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Der Pharma Chemica, 2013, 5(1):343-349
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Novel method for the synthesis of substituted tetrahydrocarbazoles using aqueous sulphuric acid

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ABSTRACT

An efficient and high yielding process has been developed for the synthesis of 6-substituted 3-hydroxy tetrahydrocarbazoles by reacting in situ generated cyclohexanones from the corresponding protected ketals with substituted hydrazine hydrochlorides in the presence of dil. Sulfuric acid. A small library of fourteen compounds has been made with 92-97% yields to check the generality of the reaction.

Keywords: Cyclisation, phenylhydrazine, cyclohexanone, Tetrahydrocarbazole.

INTRODUCTION

Thrust in the preparation of new heterocyclic molecules is increasing due to their proven significant biological activities. The paramount importance of heterocycles such as indoles[1] and their derivatives in natural product chemistry and pharmacology constantly drives the search for the new procedures for their construction and also for the preparation of variety of their derivatives to exploit their useful biological activities.

Substituted 2,3,4,9-tetrahydrocarbazoles belongs to the class of indole alkaloids that have been reported to possess an array of biological properties including central nervous system activity, antihistamine,[2] antidiabetic, antipsychotic (or neuroleptic) [3] and anti-inflammatory properties.[4] Also, they are Important as intermediates for the production of pharmaceutically active compounds like Frovatriptan(1), Flucindole (2), Ramatroban (3) and Ciclindole (4).**(Fig.1)**

Further they are also been used as building blocks for potential electroluminescent materials, polymers with useful electrical and thermal properties.

Over the past decades a large number of biologically active carbazole alkaloids have been obtained from terrestrial plants, marine resources and streptomycetes [5]. Development of new methods for the synthesis of functionalized carbazoles in particular, is attracting organic chemists due to the discovery of many carbazole alkaloids with varied pharmacological properties[7]. The emerging importance towards the various strategies applied to prepare carbazoles was due to their diverse pharmacological derivatives[6]. Recent discovery explore the cascade reaction sequences for the synthesis of biologically active organic compounds having Substituted 2,3,4,9-tetrahydrocarbazoles[8] in frame work.

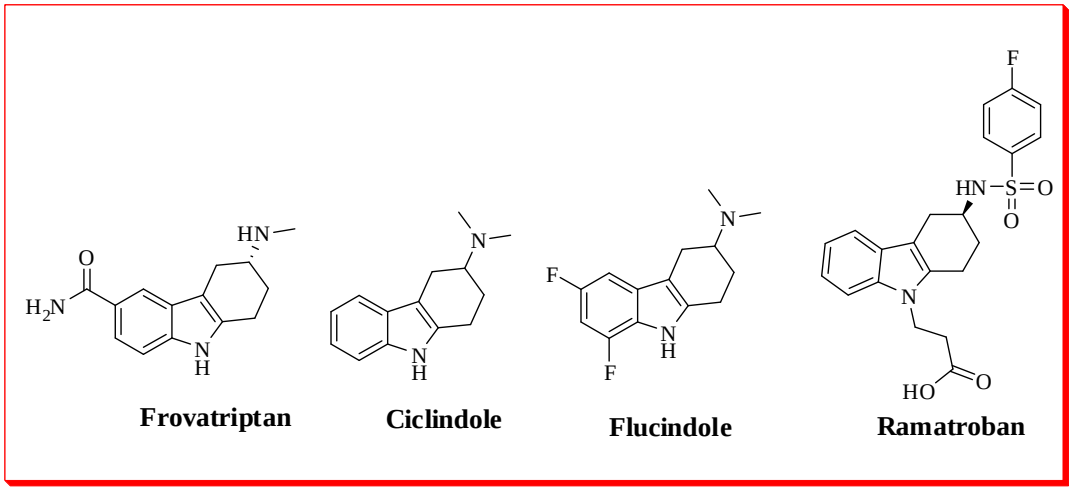
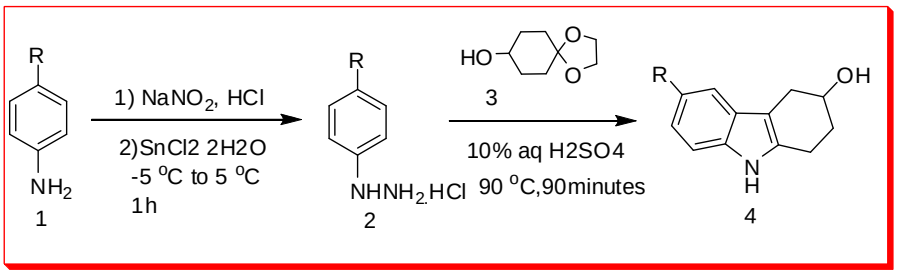


Fig.1 Substituted tetrahydrocarbazole derivatives.

