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

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ABSTRACT

In depth study of bioactive synthesis of a novel series of Schiff bases of (E)-6-(1-(phenylimino) ethyl)-9H-carbazol-3-ol and they are were synthesized by a conventional method of synthesis from substituted aromatic amines and hetero aromatic amine with compound (3) in the presence of Bronsted acid like methanesulphonic acid in ethanol as solvent and the compound (3) can be obtained P-benzoquinone with 4-amino acetophenone in the presence copper iodide in toluene with strong base such as Cs_2CO_3 at 100°C. All the newly synthesized derivatives were evaluated spectroscopic method such as IR, ^{1}H NMR and ^{13}CNMR and mass spectral analysis. The structure of the compounds was analyzed by elemental analysis. All derivatives were screened against two gram positive and two gram negative bacterial strains and three fungal strains.

KEYWORDS

(E)-6-(1-(phenylimino) ethyl)-9H-carbazol-3-ol, 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one, CuI_2, Methanesulphonic acid and Antimicrobial activity.

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INTRODUCTON

Condensation products of primary amines and carbonyl compounds are called Schiff bases (also known as imine or azomethine). They were discovered by a German chemist, Nobel Prize winner, Hugo Schiff in 1864. Organic compounds containing the azomethine (–HC=N-) group in their structure is called imines. Ring and Chain nitrogenous can use as macromolecules fundamental units or as a Schiff base for synthesis of Organometal compounds. So, these compounds are very important. Azomethine group (C=N) in

terms of structure and properties 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 with nitrogen unbounded pair electrons. Chemists still synthesized Schiff base and active Schiff base which are well designed, will be considered as compounds with special advantages. In fact, the Schiff base can stabilize many of the oxidation states of metals by controlling their performance and a wide range of catalytic converts.

Schiff base is a promising moiety in the area of synthetic organic chemistry synthesis and medical chemistry. The imine linkage has been found as an excellent bioactive and medicinally important moiety. Azomethine and their derivatives have been investigated[1,2] due to their striking complex metric behavior and pharmacological applications. Due to these properties, it plays an important major role in various biological activities[3-5] such as antimicrobial[6-15], anticancer[16-18], anticonvulsant[19,20], anti-HIV[21], anti-helminthic[22], antiviral [23], anti-malarial[24,25], anti-inflammatory[26-28], anti-oxidant[29-30].

As you know catalyst is the material that if added to the reaction mixture changes the speed of equivalence mode in the reaction system without chemical changing itself and usually increases it and finally at the end of reaction can be separated from the reaction mixture[31-35].

MATERIAL AND METHODS

Experimental

All chemical compounds, solvents, reagents here used were analytical grade and they were procured from Merck and Aldrich Company. Melting points of all newly synthesized derivatives were determined in open capillary tubes on an electro Agarwal thermal apparatus and are uncorrected. The purity of the compounds was examined by thin layer chromatography on silica gel coated aluminum plate chromatography (TLC) using n-hexane / EtOAc (2:1) as an eluent. Infrared spectra (FT-IR) of products were recorded in potassium bromide (KBr) pellets using shimidzo 400 spectrometer.^{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.

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

The mixture of p-amino acetophenone (1.150mmol), p-benzoquinone (1.0mmol) dissolved in toluene in a dry and clean four neck RBF. The copper iodide and caesium carbonate added in RBF .The total set up arranged on the magnetic stirrer and was maintained 12hrs at 100^{o}C. The reaction mixture was monitored by TLC (5:5-Ethyl acetate: n-hexane). After completion of the reaction, catalyst was filtered and the reaction mixture poured into ethyl acetate and washed solution of sodium bi carbonate. The organic layer separated kept side and aqueous layer washed with (2x10mL) 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; Yield-89%; m.p-202-204^{o}C; Rf-0.510 (n-hexane: EtOAc=5:5); IR(KBr,cm-1): 3514, 3318, 3049, 2987, 2846, 1710, 1578, 1548, 1524, 754.1HNMR(400MHz,$CDCl_3$) δppm): 10.457(s, 1H, N-H:indole), 9.041(s, 1H, -OH), 8.498(s, 1H, Ar-H), 8.012(m, 2H, Ar-H), 7.484(s, 1H, Ar-H), 7.324-7.281(m, 3H, Ar-H), 1.742(s, 3H, -CH_3);^{13}CNMR(100MHz, $CDCl_3$) δppm: 165.11, 151.45, 1424.25, 138.15, 129.07, 128.65, 128.12, 126.76, 121.55, 121.18, 114.56, 110.88, 109.54, 102.66, 19.87. LCMS (m/z): 224.66(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

