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Systematic Approach for Synthesis of Carbazole-9-acetic Acid

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A novel and systematic route to the synthesis of carbazole-9-acetic acid, a white crystalline solid and one of the most important derivative of medicinally and biologically active compound 9-*H* carbazole is explained in this paper. All the compounds formed as an intermediate during the synthesis of carbazole-9-acetic acid are themself potent and biologically active derivatives of carbazole thus making the proposed synthetic route economically favourable and easily adoptable. All the synthesized compounds were characterized by IR, mass spectrometry and ^{1}H NMR analysis.

Key Words: Carbazole-9-acetic acid, 1,2,3,4-Tetrahydrocarbazole-9-acetic acid, 4-Bromo-1,2,3,4-tetrahydrocarbazole-9-acetic acid, 1,2-Dihydrocarbazole-9-acetic acid, 2-Bromo-1,2-dihydrocarbazole-9-acetic acid.

INTRODUCTION

Numerous carbazole derivatives isolated from higher plants, microorganisms and other sources as well as their synthetic analogues[1] have attracted the attention of chemists and biochemists due to their phytophysical, phytochemical[2] properties as well as their biological[3,4] and antiviral activities[5]. Some of the carbazole derivatives have demonstrated promising medicinal properties[6]. Among these derivatives carbazole-9-acetic acid important intermediate because carboxylic group is one of the active functional group[6] and plays an important role in further transformation into other functions. A number of synthetic routes for the synthesis of carbazole-9-acetic acid are already reported among these one pot synthesis of substituted carbazole-9-acetic acid under microwave irradiation proposed by Wanjian *et al.*[1] is of considerable importance. Lao and co-workers[7] also described a feasible route to the synthesis of 3-bromocarbazole-9-acetic acid under optimal conditions and another potent synthetic route to the novel phenyl esters of carbazole-9-acetic acid is successfully explained by Shukla and Srivastava[8].

Herein, the synthesis and characterization of carbazole-9-acetic acid *via* novel route and intermediate which is formed during the formation of carbazole-9-acetic acid is reported.

EXPERIMENTAL

Synthesis of 1,2,3,4-tetrahydrocarbazole-9-acetic acid: A mixture of cyclohexanone **1** (1 mol) and acetic acid (3 mol) is heated heated under reflux for 1 h and during this period 1-phenylhydrazino-acetic acid **2** (1 mol) is added in the reaction mixture and then it is further heated for an additional 1 h. After that pour the mixture in 1.5 L beaker and stirred by hand until it solidified and after cooling to about 5 °C it is filtered with suction. The crude solid obtained is recrystallized with methanol to obtained the crystals of 1,2,3,4-tetrahydrocarbazole-9-acetic acid **3**.

Synthesis of 4-bromo-1,2,3,4-tetrahydrocarbazole-9-acetic acid: 1,2,3,4-Tetrahydrocarbazole-9-acetic acid (1 mol) and N-bromosuccinimide (0.5 mol) was taken in a round bottom flask and CCl_4 was added in it as solvent along with few crystals of dibenzyl peroxide and the whole reaction mixture is reflux on bulb (100 watts) at 50-80 °C for *ca.* 2 h. The precipitates of 4-bromo-1,2,3,4-tetrahydrocarbazole-9-acetic acid **4** formed was recrystallized with ethanol.

