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AN EFFICIENT SYNTHESIS OF (E)-6-(1-(PHENYLIMINO) ETHYL)-9H-CARBAZOL-3-OL DERIVATIVES AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITIES

N. Krishnarao*[1], P. Madhuri[1], K. D. Prabodh[1], CH. Jyothi[1]

[1*]Department of Organic Chemistry, PRISM PG and DG College (Affiliated by Andhra University), Visakhapatnam, India.

ABSTRACT

In depth study, the synthesis of a series of Schiff bases of (E)-6-(1-(phenyldiamine) ethyl)-9H-carbazol-3-ol derivatives and also exploring biological properties. These derivatives were synthesized by a conventional method from substituted aromatic amines with hetero aromatic amine with compound (3) in the presence of Bronsted acid triflouoro acetic ACD in ethanol as solvent and the compound (3) can be obtained P-benzoquinone with 4-amino acetophenone in the presence copper acetate in CH_3CN with strong base such as Cs_2CO_3 at reflux. All the synthesized analogous were confirmed by spectroscopic method such as ^1H NMR and ^{13}CNMR and mass spectral analysis. The structures of the compounds were analyzed by elemental analysis. All derivatives were evaluated against two gram (+Ve) and two gram (-Ve) bacterial strains.

KEYWORDS

(E)-6-(1-(phenyldiamine) ethyl)-9H-carbazol-3-ol, 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one, $Cu(OOCCH_3)_2$, TFAA and Antibacterial activity.

Author for Correspondence:

Krishnarao N,
Department of Organic Chemistry,
PRISM PG and DG College (Affiliated by Andhra University), Visakhapatnam, India.

Email: naallakrishnarao@gmail.com

INTRODUCTON

The condensation products of primary amines and carbonyl compound either aldehydes and ketones are known as Schiff bases. They were discovered by a German chemist, Nobel Prize winner, Hugo Schiff in 1864. Organic compounds were possessed by the azomethine (–HC=N-) group in their structure is called imines. So, these compounds are very broad significant role played in the preparation of drug moiety. Azomethine group (C=N) in terms of structure and characteristics is between two group of NH_2 and C=O and all of these groups have two

electrons in π orbital and these electrons are responsible for some of the special properties of compounds that have these groups. The synthesized imine can coordinate to metal ion combined with heteroatom such as nitrogen having nonbonding electrons. In fact, the Schiff base can stabilize many of the oxidation states of metals by controlling their. Schiff base is a prominent moiety in the broad area of synthetic organic chemistry and medical chemistry[1,2]. The imine linkage has been identified as an excellent bioactive and medicinally important moiety. Azomethine and their derivatives have been investigated[3,4] due to their striking complex metric role and pharmacological applications which due to these properties, it plays an important and prominent role in major area of biological activities[5-7] such as antimicrobial[8-17], anticancer[18-20], anticonvulsant[21,22], anti-HIV[23], anti-helminthic[24], antiviral[25], anti-malarial[26,27], anti-inflammatory[28-30], anti-oxidant[31-32].

Our going continuously investigates the preparation of Schiff's base via an intermediate such as cabriole and perfectly synthesized and an efficient synthesis of (E)-6-(1-(phenyldiamine) ethyl)-9H-carbazol-3-ol derivatives and evaluation of their antimicrobial activities.

MATERIAL AND METHODS

Experimental

All starting material, solvents, reagents were used and also analytical grade were procured from Merck and Aldrich Company. The melting points of the newly synthesized analogous were estimated in open capillary tubes on an electro Agarwal thermal apparatus and are uncorrected. The purity of the compounds was evaluated by thin layer chromatography on silica gel coated aluminum plate chromatography (TLC) using n-hexane / EtOAc (2:1) as an eluent. ^{1}H NMR and ^{13}CNMR spectra of compounds were recorded on a Brucker AMX 400 MHz spectrometer in $CDCl_3$ as a solvent using tetra methyl silane (TMS) as an internal standard. Chemical shifts and coupling constants are reported in δ and Hz respectively.

General procedure of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one

The mixture of p-amino acetophenone (1.110mmol), p-benzoquinone (1.0mmol) were dissolved in 25mL toluene in a dry and clean RBF. The copper acetate and caesium carbonate added in a RBF. The total set up arranged on the magnetic stirrer and was continued 6 hrs at 100^0C. The reaction mixture was identified by TLC (4:6-Ethyl acetate: n-hexane).After completion of the reaction, catalyst was filtered and the reaction mixture poured into a beaker which is added with ethyl acetate and washed solution of sodium bi carbonate. The organic layer separated kept side and aqueous layer washed with (10mL) after separated. Both of the organic layers combined distilled off u/vacuum. Crude product was separated by columns chromatography and recrystallization from ethanol.

