Ph_3P Base Catalyzed an Efficient Synthesis And invitro Study of 1, 5-diphenyl-1H-pyrrole Analogous

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ABSTRACT:

In an attempt to find new class antibacterial agent of series 1, 5-diphenyl-1H-pyrrole derivatives (4a–4h) were success fully synthesized from phenacyl bromide, substituted aryl amine and Acetylacetone in the presence of base such as Ph_3P employed in ethanol under reflux. The synthesized compounds were evaluated by spectroscopic techniques such as ^{1}HNMR, ^{13}CNMR and LCMS and elemental analysis. In additionally newly synthesized derivatives were evaluated for their antibacterial activity.

Keywords:

Phenacyl Bromide; Aetylacetone; substituted aromatic amines, Ph_3P, 1, 5-diphenyl-1H-pyrrole derivatives, antimicrobial activity

1. INTRODUCTION :

The Pyrrole derivatives and analogues are organic five membered heterocyclic compounds with an extensive and fascinating chemistry. Porphyrin and porphyrin analogues such as bacteriochlorine, chlorine, chlorophylls, cytochromes, hemoglobin, vitamin B_{12} (1), are naturally occurring molecules which contain Pyrrole core and the bile pigment and bioactive natural products possess Pyrrole and its derivatives (2-4).

Pyrrole is five membered heterocyclic aromatic structures including a nitrogen atom. The Pyrrole is a weakest base because the lone pair on the nitrogen contributes to the aromaticity in the structure. The Pyrrole and its analogues have interesting biological properties suchasvirusinhibitionandspecializedinhibitionofHIVvirus (5), antibacterial, antimycotic (6),

cholesterol- lowering (7), anti-psychotic, anti-carcinogen, antimalarial and anticonvulsant activity (8). compounds have played an important vital role in other areas of technological part. They can be used as drugs, dyes, catalysts, pesticides, *etc.* being used in sensor development

semiconductor synthesis (9), petrochemical analysis [10]. Luminescence chemistry [11], Catalysts [12] preservatives [13], and Corrosion inhibitors [14]. The antibacterial and antifungal activity of pyrrole and its derivatives, viz; Paromomycin's are an important antibiotic which obtained by naturally occurring compounds. They having nitro pyrrole nucleus which is chemically stable and also reactive. This bearing N-alkylation group like, Pyrrolomycins (fig-A) acts as antimicrobial activity against *Candida albicans* and *Trichophyton mentagophytes* strains was found to be reduced and N-iodo alkylation resulted in an augmentation of the active potency. Hence, it was observed that N-(iodopropargyl) and N-(triiodoallyl) Pyrrolomycins A derivatives the best signs of antifungal activity than Pyrrolomycins A and clotrimazole (**15**).Pyrrolnitrin and Pyrrolomycins are synthetically prepared pyrrole containing anti-fungal activity. This pyrrole had bulky substituent on the pyrrole ring which is responsible for the reduced in activity whereas nitro group was found to possess a potentiating effect. It was finally stated that the antifungal activity of nitro pyrrole was mainly due to electronegative nature of nitro group. Sulfonamides also have power over variety of biological properties. Antifungal activity tends to increase by the introduction of a heterocyclic sulfonamide in the pyrrolering. However, absence of substituent on sulfonamide results in partial or complete reduction in antifungal activity. It was observed that compounds showed remarkable antifungal activity compared with the standard fungicide is mycostatine **(16).**

Recently, an interested to research work continue without solvent and more emphasis is given to formulate the reactions-based principles of green chemistry [17]. Particularly, our aim to avoid the use of highly toxic reagent and chlorinated non polar solvents viz; chloroform, dichloromethane, carbon tetrachloride etc. because of direct concern with environmental hazardous. The use of aqueous medium or ethanol is dominate in organic synthesis in organic reactions which was attracted the increasing interest done in the synthesis work because of environmental and atom economy [18].In this topic there increases significant research awareness to revisit and continue develop the organic reactions in aqueous medium[19] . This is safest and abundantly available solvent. Now days, Ph3P has focused to emerge as a promoter for synthesized derivatives in various organic reactions. It is an organic base which acts as Nucleophilic, exceedingly soluble in water. The continuation our research works to develop environmentally friendly reactions.

The spontaneous emergence of resistance by bacterial and fungal stains towards existing antimicrobial potent compounds is one of the major problem as well as motivation to synthesize a new class of antimicrobial agents having potent activity compared to commonly used therapy. The analogues pyrrole is the heterocyclic compound constructed from phencyl bromide, acetyl acetone with substituted aryl amine in presence of Ph_3P in ethanol under reflux.