In general the carbazoles synthesis is carried out by multistep Fisher reaction [9] which requires the usage of organic solvents with very meager product yields. Hence a simple and efficient method for the synthesis of these pharmaceutically important class of compounds is highly desirable precluding the usage of organic solvents.

Initially Substituted phenyl Hydrazine's were used to optimize the reaction conditions such as different acids, solvents, and reaction temperature. Among, several Acids were tested, finally we found that 10% aqueous sulfuric acid given excellent yields. In presence of CH_3COOH, $ZnCl_2$ and HCl lesser amount of the desired product was obtained. The effect of solvents was also investigated and the highest yield was observed in 10% aqueous sulfuric acid, When the reaction was conducted at lower temperatures lower yields were obtained. Ideal temperature for the reaction was found to be 90°C. In the presence of electron releasing groups present in the Para position of phenyl Hydrazine's observed more yield comparatively presence of electron withdrawing groups.

To the best of our knowledge this is a first report for the efficient and economic synthesis of carbazoles using readily available laboratory reagents with short reaction times under aqueous conditions. The product yields are very high ranging between 92-94%.



Scheme 1. Reaction Scheme for Synthesis of 6-substituted tetra hydro carbazoles.

Various substituted phenyl hydrazine hydrochlorides have been reacted with 10% aqueous sulfuric acid at 90^0C to obtain the final product in high yields. The starting materials phenyl hydrazine hydrochlorides have been synthesized from the known procedure from substituted anilines.

Table1 Synthesis of 3, 6-substituted substituted tetrahydro carbazoles using 10%aqueous H_2SO_4