In this project, to of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one (1mmol), methanesulphonic acid (3mL) was added; the mixture was stirred for two

hours in room temperature, then substituted aromatic amines and heteroaromatic amines (1mmol) was added to a mixture and was stirred and heated under reflux in conditions an oil bath 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)

Pale red solid; Yield 89%; m.p-242-244^{o}C; Rf-0.457 (n-hexane: EtOAc=5:5); IR(KBr, cm^{-1}): 3512, 3308, 2978, 1575, 1537, 1502, 1216. ^{1}HNMR(400MHz, $CDCl_3$) δppm): 10.675(s, 1H, N-H: indole), 9.112(s, 1H, -OH), 8.504(s, 1H, Ar-H), 8.094(m, 2H, Ar-H), 7.492(s, 1H, Ar-H), 7.318-7.288(m, 3H, Ar-H), 7.084-6.896(m, 3H, Ar-H), 1.964(s, 3H, -CH_3); ^{13}CNMR(100MHz, $CDCl_3$) δppm: 164.56, 150.45, 143.03, 136.06, 129.16, 128.84, 128.17, 125.76, 122.96, 120.08, 113.35, 112.62, 11.55, 108.76, 102.58, 19.44. 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-(p-tolyl imino) ethyl)-9H-carbazol-3-ol (5b)

Pale red solid; Yield-91%; m.p-236-238^{o}C; Rf-0.412(n-hexane: EtOAc=5:5); IR(KBr, cm-1): 3510, 3305, 2970, 2879, 1208. ^{1}HNMR(400MHz, $CDCl_3$) δppm: 10.732(s, 1H, N-H: indole), 9.013 (s, 1H, -OH), 8.356(s, 1H, Ar-H), 8.012-7.845(m, 2H, Ar-H), 7.492(s, 1H, Ar-H), 7.310-7.272(m, 2H, Ar-H), 7.187-6.887(m, 4H, Ar-H), 1.748(s, 3H, -CH_3); ^{13}CNMR(100MHz, $CDCl_3$) δppm: 165.08, 150.22, 145.54, 140.25, 138.54, 134.58, 129.77, 128.88, 127.44, 124.56, 122.48, 114.87, 113.45, 112.98, 111.45, 110.24, 108.87, 101.58, 20.89, 19.12. LCMS (m/z): 313.65 (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)

Pale red solid; Yield 92%; m.p-225-227^{o}C; Rf-0.4607(n-hexane: EtOAc=5:5); IR(KBr, cm-1): 3512, 3507, 3298, 3057, 2965, 1206. ^{1}HNMR(400MHz, $CDCl_3$) δppm): 10.672(s, 1H, N-H: indole), .238(s, 1H, -OH), 9.073(s, 1H, -OH), 8.456(s, 1H, Ar-H), 8.074(d, J=8.4Hz, 1H, Ar-H), 8.074(d, J=8.4Hz, 1H, Ar-H), 7.768(d, J=6.4Hz, 1H, Ar-H), 7.504(s, 1H, Ar-H); 7.315-7.286(m, 2H, Ar-H), 6.986-6.672(m, 4H, Ar-H), 1.048(s, 3H, -CH3); ^{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, 111.60, 110.83, 109.37, 107.74, 101.62, 19.78. LCMS (m/z): 301.24(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)

Pale red solid; Yield-88%; m.p-247-249^{o}C; Rf-0.457(n-hexane: EtOAc=5:5); IR(KBr, cm-1): 3505, 3294, 3045, 2959, 1198, 687; ^{1}HNMR(400MHz, $CDCl_3$) δppm): 10.894(s, 1H, N-H: indole), 9.034(s, 1H, -OH), 8.436(s, 1H, Ar-H), 8.092-7.884(m, 2H, Ar-H), 7.793(s, 1H, Ar-H), 7.384-7.324 (m, 3H, Ar-H), 7.123-6.942(m, 3H, Ar-H), 1.046(s, 3H, -CH3); ^{13}CNMR(100MHz, $CDCl_3$) δppm: 164.56, 150.45, 143.03, 136.06, 129.16, 128.84, 128.17, 125.76, 122.96, 120.08, 113.35, 112.62, 11.55, 108.76, 102.58, 19.44. 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)