Pale red solid; Yeild-89%; m.p-202-204^{o}C; .1HNMR(400MHz, $CDCl_3$) δppm: 10.571 (s, 1H, N-H: indole), 9.241 (s, 1H, -OH), 8.448 (s, 1H, Ar-H), 8.145-7.879 (m, 2H, Ar-H), 7.475 (s, 1H, Ar-H), 7.424-7.215 (m, 3H, Ar-H), 1.795 (s, 3H, -CH_3); ^{13}CNMR (100MHz, CDCl3) δppm: 166.58, 152.77, 144.28, 137.58, 129.45, 128.60, 128.55, 126.96, 122.26, 121.08, 114.06, 110.81, 108.54, 103.64, 20. 84. LCMS (m/z): 224.65(M-H); Molecular formule: $C_{14}H_{11}NO_2$. Elemental analysis: Calculated: C-74.65, H-4.92, N-6.22; Obtained: C-74.57, H-4.91, N-6.29.

General procedures of (E)-6-(1-(phenylimino) ethyl)-9H-carbazol-3-ol (5a-f)

General procedures for synthesis of Schiff base compounds

The mixture 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one (1mol), Trifluoroacetic acid (3mL) was added slowly with dropping funnel. The mixture was carried out for two hours in room temperature, then substituted aromatic amines (1mol) was added to above mixture and was stirred and heated under reflux in conditions at 60^{o}C. The progress of reaction was checked by thin layer chromatography (TLC). After the completion of reaction, cold water was added to the mixture. Then solid crystals were formed at the bottom of the beaker and after that, they were filtered. Finally, the solid product was

washed with water, ethanol and n-hexane and dried in desiccator in R.T. The pure derivatives were obtained in good yields.

(E)-6-(1-(phenylimino) ethyl)-9H-carbazol-3-ol (5a)

Red solid; Yeild-87%; m.p-243-245^{o}C ^{1}HNMR (400MHz, $CDCl_3$) δppm): 10.612 (s, 1H, N-H: indole), 9.257(s, 1H, -OH), 8.525 (s, 1H, Ar-H), 8.294-8.015(m, 2H, Ar-H), 7.514(s, 1H, Ar-H), 7.418-7.284 (m, 3H, Ar-H), 7.214-6.965 (m, 3H, Ar-H), 1.845 (s, 3H, -CH3); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 165.58, 151.57, 143.09, 136.12, 129.32, 128.85, 128.24, 125.44, 122.58, 120.07, 113.36, 112.61, 111.54, 108.07, 102.54, 19.42. LCMS (m/z): 317.58(M+H); Molecular formule: $C_{20}H_{16}N_2O_2$. Elemental analysis: Calculated: C-75.93, H-5.10, N-8.85; Obtained: C-75.86, H-5.08, N-8.93.

(E)-6-(1-(p-tolyl imino) ethyl)-9H-carbazol-3-ol (5b)

Red compound; Yeild-93%; m.p-238-240^{o}C; .^{1}HNMR (400MHz, $CDCl_3$) δppm: 10.845 (s, 1H, N-H:indole), 9.257 (s, 1H, -OH), 8.304 (s, 1H, Ar-H), 8.113-7.895(m, 2H, Ar-H), 7.592 (s, 1H, Ar-H), 7.410-7.271 (m, 2H, Ar-H), 7.287-6.845 (m, 4H, Ar-H), 1.728 (s, 3H, -CH_3); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 164.58, 151.23, 146.87, 140.46, 139.55, 136.52, 129.54, 128.58, 127.04, 126.56, 123.18, 115.57, 114.78, 112.69, 112.44, 110.72, 108.82, 102.57, 20.83, 18.12LCMS (m/z): 315.87 (M+H); Molecular formule: $C_{21}H_{18}N_2O$. Elemental analysis: Calculated: C-80.23, H-5.77, N-8.91; Obtained: C-80.15, H-5.75, N-8.98.