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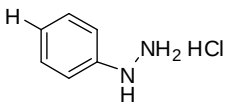
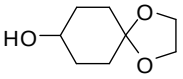
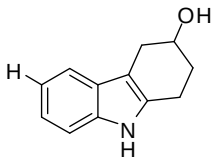
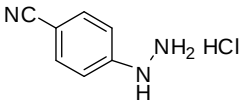
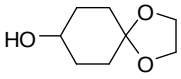
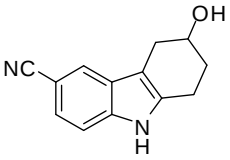
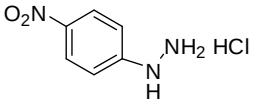
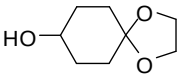
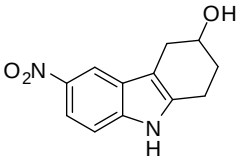
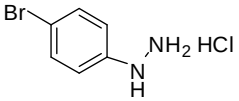
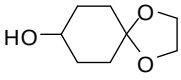
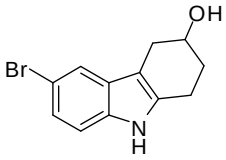
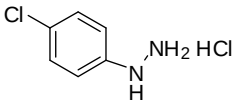
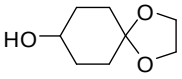
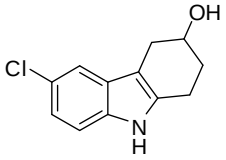
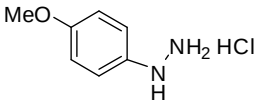
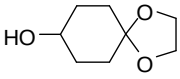
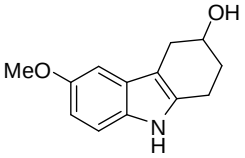
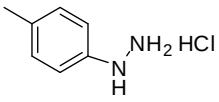
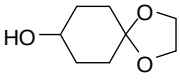
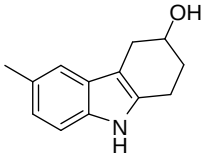
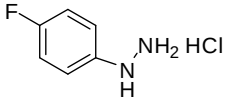
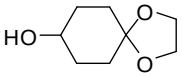
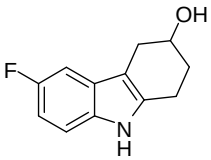
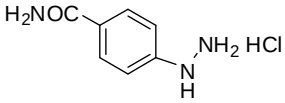
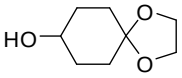
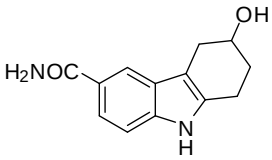
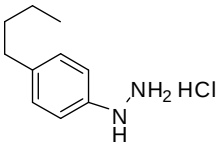
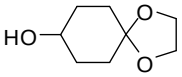
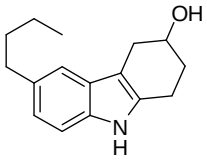
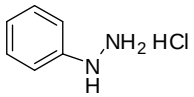
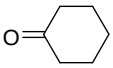
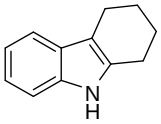
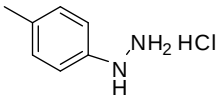
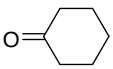
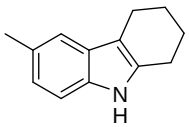
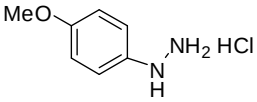
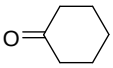
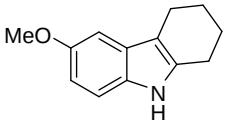
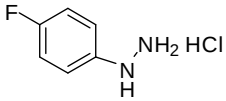
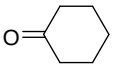
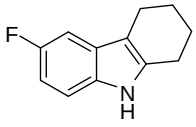
1				90	93
2				90	96
3				90	95
4				90	93
5				90	92
6				90	97
7				90	94

Table contd.

Table 1 Synthesis of 3,6-substituted substitued tetrahydro carbazoles using 10 % aqueous H_2SO_4

Entry	Hydrzine	1,4-dioxaspiro[4.5] decan-8-ol	Product [a]	Time(min)	Yield (%)[b]
8				90	93
9				60	96
10				60	95
11				60	93
12				30	92
13				40	97
14				60	94

[a]Reaction conditions: Ketal/Ketone (1.0mmol), 4-substitutedphenylhydrazinehydrochloride (1.2 mmol), aq H_2SO_4 (10 Vol), Temprature 90-95^{0}C, 90-30 min. [b] Isolated yield.

MATERIALS AND METHODS

All the reagents and starting materials used in this study are of reagent grade which were procured from Sigma Aldrich and were used as received. All melting points were uncorrected. IR spectra were recorded on KBr pellets on a Perkin Elmer 1650 spectrophotometer (USA). ^{1}H NMR spectra were determined using Varian (400MHz) spectrometer and chemical shifts were expressed as ppm. All the structures of the molecules reported herewith are determined by the corresponding spectral and analytical data.

Typical procedure for the synthesis of 6-substitutedtetrahydrocarbazole-3-ol:
Cyclisation: In a two neck round bottom flask Hydrazine was added to 10% aqueous H_2SO_4 solution at 0^oC. The reaction mass was slowly heated to 50^oC and a clear solution was obtained then to this ketal compound was added slowly for 20minutes at 50^oC. After the completion of addition, reaction temperature was increased to 90^oC for 90 min. After the completion of reaction monitored by TLC, the reaction mass was cooled to 0^oC and the precipitate was formed, it was filtered off, washed with hot water and dried to afford the title compound.