Pale yellow solid; Yield -85%; m.p-251-253^{o}C; Rf-0.474(n-hexane: EtOAc=5:5); IR(KBr, cm-1): 3507, 3489, 3306, 2950, 1203, 715. Yeild-85%; 1HNMR(400MHz, CDCl3) δppm): 10.892(s, 1H, N-H: indole), 9.023(s, 1H, -OH), 8.446(s, 1H, Ar-H), 8.089-7.764(m, 4H,Ar-H), 7.312-7.274 (m, 2H, Ar-H), 6.903-6.713(m, 2H, Ar-H), 0.975(s, 3H, -CH3); ^{13}CNMR(100MHz, CDCl3) δppm: 168.74, 150.36, 140.02, 136.42, 135.62, 134.84, 129.12,

128.17, 127.46, 125.73, 122.88, 113.76, 112.65, 112.09, 110.62, 108.79, 101.96, 18.64. 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; Yield -89%; m.p-231-233^oC; Rf-0.457(n-hexane: EtOAc=5:5); IR(KBr, ?cm-1): 3500, 3309, 3064, 2978, 700; ^{1}HNMR(400MHz, $CDCl_3$) δppm): 10.864(s, 1H, N-H:indole), 9.105(s, 1H, -OH), 8.456(s, 1H, Ar-H), 8.023-7.912(m, 2H, Ar-H),7.694-7.472(m, 2H, Th-H), 7.410 (s, 1H, Ar-H), 7.312-7.284(m, 2H, Ar-H), 0.976(s, 3H, -CH_3); ^{13}CNMR(100MHz, $CDCl_3$) δppm: 167.24, 150.37, 140.03, 136.76, 129.12, 128.36, 128.14, 127.36, 124.65, 120.44, 113.74, 112.46, 112.09, 111.68, 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 anti-bacterial activities of newly synthesized compounds are examined against 5 pathogenic bacteria strains. The gram negative bacteria screened were Escherichia coli and Pseudomona aeruginosa. The gram positive bacteria screened were *S. ureas* and *B. substills*. The target compounds were used at the concentration of 250µg/mL and 500µg/mL using DMSO as a solvent the amoxylin 10µg/mL disc were 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 450Ctemperature. 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 370C. 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 new schiff bases were synthesized in two steps (Scheme No.1). At first, Synthesis of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one was synthesized according to a method with a two component reaction comprising of P-amino acetophenone and P-benzoquinone in toluene as solvent using copper iodide with strong base such as Cs_2CO_3 at 100^oC. 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 1mmol) and P-benzoquinone (1mmol) toluene was stirred for an appropriate time as indicated by TLC using different 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 required for this reaction, of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one was used as a model compound and different amounts of catalyst were tested under the same conditions. It was found that 5 mol% of catalyst was enough for a desired yield of the product (Table No.1). On the other hand, an amount of catalyst more than 5mol% did not increase the yield of desired product.

To show that copper iodide is an efficient catalyst, this two components› reaction was accomplished in the absence of catalyst at room temperature for 12 hrs. 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 5mol% (entry 2); 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 methane sulfonic acid under reflux conditions . All reactions produced corresponding Schiff-bases (5a-j) in good yield; the results were summarized in Table No.3.

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The structures of the desired compounds were characterized by IR, ^{1}HNMR, ^{13}C NMR, mass spectral and elemental analyses. The IR spectrum of compounds (5a-5f) exhibited absorption bands at 3512, 3308, 3057, 2985, 1575, 1589, 1541, 1506, 612cm $^{-1}$ which corresponds to O-H,N-H, aromatic C-H, CONH, C=O and C=N stretching respectively. Similarly, ^{1}H NMR spectrum of the desired compounds exhibited in various aromatic protons appears at δ 8.456 to 6.713ppm. The hydroxyl protons appear at δ 9.112ppm, The NH protons of the derivatives appear at δ 10.894ppm 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-III). .As indicated in Table-III most of the synthesized derivatives generally exhibited potent activity against all the tested bacterial strains. Compound "5d and 5f" 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* with zones of inhibition of 22, 21, 22, 20mm and 20, 21, 19, 20mm respectively. The compound 5c showed good activity against the bacterial stains such as *E.coli, B.subtilis* and *Staphylococcusaureus* are 18, 17, 17 and 18mm respectively. The derivatives 5b showed moderate active potent against bacterial strains are 14, 12, 14, 15. The compounds" 5e and 5a" showed low activity against bacterial stains and the values are 11, 13, 10, 11 and 07, 09, 07, 06 respectively. These results represents that the compounds containing releasing groups showed good activity than the compounds having electron withdrawing groups. The tested derivatives containing halogen and heteroaromatic compounds which were exhibited excellent potent activity.