(E)-6-(1-((3-hydroxyphenyl) imino) ethyl)-9H-carbazol-3-ol (5c)

Palered solid; Yeild-91%; m.p-231-233^{o}C; ^{1}HNMR (400MHz, $CDCl_3$) δppm): 10.744 (s, 1H, N-H: indole), 9.515 (s, 1H, -OH), 9.146 (s, 1H, -OH), 8.467 (s, 1H, Ar-H), 8.116 (d, J=8.6Hz, 1H, Ar-H), 8.054 (d, J=8.0Hz, 1H, Ar-H), 7.868 (d, J=6.8Hz, 1H, Ar-H), 7.557 (s, 1H, Ar-H); 7.476-7.146 (m, 2H, Ar-H), 7.127-6.985 (m, 4H, Ar-H), 1.078 (s, 3H, -CH_3); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 164.73, 155.94, 150.16, 148.38, 140.11, 138.35, 130.24, 128.83, 125.68, 122.31, 117.95, 115.08, 113.63, 112.84, 112.64, 110.85, 109.38, 107.75, 101.69, 19.77. LCMS (m/z): 301.68 (M+H); Molecular formule: $C_{20}H_{16}N_2O$. Elemental analysis: Calculated: C-79.90, H-5.37, N-9.33; Obtained: C-79.84, H-5.36, N-9.39.

(E)-6-(1-((4-chlorophenyl) imino) ethyl)-9H-carbazol-3-ol (5d)

Red compound; Yeild-89%; m.p-240-242^{o}C; ^{1}HNMR (400MHz, $CDCl_3$) δppm): 10.814 (s, 1H, N-H: indole), 9.321 (s, 1H, -OH), 8.458 (s, 1H, Ar-H), 8.192-7.984 (m, 2H, Ar-H), 7.814 (s, 1H, Ar-H), 7.556-7.287 (m, 3H, Ar-H), 7.224-6.923 (m, 3H, Ar-H), 1.065 (s, 3H, -CH_3); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 166.57, 150.87, 143.54, 136.08, 129.47, 128.87, 128.13, 126.71, 123.957120.26, 113.47, 111.64, 109.55, 107.71, 102.54, 19.41. LCMS (m/z): 317.37 (M+H); Molecular formule: $C_{20}H_{16}N_2O_2$. Elemental analysis: Calculated: C-75.93, H-5.10, N-8.85; Obtained: C-75.86, H-5.08, N-8.93.

(E)-6-(1-((4-nitrophenyl) imino) ethyl)-9H-carbazol-3-ol (5e)

Yellow solid; Yeild-87%; m.p-250-252^{o}C; 1HNMR (400MHz, $CDCl_3$) δppm): 10.902 (s, 1H, N-H: indole), 9.247 (s, 1H, -OH), 8.547 (s, 1H, Ar-H), 8.182-7.712 (m, 4H, Ar-H), 7.413-7.284 (m, 2H, Ar-H), 7.039-6.874 (m, 2H, Ar-H), 1.012 (s, 3H, -CH_3); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 168.55, 151.65, 141.78, 137.65, 136.74, 135.84, 129.33, 128.57, 127.04, 125.72, 122.81, 113.07, 112.74, 111.44, 110.13, 108.70, 101.06, 18.04. LCMS (m/z): 346.07(M+H); Molecular formule: $C_{20}H_{15}N_3O_3$. Elemental analysis: Calculated: C-69.56, H-4.38, N-12.17; Obtained: C-69.48, H-4.36, N-12.24.

(E)-6-(1-(thiophen-2-ylimino) ethyl)-9H-carbazol-3-ol (5f)

Pale yellow solid; Yeild-85%; m.p-230-232^{o}C; ^{1}HNMR (400MHz, $CDCl_3$) δppm): 10.864 (s, 1H, N-H: in dole), 9.145 (s, 1H, -OH), 8.446 (s, 1H, Ar-H), 8.055-7.903 (m, 2H, Ar-H), 7.691-7.470 (m, 2H, Th-H), 7.433 (s, 1H, Ar-H), 7.413-7.285 (m, 2H, Ar-H), 0.987 (s, 3H, -CH_3); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 167.28, 151.38, 140.54, 136.55, 129.55, 128.76, 128.07, 127.55, 124.15, 120.78, 114.76,112.40, 112.11, 111.08, 108.76, 101.62, 18.66. LCMS (m/z): 306.52(M+);

Molecular formule: $C_{18}H_{14}N_2OS$. Elemental analysis: Calculated: C-70.56, H-4.61, N-9.14; Obtained: C-70.48, H-4.60, N-9.22.