Hence, we wish to report a simple, an efficient, practical and general one pot synthesis multi component reaction for the construction of titled derivatives by the reaction of substituted phenacyl bromide, substituted aryl amines with Acetylacetone in aqueous medium in the presence of Ph_3P **and** also study the antimicrobial activity as shown in (**Scheme-1**).

MATERIALS AND METHODS:

3. Experimental:

Sigma-Aldrich commercial vendors supplied all reagents and starting ingredients, which were used without additional purification. Using aluminum plates coated with silica gel F254 plates (Merck) and ethyl acetate and n-hexane (4:6) as eluents, thin-layer chromatography (TLC) was used to monitor all reactions and the purity of the freshly synthesized derivatives. The desired product's spots were found by either placing them in an iodine chamber or using UV light.

Every compound was regularly examined using a mass spectrometer, ^{1}H NMR. Bruker AVANCE II 400 MHz was used to record 1H NMR spectra, while 100 MHz was used to record ^{13}C NMR spectra. Using TMS as an internal reference, the chemical change was measured in parts per million (ppm). Argon/Xenon (6 kV, mB) gas was used to record mass spectra on water using a QT-OF micro mass (LCMS) mass spectrometer. Silica gel (Merck) was used for column chromatography. The organic phase was dried using anhydrous sodium sulfate.

2.1. GENERAL PROCEDURE

15 milliliters of ethanol were mixed with phenacyl bromide (1 mol), acetyl acetone (1 mol), substituted aromatic amine (1 mol), and catalyst (5 mol%) at 76°C for the designated amount of time. The reaction mixture was diluted with water and extracted with ethyl acetate once the reaction was finished, as determined by TLC. Following a brine solution wash, the mixed organic layers were dried over Na2SO4. The equivalent pure product was obtained by concentrating the organic layer under vacuum, charging the resultant product directly on a silica gel (Merck, 100 mesh) column, and eluting it with a 4:6 ethyl acetate/n-hexane mixture. NMR and mass spectroscopy were used to characterize each product.

3.3. Characterizations of 1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl) ethenone derivatives:

1). Compound(4a):

Yellow liquid ;Yeild-80%; M.p-178-180^{0}C; ^{1}HNMR(400MHz, $CDCl_3$) δppm :7.874-7.325(m,10H,Ar-H), 6.124 (s, 1H, pyrrole) , 1.587(s,3H,CH_3), 0.957 (s,3H, CH_3), ^{13}CNMR (100MHz, $CDCl_3$) ppm: 194.14, 139.46, 135.77, 130.57, 129.65, 128.91, 128.25, 127.77, 126.66, 125.75, 123.82, 121.59, 118.45, 109.57, 28.94, 15.86 .LCMS(m/z):275.76[M^{+}-+H)]; Molecularformule:$C_{19}H_{17}NO$. Elemental analysis: calculated: C-82.78, H-6.21, N-5.08, Obtained: C-82.70, H-6.20, N-5.15.

2). Compound (4b):

PaleYellowliquid;Yeild-88%,^{1}HNMR(400MHz,$CDCl_3$)δppm:8.912(s,1H,-OH),7.736-7.583 (m, 2H,Ar-H),7.514-6.90(m,9H,Ar-H)),6.118(s,1H,pyrrole),1.676(s,3H,CH_3),0.974(s,3H,CH_3); ^{13}CNMR(100MHz,$CDCl_3$)ppm:195.52, 140.95, 135.47, 131.38, 129.70, 128.77, 127.24, 126.07, 124.16, 123.72, 120.95, 120.12, 117.77, 109.92, 28.47, 16.24 ;LCMS(m/z):292.78 [M+H];Molcularformulae:$C_{19}H_{17}NO_2$;.Elementalanalysis:calculated:C-78.35,H-5.87,N-4.82, Obtained:C-78.27,H-5.85,N-4.88.

3). Compound (4c):

Yellow liquid;Yeild-90%.^{1}HNMR(400MHz,$CDCl_3$)δppm:9.124(s,1H,-OH),7.768-7.315 (m,7H, Ph), 6.148 (s,1H), 2.125 (s, 3H, CH_3), 1.659 (s, 3H, CH_3) ; ^{13}CNMR (100MHz, $CDCl_3$) :194.77, 142.56, 137.61, 134.45, 129.52 , 128.54, 127.16, 126.12, 124.48, 121.66, 121.07, 118.62, 108.82, 28.74, 14.02 : LCMS(m/z) = 292.74[M+H]; Molecularformule: $C_{19}H_{17}NO_2$. ElementalAnalaysis: Calculated: C-78.32, H-5.87, N-4.80, Obtained:C-78.26, H-5.85, N-4.87

