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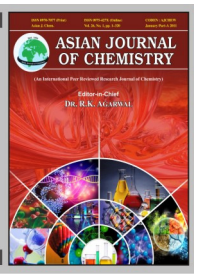

Eco-friendly Synthesis of Functionalized Tetrahydrocarbazoles

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An efficient and quick approach for the synthesis of the novel derivatives of tetrahydrocarbazoles have been reported in this paper. Highly significant analogues of tetrahydrocarbazoles were obtained *via* conventional methodologies as well as by green procedures of microwave technology. Advantages of synthetic procedures for targeted compounds *via* microwave radiations were also highlighted in terms of better yield, less reaction time and no to minimal usage of solvents and no emissions in environment.

Keywords: Acetyl tetrahydrocarbazole, Synthesis, Microwave.

INTRODUCTION

Carbazole being heterocyclic compound endows special behaviour towards a range of interesting medicinal activities. Its well known remedial usage includes antimicrobial, anti-cancer, antiinflammatory and antioxidant character[1] except being a vital part of many drugs like carvedilol (antihypertensive agent), carprofen (non-steroidal antiinflammatory drug-NSAID) and carazostatin (free radical scavenger)[2]. Besides pharmaceutical importance, electrochemical properties of this molecular scaffold have been extensively studied in realistic grounds because of having efficient delocalized π-system as well as prominent luminescence efficiency. Due to versatility in functionalization of carbazole nucleus, its polymers and low-molar mass derivatives are productively utilized in constructing organic light emitting diodes (OLED)[3] host materials. Infect this moiety is a structural unit in developing OLED due to having reasonably high triplet energy[4] and exceptional hole transporting capability[5]. Recently carbazole based fullerene derivatives have been synthesized and their photophysical and photovoltaic properties have also been compared[6].

In a continuing search, researchers are much engaged to report versatile and novel carbazole analogues pursuing eco-friendly and economically valuable synthetic approaches. As a contribution to this work, we are presenting three new carbazole derivatives by using simple chemical library *via* both traditional and environmentally safe technique of microwave. Moreover, the present work focuses on comparative issues between conventional and green synthetic routes of these potentially important synthesized carbazoles.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectral data were recorded using Varian-Inova 500 NMR spectrometer in DMSO-d_6. Chemical shifts (δ) are reported in ppm with tetramethylsilane (TMS) as an internal reference. Signals are described as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiple) and q (quartet) and coupling constants (*J* values) are given in Hz. FTIR spectra were recorded using FTIR spectrophotometer (JASCO-4100). Mass spectra (MS) were obtained and recorded at an ionizing voltage of 70 eV on a Finnigan/MAT95 spectrometer. Reaction monitoring by thin layer chromatography was carried out using Merck silica plates. Solvent used for TLC was the mixture of 10 % ethyl acetate and dichloromethane. TLC plates were visualized under UV light. All reagents used were of analytical grade and were purchased from Fluka, Sigma-Aldrich and Alfa Aesar. Elemental analysis on Perkin Elmer 2400 CHN elemental analyzer.

Procedures

2-(1-Acetyl-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)-2,2-dichloroacetic acid (2): 0.01 mol (2.13 g) of compound **1** was dissolved in 5 mL of DMF followed by equimolar addition of sodium hydride. Then to this stirring reaction mixture, 0.01 M (1.63 g) trichloroacetic acid was introduced during 0.5 h. The reaction mixture exhibited yellowish orange colour after the addition of whole reagent. Then it was stirred for 3 h at

room temperature under nitrogen until the completion of reaction was indicated by TLC (10 % ethyl acetate and dichloromethane system) after 3 h. The reaction mixture was cooled in an ice bath and then filtered to obtain the yellowish solid product in 71 % yield.

Green approach to 2: A mixture of 0.01 mol (2.13 g) of compound **1**, 0.01 mol (0.24 g) of sodium hydride and 0.01 mol (1.63 g) of trichloroacetic acid was placed under microwave radiations for 120 s to obtain the yellowish product in 88 % yield.