Antimicrobial Evaluation

Anti-bacterial activity

The *invitro* anti-bacterial activities of desired synthesized derivatives are evaluated against 4 pathogenic bacteria strains. The gram negative bacteria screened were *E.coli* and P. *aeruginosa*. The gram positive bacteria screened were *S.aureus* and *B.substill*. The target compounds were used at the concentration of 250µg/mL and 500µg/mL using DMSO as a solvent the 10µg/mL disc and were Streptomycin used as a standard. The rest of the compounds were found to be moderate active against the tested microorganism.

Antifungal assay

Sterile molten potato dextrose agar (PDA) medium was inoculated with 50lL of fungal spore suspension aseptically and maintained at 45^{o}Ctemperature. The inoculated medium was mixed well and poured immediately in sterilized petriplates. Then five wells of 6mm diameter were punched using sterile borer and filled with 100lg/mL of test compounds (6a-l) as well as sterile DMSO 100% as negative control. Plates were incubated for 24 h at 37^{o}C. Antifungal activity was determined by measuring the zone of inhibition. The zones produced by the test compounds were compared with the "ketoconazole".

RESULTS AND DISCUSSION

Chemistry

The titled derivatives were obtained in two steps (Scheme No.1). At first, Synthesis of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one was prepared, according to a method with a two component reaction comprising of P-amino acetophenone and P-benzoquinone in acetonitrile as solvent using copper iodide with strong base such as Cs_2CO_3 at 75^{o}C. The reaction of P-benzoquinone and P-amino acetophenone were employed as a template to optimize the reaction conditions (Scheme No.1).

Therefore, a mixture of P-amino acetophenone (1mol) and P-benzoquinone (1mol) acetonitrile was stirred for suitable time as represented by TLC using the various amounts of catalyst at the end of reaction, the cyclisation between P-amino acetophenone and P-benzoquinone followed with addition catalyst resulted in only one product called (3).

For optimization of the amount of catalyst needed for this reaction, of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one was applied as a model analogous and different amounts of catalyst were tested under the same conditions. It was found that 5mol% of catalyst was enough for a desired yield of the product (Table No.1). On the other hand, an amount of catalyst

To show that copper iodide is an efficient catalyst, this two components› reaction was accomplished in the absence of catalyst at room temperature for12 h. This reaction just produced the product of cyclisation between components (1) and (2). The efficiency of the reaction is mainly affected by the amount of the catalyst (Table No.1). The optimal amount of the catalyst was 3 mol% (entry3); the higher amount of the catalyst did not noticeably increase yield (entry 4).

After synthesis of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one, their schiff base derivatives (5a-j) were prepared by the condensation reaction between compound (3) and the substituted amines in ethanol with trifluorocetic acid under reflux conditions. All reactions improved corresponding Schiff-bases (5a–j) in excellent yield the results were summarized in Table No.3.

After synthesis of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one, their Schiff base analogous (5a-5f) were prepared by the condensation reaction between compound (3) and the substituted aromatic amines in ethanol with trifluorocetic acid under reflux conditions. All reactions produced corresponding Schiff-bases (5a–5fj) in good yield; the results were summarized in Table No.3.

The structures of the desired compounds were constructed on the basis of characterized by 1HNMR, ^{13}C NMR, mass spectral and elemental analyses. The proton NMR evidences of corresponds to O-H, N-H, aromatic C-H, CONH, C=O and C=N stretching respectively. Similarly, ^{1}HNMR spectrum of the required compounds

showed in various aromatic protons appears at δ 8.456 to 6.713ppm, the hydroxyl protons appear at δ 9.515ppm, The NH protons of the derivatives appear at δ 10.917ppm and methyl protons appear at 1.748ppm. The mass spectrum of "5d" showed molecular ion peak at 317.37 (M+H) which is in agreement with the molecular formula $C_{20}H_{16}ClN_2O_2$.

Antibacterial activity

The *in vitro* antibacterial activity of the newly synthesized derivatives (5a-5f) was compared with standard" Streptomycin'' as collected in (Table No.4). As indicated in Table No.4, most of the synthesized derivatives generally exhibited potent activity against all the tested bacterial strains. Compound "5c and 5e" showed excellent antibacterial activity against gram-positive bacterial strains viz; E.coli, P.aeruginosa and gram negative bacterial strains viz; B. Subtilis, and Staphylococcus aureus. The derivatives "5b and 5d" showed moderate active potent against bacterial strains. The compounds"5a" showed low activity against bacterial strains. These results reveals that the compounds having electron releasing groups showed good activity than the compounds having electron withdrawing groups.