Data for representative examples:
2,3,4,9-tetrahydro-1H-carbazol-3-ol (entry 1) :
Off white solid; M.P : 132-133^oC; ^1H NMR ($CDCl_3$, 400 MHz): δppm 7.64(br s, 1H), 7.49(m, 1H), 7.29(m, 1H), 7.08-7.71(m, 2H), 2.74(brt, 4H), 1.86-1.99(m, 4H);^{13}CNMR($CDCl_3$, 400MH): δ134.66, 133.3, 126.8, 119.9, 118.12, 116.8, 109.6, 108.3, 68, 33.7, 31.3, 22.05; IR (KBr)cm^{-1}: 3215, 2920, 1620, 1448, 1367, 1055, 742; Elemental Analysis: C, 76.98; H, 7.00; N, 7.48; O, 8.54. MS (ESI): *m/z* 188 $[M+H]^+$

3-Hydroxy-2,3,4,9-tetrahydro-1H-carbazole-6-carbonitrile (entry2):
White color solid; M.P 218-219 ^oC; ^{1}H-NMR (DMSO-d_6, 400 MHz) : δ ppm 11.2-11.5 (brs, 1H), 7.8-7.9 (s, 1H), 7.5(d, 2H, J= 8.2Hz), 4.7-4.8 (s, 1H), 3.9- 4.1(m,1H), 2.6-3.0(m, 2H), 2.4-2.5(m, 1H), 1.9-2.05(m, 1H), 2.7-2.8(m, 1H);^{13}C NMR (DMSO-d_6, 400MHz): 138, 136.6, 127.2, 123, 122.5, 121, 111.6, 107.7, 99.9, 65.7, 31.1, 29.8, 20.5.; IR (KBr) cm^{-1}: 3410, 3226, 2920, 2225, 1625, 1485, 1367, 1050; MS (ESI): 213 [M+H]+

6-Nitro-2, 3,4,9-tetrahydro-1H-carbazol-3-ol(entry 3):
Orange color solid, M.P 200-202 ^0C; ^{1}H NMR (DMSO-d_6, 400 MHz) : *δ* 11.8-11.9(brs, 1H), 8.2-8.3(s, 1H), 7.85-7.9 (d, 1H, *J*=8.4Hz), 7.7-7.8 (d, 1H, J=8.0Hz), 4.7-4.8 (s, 1H), 4.22-4.1(m, 1H), 3.2-3.3(d, 1H, J=2.4Hz), 2.7-3.0 (m, 3H), 2.05-2.1(m, 1H), 1.9-2.05(m, 1H). IR (KBr) cm^{-1}: 3480, 3236, 2902, 1560, 1300, 1068; MS (ESI) : m/z 233 [M+H]+.

6-Bromo-2,3,4,9-tetrahydro-1H-carbazol-3-ol (entry 4):
M.P.181-182^oC; ^{1}HNMR($CDCl_3$, 400MHz): *δ*7.6-7.9(brs, 1H),7.0-7.2(S, 1H,), 6.85-6.9(d, 2H, J=7.4Hz), 4.2-4.4(m, 1H), 3.0-3.05 (d, 1H), 2.6-2.95 (m, 3H), 2.0-2.15 (m,2H), ^{13}CNMR ($CDCl_3$, 400MHz): 134.7, 132.7, 128.1, 114.5, 110.9, 109.3, 107.4, 102.9, 67.3, 30.2, 20.4. IR (KBr) cm^{-1}: 3395, 3290, 2980, 1585, 1493, 1450, 1370, 1176, ESI : *m/z* 266 $[M+H]^+$

6-Chloro-2,3,4,9-tetrahydro-1H-carbazol-3-ol (entry 5):
Brown color solid, M.P. 125-126 ^oC; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* ppm 7.9-8.0(brs,1H), 7.0-7.2 (s, 1H),6.85-6.95(d,2H,J=8.2Hz),4.2-4.4(m,1H),3.0-3.05(d,1H),2.6-2.95(m,3H),2.0-2.15(m,2H); ^{13}CNMR($CDCl_3$,75MHz) : 134.7,132.7,128.1,126.2,110.9,109.3,107.4, 102.9, 67.3, 30.2, 20.4.; IR (KBr) cm^{-1} 3410, 3230, 2955, 1585, 1483, 1450, 1354, 1175; MS (ESI): *m/z* 222 $[M+H]^+$