Anal. calcd. (%) for $C_{16}H_{15}NO_3Cl_2$: C, 56.49; H, 4.44; Cl, 20.84; N, 4.12; O, 14.11 Found (%): C, 56.44; H, 4.40; Cl, 20.63; N, 4.92; O, 14.45; IR (KBr, ν_{max}, cm^{-1}): 3298, 3033, 2245, 1680, 1570, ^{1}H NMR (DMSO) δ: 1.88 (m, 2H), 1.90 (m, 2H), 2.03 (s, 1H), 2.70 (t, *J* = 8.4 Hz, 2H), 3.53 (t, *J* = 7.8 Hz, 1H) 7.01 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H),7.12 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.95 (dd, *J* = 8.5, 8.0 Hz, 1H), 10.9 (s, 1H). ^{13}C NMR (DMSO) δ: 20.9, 21.2, 25.3, 32.0, 52.9, 110.1, 118.3, 118.9, 120.1, 121.5, 127.3, 136.0, 137.1, 171.1; MS *m/z*: 339.1 (M^+).

(Z)-1-[1-(2-{2,4-Dinitrophenyl)hydrazono}ethyl]-2,3,4,9-tetrahydro-1*H*-carbazole (3): 0.001 mol (0.213 g) of **1** was refluxed with equimolar amount of 6,8-dinitro phenylhydrazine in presence of 6 mL glacial acetic acid under inert atmosphere for 2.5 h until the completion of reaction was indicated by TLC. The reaction mixture was poured in crushed ice and was then filtered. Final product was obtained in 70 % yield after recrystallization in methanol.

Green approach to 3: 0.213 g (0.001 mol) of **1** in equimolar amount of 6,8-dinitrophenyl hydrazine in presence of few drops of glacial acetic acid was placed under microwave radiations for 60 s. The crude product obtained was poured in crushed ice and was then filtered to obtain the pure compound in 92 % yield.

Anal. calcd. (%) for $C_{20}H_{19}N_5O_4$: C, 61.06; H, 4.87; N, 17.80; O, 16.27. Found (%): C, 61.00; H, 4.37; N, 17.53; O, 16.19; IR (KBr, ν_{max}, cm^{-1}): 3398, 3033, 2879. ^{1}H NMR (DMSO) δ: 1.84 (m, 2H), 1.77 (m, 2H), 1.90 (s, 3H) 2.54 (t, 1H), 2.68 (t, *J* = 7.7 Hz, 2H), 8.02 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H) 8.44 (d, *J* = 8.0 Hz, 1H), 8.83 (s, 1H), 11.99 (s, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 8.5, 8.0 Hz, 1H), 7.03 (dd, *J* = 7.5, 8.0 Hz, 1H) 7.19 (d, *J* = 8.0 Hz, 1H) ^{13}C NMR (DMSO) δ: 14.5, 19.9, 21.5, 25.8, 34.7, 108.3, 111.7, 115.3, 118.0, 119.5, 121.7, 123.0, 127.9, 128.9, 130.1, 131.7, 137.0, 139.0, 152.2, 156.3. MS *m/z*: 393.1 (M^+).

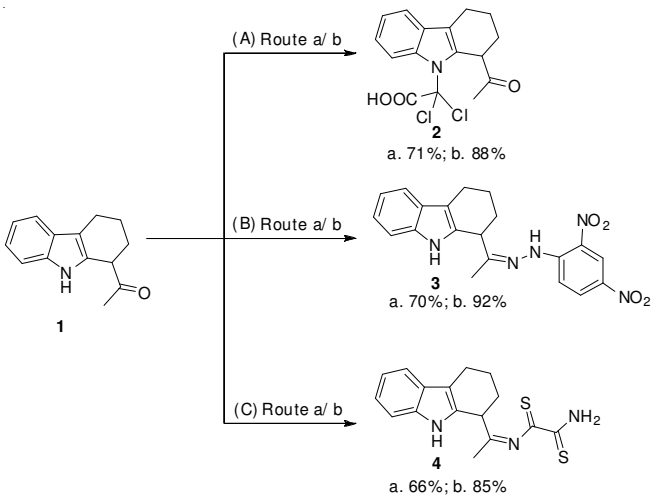
(Z)-N1-[1-(2,3,4,9-Tetrahydro-1*H*-carbazol-1-yl)-ethylidene]ethane*bis*(thioamide) (4): 0.213 g (0.001 mol) of acetyltetrahydro carbazole was dissolved in 5 mL glacial acetic acid. The addition of 0.1206 g (0.001 mol) of rubeanic acid in the reaction mixture exhibited reddish orange colour. Then it was converted to reflux for 3.5 h as monitored by TLC in 10 % ethyl acetate and dichloromethane system. The reaction mixture was then poured in crushed ice. The filtrate was concentrated to obtain the product in 66 % yield.