Antifungal activity

The *in vitro* antifungal activity of the newly synthesized derivatives (5a-5f) was compared with standard drug" Ketonozole.'' as collected in (Table No.4). The *in vitro* antifungal activity of the newly synthesized derivatives (5a-5fl) was studied against *A.Ngier* and *C.albicans*. Compounds 5d and 5f showed significant activity against "*A.Ngier*" than the fungal strain "C.albicans". 5b and5d were found to be moderately active against tested fungal strain. From the results it is evident that most of the compounds showed significant activity and few are moderately active as shown in Table No.5.

The compound 5i, 5b, 5c exhibited the highest potent active against Aspergillusfavus. The compound "5a", exhibited lowest values The remaining derivatives showed moderate potent activities against Aspergillusfavus. These results evidences that the compounds possess electron donating groups exhibited good activity than the compounds possesses electron attracting groups.

Table No.1: Screening of amount catalyst in the formation of compound 3

Entry	(Catalyst mol %)	Time (min)	Yield (%)
1	1mol	120	59
2	2mol	120	62
3	3mol	120	85
4	4mol	120	85

Table No.2: Reaction of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one in various catalysts in Toluene

Entry	Various catalyst	Time (min)	Yield (%)
1	$CuCl_2$	120	55
2	$Cu(OAc)_2$	120	89
3	Copper triflate	120	66

Table No.3: Antibacterial activity of the newly synthesized compounds (5a-f): Zones of inhibition (mm)a of compounds 5a–f against tested bacterial strains and fungal strains

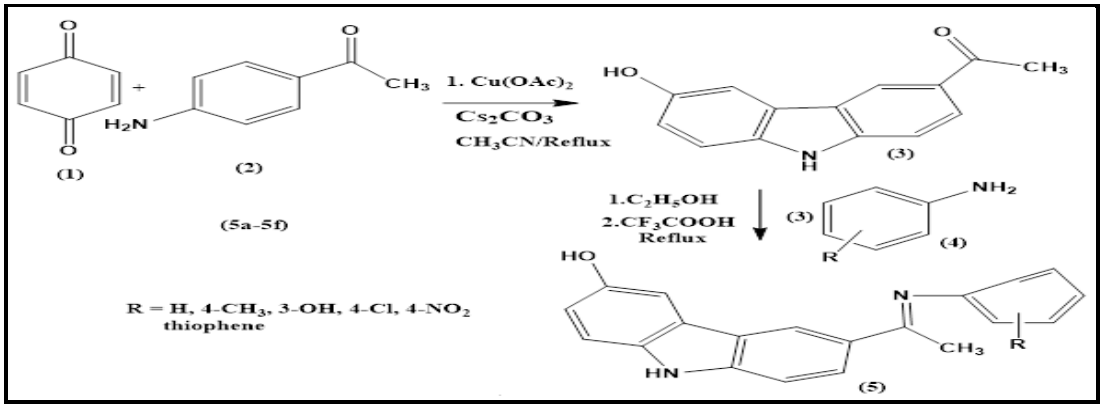
Compound	Anti-Bacterial Activity			
	Gram(+ve) bacteria		Gram(-ve) bacteria	
	E. c.	P.a.	B. s.	S.a.
5a	07	09	07	06
5b	14	12	14	15
5c	18	17	17	18
5d	22	20	22	21
5e	11	13	10	11
5f	20	21	19	20
Streptomycin	25	25	25	25
DMSO	-	-	-	-

Streptomycin is used as standard. a 100 lg/mL of compound in each well. Values are average of three readings'.

Table No.4: Antifungal activity of the synthesized compounds (5a-f): Zones of inhibition (mm)a of compounds (5a–f) against tested fungal strains

Entry	Antifungals activity		
	Aspergillus Niger	*Candida albicans*	*Aspergillusfavus*
5a	04	07	08
5b	14	14	16
5c	15	13	13
5d	19	13	13
5e	19	16	17
5f	18	16	17
Ketonozole	22	22	22
DMSO			

Values are the average of three readings. Ketoconazole was used as standard. a 100 lg/mL of compound in each well.



Scheme No.1

CONCLUSION

A convenient route synthesis of trifluorocetic acid from readily available bulk chemicals has been reported and the full scope of its application in direct imines reactions has been explored. A broad range of ketone and substituted amines containing varying functionalities can be successfully used in triflouoro acetic acid mediated animation reactions, and the pure Schiff's base products can be isolated following an operationally simple solid phase workup procedure using commercially available resins, avoiding the required for aqueous workup or chromatographic purification.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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