then cooled to 0 ºC and the excess of lithium aluminum hydride destroyed with water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure and the resulting residue was obtained as an oil 1.4 g (49 %) of **9b**. IR (KBr, ν_{max}, cm^{-1}): 3334 (NH), 3060-2770 (CH). ^1H NMR ($CDCl_3$): δ 2.04-2.14 (m, 3H, CH, CH_2), 2.25-2.32 (m, 1H, CH), 2.34 (s, 3H, NCH_3), 2.43 (d, 2H, *J* = 7.2 Hz, CH_2), 2.52-2.63 (m, 2H, CH_2), 2.72-2.82 (m, 2H, CH_2), 2.92 (dd, 1H, *J* = 4.8 Hz ve 15.2 Hz, CH), 3.36 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 4.50 (t, 1H, *J* = 4.8 Hz, $CH(OCH_3)_2$), 7.02-7.12 (m, 2H, ArH), 7.25 (d, 1H, *J* = 7.6 Hz, ArH), 7.45 (d, 1H, *J* = 7.6 Hz, ArH), 7.70 (s, 1H, NH).

N-(2,2-Dimethoxyethyl)-4-methyl-N-(2,3,4,9-tetrahydro-1*H*-carbazol-3-ylmethyl) benzenesulfonamide (10): A solution of 1 g (3.5 mmol) of **9a** in 20 mL pyridine was cooled and after 1.73 g (7.7 mmol) of *p*-toluene sulphonyl chloride was added portion wise and stirred for 18 h at room temperature. The mixture was washed with 100 mL of 10 % hydrochloric acid and the organic layer was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure and the resulting residue was obtained as an oil to yield 1.2 g (72 %) of **10**. IR (KBr, ν_{max}, cm^{-1}): 3394 (NH), 3050-2800 (CH), 1332 (SO_2). ^1H NMR ($CDCl_3$): δ 1.83-1.87 (m, 1H, CH), 2.05-2.15 (m, 1H, CH), 2.17-2.35 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.70-2.87 (m, 3H, CH, CH_2), 3.10-3.21 (m, 2H, CH_2), 3.22-3.33 (m, 1H, CH), 3.35 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 3.71-3.77 (m, 1H, CH), 4.56 (dd, 1H, *J* = 5.2 Hz and 6 Hz, $CH(OCH_3)_2$), 7.03-7.12 (m, 2H, ArH), 7.26 (d, 1H, *J* = 8.0 Hz, ArH), 7.30 (d, 2H, *J* = 7.6 Hz, ArH), 7.37 (d, 1H, *J* = 7.6 Hz, ArH), 7.72 (d, 2H, *J* = 8.0 Hz, ArH).

N-(2,2-Dimethoxyethyl)-4-methyl-N-[(1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)methyl] benzenesulfonamide (11a): A solution of 1 g (2.26 mmol) of **10** in 25 mL methanol was added dropwise to a solution of 1.03 g (4.52 mmol) of periodic acid in 100 mL methanol-water (1:1) at 0 ºC. The reaction mixture was stirred for 1 h at 0 ºC, then stirring was continued for a further 2 h at room temperature. The solvent was evaporated, then the residue was dissolved in chloroform and washed first with sodium chloride and then with sodium bisulfite. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated. The resulting residue was crystallized from methanol to yield 0.52 g (50 %) of **11a**, m.p. 213 ºC. IR (KBr, ν_{max}, cm^{-1}): 3270 (NH), 3065-2800 (CH), 1643 (C=O), 1339 (SO_2). ^1H NMR (DMSO): δ 2.38 (s, 3H, CH_3), 2.40-2.47 (m, 1H, CH), 2.50-2.70 (m, 3H, CH, CH_2), 3.07 (dd, 1H, *J* = 15.6 Hz and 4 Hz, COCH), 3.14 (d, 2H, *J* = 4.8 Hz, -NCH_2-), 3.18-3.20 (m, 5H, OCH_3, CH_2), 3.22 (s, 3H, OCH_3), 4.49 (t, 1H, *J* = 5.2 Hz, $CH(OCH_3)_2$), 7.06 (t, 1H, *J* = 7.6 Hz, ArH), 7.28 (t, 1H, *J* = 8.0 Hz, ArH), 7.38 (d, 1H, *J* = 8.8 Hz, ArH), 7.42 (d, 2H, *J* = 8 Hz, ArH), 7.60 (d, 1H, *J* = 8.0 Hz, ArH), 7.72 (d, 2H, *J* = 8.0 Hz, ArH), 11.56 (s, 1H, NH).



Scheme-I: Reagent and conditions: (i) Methyl cyanoacetate, NaOMe/MeOH, 0 ºC, 15 min, then rt, 16 h, 92 %; (ii) $PhNHNH_2$, AcOH, N_2, reflux, 6 h, 64 %; (iii) NaCl, DMSO, H_2O, 160 ºC, 16 h, 55 %; (iv) DDQ, THF (90 %), N_2, 0 ºC, 4 h, 53 %; (v) TBAHS, NaOH (20 %), CH_2Cl_2, $PhSO_2Cl$, 0.5 h 0 ºC, rt 2 h, 90 %



Scheme-II: Reagent and conditions: (i) $N(C_2H_5)_3$, CH_2Cl_2, ethyl chloroformate, aminoacetaldehyde dimethyl acetal or N-methyl aminoacetaldehyde dimethyl acetal, stirring, 20 h; (ii) $LiAlH_4$, THF, N_2, reflux, 5 h; (iii) **9a**, *p*-TsCl, pyridine, stirring, 18 h; (iv) periodic acid, methanol-water (1:1), methanol-THF (1:1), stirring, 3 h

RESULTS AND DISCUSSION

In this study, we have synthesized 1-oxo- and 4-oxo-tetrahydrocarbazole derivatives **6** and **11** which can give rise to synthesize indole or carbazole alkaloids. Compound **1** was selected a starting compound which was synthesized in previous study[11] (**Scheme-I**). The ketone **2** was formed by the reaction of 4-ethyl 2-cyclohexenone with methyl cyanoacetate by a Michael reaction[12]. Reaction of the compound **2** with phenyl hydrazine by Fischer indol reaction gave the tetrahydracarbazole derivative **3**[13]. Compound **4** was obtained by decarboxylation of **3** at high temperature, was oxidized[6] using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone yielded compound **5**. In the next step the indole nitrogen atom of **5** was protected with benzenesulfonyl chloride using the phase transfer technique which resulted in compound **6**.

In next study (**Scheme-II**), starting compound[14] acid **7** was reacted with amino methyl acetals and ethyl chloroformate to synthesize compounds **8a**[14] and **8b**. Reduction of **8a** and **8b** with lithium aluminum hydride gave amines **9a** and **9b**[15]. Amine **9a** was converted into sulfonamide derivative **10** with *p*-toluene sulfonyl chloride[15]. Selective oxidation of amine **9b** and sulfonamide **10** at 1-position with periodic acid was achieved only for **10** and gave 1-oxo tetrahydrocarbazole derivative **11a**[14].

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