Green approach to 4: A mixture containing 0.213 g (0.001 mol) of **1**, 0.1206 g (0.001 mol) of rubeanic acid and few drops of glacial acetic acid was placed under microwave radiations for 60 s at power level of 100 watt. Pure solid product obtained was poured in crushed ice and the filtrate obtained was concentrated to furnish **4** in 85 % yield.

Anal. calcd. (%) for $C_{16}H_{17}N_3S_2$: C, 60.92; H, 5.43; N, 13.32; S, 20.33. Found (%): C, 60.32; H, 5.32; N, 13.02; S, 19.99; IR (KBr, ν_{max}, cm^{-1}): 3325, 3233, 2240, 1370; ^{1}H NMR (DMSO) δ: 1.78 (m, 2H), 1.89 (m, 2H), 1.94 (s, 3H), 2.76 (t, *J* = 7.7 Hz, 2H), 2.85 (t, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 8.0, 7.3 Hz, 1H),7.19 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 8.0, 8.5 Hz, 1H), 11.16 (s, 1H), 12.05 (s, 1H); ^{13}C NMR (DMSO) δ: 20.3, 20.9, 21.7, 25.8, 36.4, 108.2, 111.1, 121.7, 119.8, 118.8, 127.3, 131.0, 136.2, 164.6, 192.8, 212.3, MS *m/z*: 315.1 (M^+).

RESULTS AND DISCUSSION

Research from last decade has explored convincing evidence for the medicinal importance of different substituent present on carbazole ring. Efficient synthetic plans for the introduction of structurally modified carbazoles have been encouraged. Keeping this in mind three highly significant derivatives of tetrahydrocarbazole was prepared from acetyltetrahydro carbazole. In the adopted reaction strategy acetyltetrahydro carbazole is substituted at N position in presence of trichloroacetic acid and sodium hydride in DMF. After stirring for 3 h, under nitrogen was found sufficient to obtain product **2** in 71 % yield. Preparation of same product in microwave took only 120 s and 88 % yield of **2** was obtained without use of any solvent. Compound **1** in presence of 6,8-dinitrophenyl hydrazine in glacial acetic acid afforded **3** in 70 % yield after a reflux of 2.5 h under nitrogen while the same product **3** was obtained in excellent yield of 92 % just in 60 s under microwave radiations. Another interesting reaction of compound **1** was towards the synthesis of novel compound **4** which was obtained in 66 % yield when **1** was coupled with rubeanic acid in presence of glacial acetic acid and was refluxed for 3.5 h under nitrogen. While the same product was obtained in effectively good yield of 85 % in 60 s only under microwave radiations (**Scheme-I**).



Scheme-I: Reagents and conditions: (A) Route a: Cl_3CCOOH, DMF, NaH, 3 h, N_2 b: Cl_3COOH, NaH, microwave, 120 s (B) Route a: 6,8-dinitro phenylhydrazine, glacial acetic acid, 2.5 h reflux, N_2. b: 6,8-Dinitrophenylhydrazine, glacial acetic acid, 60 s, microwave. (C) Route a: Rebeanic acid, glacial acetic acid, 3.5 h reflux, N_2. b: Rebeanic acid, glacial acetic acid, 60 s microwave

As the two approaches *i.e*., traditional and microwave furnish the same targeted compounds but it is obvious that large amount of solvents were utilized in case of conventional routes and the reaction time is also enhanced. During conventional heating volatile organic compounds (VOC) were also emitted in atmosphere thus contributing a lot towards environmental pollution when the reaction was putted up at large scale while in case of green technology of microwave either no solvent is used or only minimal quantities of solvents are used and there are no emissions in form of volatile organic compounds towards environment. The yields are also enhanced in case of microwave heating as was observed in all three reactions presented in this paper. By adoptations of green technology more pure product is obtained in less reactions time.

Our reactions present best comparison that proves the suitability of microwave irradiation as best energy source for chemical reactions. Reduced reaction time, cleaner product formation, better yield and no emission of hazardous chemicals make this ecofriendly approach a center of attention for the scientists. This green technology is also independent of water as a cooling substance, saves man power, energy and more importantly it contributes to achieve cleaner environment products.

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