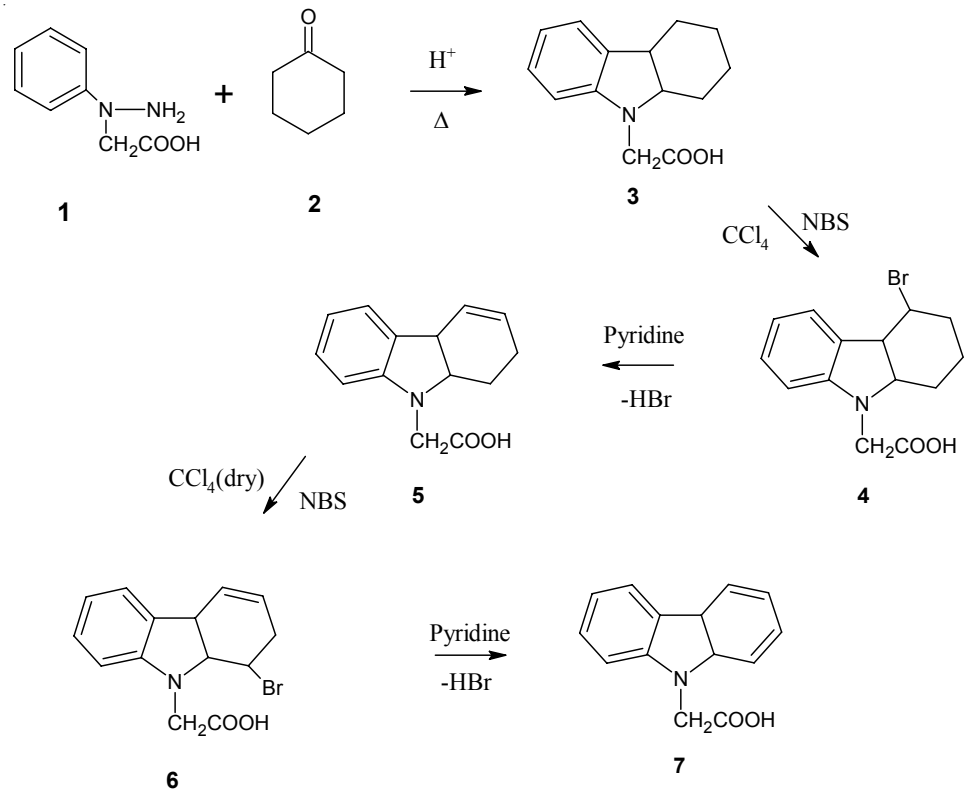
Synthesis of 1,2-dihydrocarbazole-9-acetic acid: 4-Bromo-1,2,3,4-tetrahydrocarbazole-9-acetic acid (1 mol) and pyridine (2-3 mol) was taken in a round bottom flask equipped with a reflux condenser and the mixture is heated in an oil bath with constant stirring. When the temperature raised up to 150-180 °C then it is allowed to heat for an additional 1 h by keeping temperature between 150-180 °C. Then the pyridine was distilled off by distillation. The residue left was 1,2-dihydrocarbazole-9-acetic acid **5** which was recrystallized with ethanol to get precipitates.

Synthesis of 2-bromo-1,2-dihydrocarbazole-9-acetic acid: 1,2-Dihydrocarbazole-9-acetic acid (1 mol) and N-bromosuccinimide (0.5 mol) was taken in a round bottom flask and CCl_4 was added in it as solvent along with few crystals of dibenzyl peroxide and the whole reaction mixture is reflux on bulb (100 watts) at 50-80 °C for *ca.* 2 h. The precipitates of 2-bromo-1,2-dihydrocarbazole-9-acetic acid **6** formed was recrystallized with ethanol.

Synthesis of carbazole-9-acetic acid: 2-Bromo-1,2-dihydrocarbazole-9-acetic acid (1 mol) and pyridine (2-3 mol) was taken in a round bottom flask equipped with a reflux condenser and the mixture is heated in an oil bath with constant stirring. When the temperature raised up to 150-180 °C then it is allowed to heat for an additional 1 h by keeping temperature between 150-180 °C. Then the pyridine was distilled off by distillation. The residue left was carbazole-9-acetic acid (**7**) which was cooled in ice recrystallized with ethanol to get precipitates (**Scheme-I**).