6-Methoxy-2,3,4,9-tetrahydro-1H-carbazol-3-ol (entry 6):
Dark brown color solid, M.P. 172-173^oC; ^{1}HNMR($CDCl_3$, 400MHz): *δ* ppm 7.7-7.9(brs, 1H), 7.22-7.25 (s, 1H), 6.85-6.95(d, 2H, J=8.0Hz), 4.2-4.4(m, 1H), 3.8-3.9(s, 1H), 3.0-3.05(d, 1H, J=5.2Hz), 2.6-2.95 (m, 3H), 2.0-2.15(m, 2H). ^{13}C NMR(CDCl3, 400MHz):156.5, 134.7, 132.7, 128.1, 110.9, 109.3, 104, 102.9, 67.3, 56, 30.2, 20.4.; IR(KBr) cm^{-1}: 3412, 3215, 2920, 1620, 1448, 1367, 1055, 742; MS(ESI): *m/z* 218 $[M+H]^+$

Synthesis of 6-methyl-2,3,4,9-tetrahydro-1H-carbazol-3-ol (entry 7):
Off white solid. M.P.155-156^oC; ^{1}HNMR($CDCl_3$, 400MHz): *δ*ppm 7.7-7.9(brs, 1H), 7.05-7.1(d, 1H, J=8.0Hz), 6.85-6.95(d, 1H, J=8.2Hz), 6.75-6.8(s,1H), 4.2-4.4(m, 1H), 3.8-3.9(s, 1H), 3.0-3.05(d, 1H, 5.2Hz), 2.6-2.95(m, 3H), 2.0-2.15(m, 2H); ^{13}CNMR($CDCl_3$, 400MHz): 134.7, 132.7, 129.5, 28.1, 110.9, 109.3, 107.4, 102.9, 67.3, 30.2, 21.7, 20.4.; IR (KBr)cm^{-1}: 3385 3215, 2920, 1620, 1448, 1367, 1055, 742; MS (ESI): *m/z* 202 $[M+H]^+$

6-Fluoro-2,3,4,9-tetrahydro-1H-carbazol-3-ol 7 (entry 8):
Off white solid; M.P 119-120^oC; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* ppm 7.6-7.9 (brs, 1H), 7.0-7.2 (m, 2H), 6.8(t, 1H, J=10Hz, J=4.8Hz), 4.2-4.4(m, 1H), 3.0-3.05(m, 1H), 2.86-2.95(m, 3H), 2.0-2.15(m, 2H); ^{13}CNMR ($CDCl_3$, 400MHz): 158.8, 156.5, 134.7, 132.7, 128.1, 110.9, 109.3, 107.4, 102.9, 67.3, 30.2, 20.4; IR (KBr)cm^{-1}: 3417, 3250, 2920, 1585, 1483, 1450, 1354, 1170, 956, 800,744; MS (ESI): *m/z* 204$[M-H]^+$

3-Hydroxy-2,3,4,9-tetrahydro-1H-carbazole-6-carboxamide (entry 9):
Dark brown solid, M.P.183-184 ^oC; ^{1}H NMR (DMSO-D6, 400 MHz) : *δ* ppm11.2-11.3(brs, 1H), 9.9(brs, 1H), 8.2-8.3(s, 1H), 7.8.(s, 1H), 7.2-7.3(d, 2H, J=8.0Hz), 4.7- 4.8 (s, 1H), 3.9-4.1(m,1H), 2.6-3.0 (m, 2H), 2.4-2.5(m,1H),

1.9-2.05(m, 1H), 2.7- 2.8(m, 1H).; IR (KBr) cm^{-1} : 3504, 3291, 2924, 1649, 1473, 1288, 1038. MS (ESI) : *m/z* 231 $[M+H]^+$

6-Butyl-2,3,4,9-tetrahydro-1H-carbazol-3-ol 4 (entry 10) :
Brown solid, M.P. 81-82^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ ppm 7.66-7.8 (s, 1H), 7.22(s, 1H), 7.12-7.14(d, 1H, J=8.4Hz), 6.94-6.96(dd, 1H, *J*=1.6, J=7.2Hz), 4.2-4.4(m, 1H), 3.05-3.15(d, 1H, J=), 2.62-2.95(m, 5H), 2.0-2.15(m, 3H),1.6-1.72(m, 2H),1.35-1.45(m, 2H), 0.9-1.0(t, 3H). ^{13}CNMR ($CDCl_3$, 400MHz): 134, 133.8, 132.7, 127.7 , 116.8, 110, 106.6, 67.5, 35.7, 34.7, 30.9, 22.3, 13.99; IR (KBr) cm^{-1}: 3424, 2922, 1593, 1462, 1327, 867, 771; Elemental Analysis: C, 78.87; H, 8.70; N, 5.66; O, 6.67; MS (ESI): *m/z* 244 $[M+H]^+$