Zones of inhibition (mm)a of compounds 5a–f against tested bacterial strains and fungal strains:

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

Antifungal activity

The *in vitro* antifungal activity of the newly synthesized derivatives (5a-5f) was compared with standard drug" Ketonozole.'' as collected in (Table-IV).

The *in vitro* antifungal activity of the titled derivatives (5a-5f) was studied against *A. Ngier and C.albicans*. Compound 5e exhibited significant antifungal activity (*A. Niger, C.albicans*). Compounds 5f showed significant activity against "*A.Ngier*" than the fungal strain "*C.albicans*". 5b, 5c, and 5d were found to be moderately active against tested fungal strain. All compounds have demonstrated significant antifungal activity comparable to standard. From the results it is evident that most of the compounds showed significant activity and few are moderately active as shown in Table No.4.

Zones of inhibition (mm) a of compounds (5a–f) against tested fungal strains

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

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

Entry	(Catalyst mol %)	Time (min)	Yield (%)
1	3mol	90	59
2	5mol	60	85
3	7mol	75	85
4	10mol	120	85

Table No.2: Reaction of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one in different catalyst in toluene

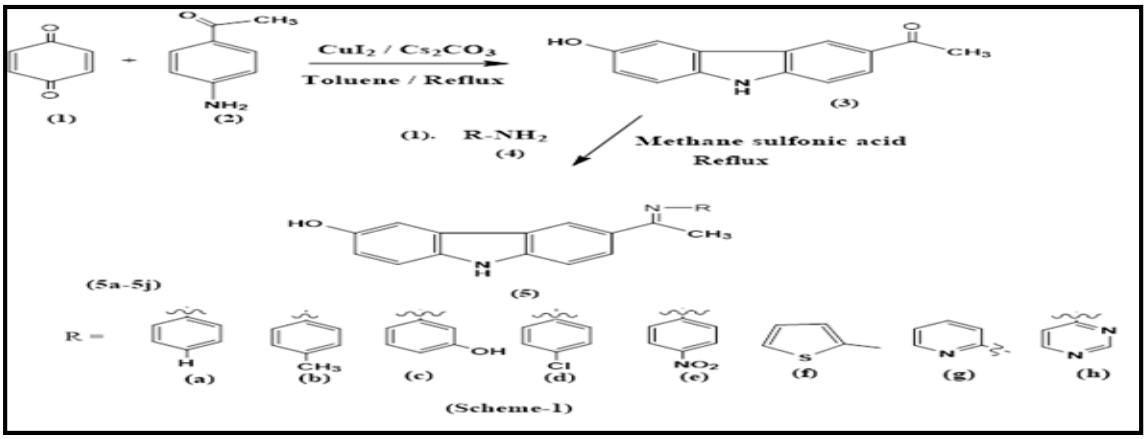
Entry	Various catalyst	Time (hrs.)	Yield (%)
1	$CuCl_2$	6	58
2	$Cu(OAc)_2$	8	68
3	Copper triflate	10	70
4	CuI_2	3.5	85

Table No.3: Antibacterial activity of the newly synthesized compounds (5a-f)

S.No	Compound	Anti-Bacterial Activity			
		Gram(+ve) bacteria		Gram(-ve) bacteria	
		E. c.	P.a.	B. s.	S. a.
1	5a	07	09	07	06
2	5b	14	12	14	15
3	5c	18	17	17	18
4	5d	22	20	22	21
5	5e	11	13	10	11
6	5f	20	21	19	20
7	Streptomycin	25	25	25	25
8	DMSO				

Table No.4: Antifungal activity of the synthesized compounds (5a-f)

S.No	Entry	Antifungals activity	
		Aspergillus Niger	Candida albicans
1	5a	04	07
2	5b	10	12
3	5c	13	11
4	5d	15	13
5	5e	19	16
6	5f	18	16
7	Ketonozole	22	22
8	DMSO		



Scheme No.1: The new schiff bases were synthesized in two steps

CONCLUSION

A convenient synthesis of methane sulfonic 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 methane sulfonic acid mediated amination 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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