RESULTS AND DISCUSSION

Although the many synthetic routes to carbazole-9-acetic acid was described before but the pathway proposed in this paper is not only economically very favourable yet each and every step of this pathway is itself explaining the formation of potential derivatives of carbazole-9-acetic acid. All the synthesized compounds **3-7** (**Scheme-I**) are characterized by IR, NMR and mass spectrometry for structural confirmation. The detailed characterization of all the compounds is as:



Scheme-I: Systematic approach to carbazole-9-acetic acid

1,2,3,4-Tetrahydrocarbazole-9-acetic acid: 1,2,3,4-Tetrahydrocarbazole-9-acetic acid is a white crystalline solid which was obtained in 70.2 % yield. Found: ^{1}H NMR δ 3.21 (s, 2H), 4.40 (s, 1H), 6.93 (t, *J* = 7.1 Hz, 2H), 7.21 (m, 2H), 7.25 (dd, *J* = 7.3, 7.2 Hz, 1H), 7.36 (dd, *J* = 7.4, 7.3 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.53 (m, 2H), 8.07 (t, *J* = 7.3 Hz, 2H), 8.17 (d, *J* = 7.7 Hz, 1H). IR (KBr, ν_{max}, cm^{-1}) 3398, 3133, 2928, 1603, 1399, 1234, 741. MS (ES$^+$): 230 (MH$^+$).

4-Bromo-1,2,3,4-tetrahydrocarbazole-9-acetic acid: 4-Bromo-1,2,3,4-tetrahydrocarbazole-9-acetic acid, a brown coloured compound, was obtained in 72.0 % yield. Found: ^{1}H NMR δ 3.23 (s, 2H), 4.40 (s, 1H), 7.20 (dt, *J* = 7.3, 7.6 Hz, 2H), 7.24 (dd, *J* = 7.3, 7.4 Hz, 1H), 7.34 (dd, *J* = 7.4, 7.6 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.50 (m, 2H), 7.89 (t, *J* = 7.1Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 8.04 (t, *J* = 7.4 Hz, 2H). IR (KBr, ν_{max}, cm^{-1}) 3390, 3030, 2964, 1645, 1595, 1050, 720, 575. MS (ES$^+$): 309 (MH$^+$).

1,2-Dihydrocarbazole-9-acetic acid: 1,2-Dihydrocarbazole-9-acetic acid, a white crystalline compound was obtained in 71.2 % yield. Found: ^{1}H NMR δ 3.22 (s, 2H), 4.38 (s, 1H), 7.14 (d, *J* = 7.4 Hz, 1H),7.19 (dt, *J* = 7.4, 7.7 Hz, 1H), 7.20 (dd, *J* = 7.3, 7.4 Hz, 1H), 7.35 (dd, *J* = 7.8, 7.5 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H),

7.49 (dt, *J* = 7.2, 7.4 Hz, 2H), 8.02 (t, *J* = 7.3 Hz, 2H), 8.09 (d, 8.0 Hz, 1H). IR (KBr, ν_{max}, cm^{-1}) 3385, 3330, 2950, 1640, 1595,1534,1050, 743. MS (ES^+): 228 (MH^+).

2-Bromo-1,2-dihydrocarbazole-9-acetic acid: 2-Bromo-1,2-dihydrocarbazole-9-acetic acid a brownish compound, was obtained in 70.1 % yield. Found: ^1H NMR δ 3.23 (s, 2H), 4.38 (s, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.16 (dt, *J* = 7.4, 7.5 Hz, 1H), 7.22 (dd, *J* = 7.4, 7.5 Hz, 1H), 7.35 (dd, *J* = 7.7, 7.4 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.48 (dd, *J* = 7.2, 7.5 Hz, 2H), 8.02 (t, *J* = 7.3 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H). IR (KBr, ν_{max}, cm^{-1}) 3385, 3350, 2980, 1725, 1595, 1590, 740, 580. MS (ES^+): 307 (MH^+).

Carbazole-9-acetic acid: Carbazole-9-acetic acid, a white crystalline solid, was obtained in 72.7 % yield. Found: ^1H NMR δ 3.23 (s, 2H), 4.42 (s, 1H), 7.24 (dd, *J* = 7.7, 7.2 Hz, 1H), 7.39 (d, *J* = 8.0, 7.2 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 8.09 (dd, *J* = 7.7, 7.4 Hz, 1H). IR (KBr, ν_{max}, cm^{-1}) 3380, 3355, 2980, 1725, 1595, 1590, 1460, 748. MS (ES^+): 226 (MH^+).

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