1,2,3,4-tetrahydrocarbazole(entry 11) :
Pale brown solid MP 116-118 °C; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.86-1.99 (br m, 4H), 2.74(br t, 4H, J= 6.2), 7.08-7.71 (br m, 2 H), 7.29 (m, 1 H), 7.49 (m, 1 H), 7.64 (br s, 1 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.05, 22.20, 22.32, 22.42, 108.98, 109.61, 116.81, 118.12, 119.96, 126.82, 133.30, 134.66 IR (neat) cm^{-1}: 3401, 2928, 2848, 1470, 1305, 1235, 739 ; Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 82.87; H, 7.53; N, 7.84.

6-Methyl-2,3,4,9-tetrahydro-1H-carbazol (entry 12):
Off white solid, MP 101-103 ^oC;^1H NMR (DMSO-d_6, 400 MHz) : δ ppm 10.5 (brs, NH), 7.1-712(d, 1H, J=8.2Hz), 6.8(s,1H), 6.6-6.63(d, 1H, J=2.08), 2.56-2.74(m, 4H), 2.34(s, 3H), 1.75-1.95 (m, 4H) ; ^{13}C NMR (DMSO-D_6 , 75MHz) : 135, 133.2, 131.1, 130.9, 121.2, 120, 112.5, 110.5, 35.3, 26.5, 25.2, 21.2. IR (KBr) cm^{-1}: 3399, 3215, 2920, 1620, 1448, 1367, 1055, 742; Elemental Analysis: C, 77.58; H, 7.51; N, 6.96; O, 7.95; MS (ESI): *m/z* 186.2$[M+H]^+$

6-Methoxy-2,3,4,9-tetrahydro-1H-carbazol (entry 13):
Dark brown solid. MP 101-103^oC; ^1H NMR (DMSO-D_6, 400 MHz) : δ ppm 10.5 (brs, NH), 7.1-712 (d, 1H, J=8.6Hz), 6.8 (s, 1H), 6.6-6.63(d, 1H, J=2.08), 3.7(s, 3H), 2.56-2.74(m, 4H), 1.75-1.95(m, 4H); ^{13}CNMR(DMSO-D_6 400MH_z): 155, 135.3, 132, 128.1, 112.5, 112.2, 106, 105.5, 55.9, 35.5, 35.2, 26.5, 25.; IR (KBr) cm^{-1} : 3381, 3387, 1620, 1448, 1367, 1055, 742.

6-Fluoro-2,3,4,9-tetrahydro-1H-carbazol (entry 14):
Off white solid, MP 90-93^oC ;^1H NMR (DMSO-D_6, 400 MHz) :δ ppm 10.7(brs, NH), 7.18-7.2 (d, 1H, J=4.64Hz), 7.02-7.05(d, 1H, J=7.2Hz), 6.8(s, 1H), 6.6-6.63(d, 1H, J=2.08), 3.7(s, 3H), 2.56-2.74(m, 4H), 1.75-1.95(m, 4H); ^{13}C NMR (DMSO-D_6 400MH_z) : 154, 134.3, 132, 130.7, 112.5, 112.4, 107, 106.5, 35.5, 35, 26.5, 24.5. IR (KBr) cm^{-1}: 3395, 3386, 1620, 1448, 1367, 1055, 742; MS (ESI): *m/z* 190$[M+H]^+$

CONCLUSION

In conclusion, we have developed a novel protocol for high yielding method for the synthesis of 6-substituted 3-hydroxytetrahydrocarbazoles. This new protocol underlines the potential use of diluted sulphuric acid which is inexpensive. This methodology can be exploited for the synthesis of various carbazole skeletons with the required substituents.

Acknowledgements
Authors thank UGC, New Delhi for the financial assistance under Major Research Project. Y.M. is thankful to JNTU -Anantapur, S.R. is thankful to KL University.

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