4). Compound(4d):

Yellow oil ; Yeil-89% ; ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 7.779-7.141(m, 9H, Ar-H), 6.012(s,1H), 3.772 (s, 3H, OCH_3) , 1.547 (s, 3H, CH_3), 0.978 (s, 3H, CH_3); ^{13}CNMR (100MHz, $CDCl_3$) ppm : 192.51, 134.68, 132.36, 130.85, 129.24, 128.74, 127.46, 126.18, 124.87, 121.45, 120.25, 109.96, 54.48, 28.49, 14.88 : LCMS(m/z) : 306.57 [M^++H]; Molecularformule: $C_{20}H_{19}NO_2$. Elemental Analysis: Calculated: C-78.67, H-6.23, N-4.58; Obtained: C-78.60, H-6.22, N-4.64

5). Compound(4e):

Yellow oil; Yeild-87%; ^{1}HNMR (400MHz, $CDCl_3$) δppm : 7.770-7.312 (m, 9H, Ar-H), 6.110 (s, 1H), 1.986 (s, 3H, CH_3), 0.899 (s, 3H, CH_3) ; ^{13}CNMR (100MHz, $CDCl_3$) δppm: 195.43, 143.56, 138.92, 135.32, 129.71, 128.78 , 128.12, 127.54, 126.67, 122.35, 118.45, 116.64, 29.58, 14.47: LCMS (m/z) = 311.78 [M+2]; Molecular formulae :$C_{19}H_{16}ClNO$. ElementalAnalaysis: Calculated: C-73.60, H-5.21, N-4.52, Obtained:C-73.56, H-5.20, N-4.59

6). Compound (4f):

Yellowoil;Yeild-85%; ^{1}HNMR (400MHz, $CDCl_3$)δppm : 7.807 - 7.286(m, 7H, Ar-H), 7.128 (s, 1H, Ar-H), 6.115(s,1H), 1.775 (s, 3H, CH_3), 1.113 (s, 3H, CH_3), 0.952 (s, 3H, CH_3) ; ^{13}CNMR 100MHz, $CDCl_3$) δppm : 195.92, 138.25, 135.43 , 129.88, 129.14, 128.81, 128.24, 127.25, 125.71, 123.84, 121.78, 120.60, 119.94, 110.45, 28.56, 17.73, LCMS (m/z) = 367.81 [M+H] ; Molecularformule:$C_{20}H_{18}BrNO$: Elemental Analysis : Calculated : C-65.25, H-4.90, N-3.82: Obtained: C-65.18, H-4.88, N- 3.87

7). Compound (4g):

Yellowoil;Yeild-89%; ^{1}HNMR (400MHz, $CDCl_3$) δppm: 8.117-7.220 (m, 9H, Ar-H)), 6.270 (s, 1H),1.171 (s, 3H, CH_3), 1.544 (s, 3H, CH_3), 0.994 (s, 3H, CH_3), ^{13}CNMR (100MHz, $CDCl_3$)δppm;192.72,135.75,132.74, 131.02, 130.17, 129.76, 128.45, 127.73, 127.12, 126.74, 124.09,123.18,120.09,108.62,29.74,13.41;Molcularformulae:$C_{19}H_{16}BrNO$; LCMS (m/z) = 356.41[M+2].ElementalAnalaysis:calculated:C-64.42,H-4.55,N-3.95,Obtained:C-64.36,H-4.54,N-4.03.Molcularformulae:$C_{20}H_{17}NO_3$;ElementalAnalaysis: Calculated: C-75.22, H-5.37, N-4.39, Obtained: C-75.15, H-5.36, N-4.45.

8). Compound (4h):

Yellow oil; Yeild-85%; ^{1}HNMR (400MHz, $CDCl_3$) δppm: 8.015-7.445 (m, 7H, Ar-H), 6.20 (s, 1H),1.759(s,3H, CH_3), 1.198 (s,3H, CH_3)),^{13}CNMR (100MHz, $CDCl_3$)δ ppm: 195.28,145.90, 139.41, 132.71, 129.60, 128.77, 128.24, 126.51, 124.15, 123.62, 121.55, 120.71, 119.14,108.60, 29.77, 14.46. LCMS (m/z) δ ppm: 319.49[M+-H); Molecularformule: $C_{20}H_{17}NO_3$Elemental Analysis: Calculated: C-71.24, H-5.03, N-8.74, Obtained: C-71.18, H-5.02, N-8.81.

3. BIOLOGICAL ASSAY:

ANTIBACTERIAL SCREENING:

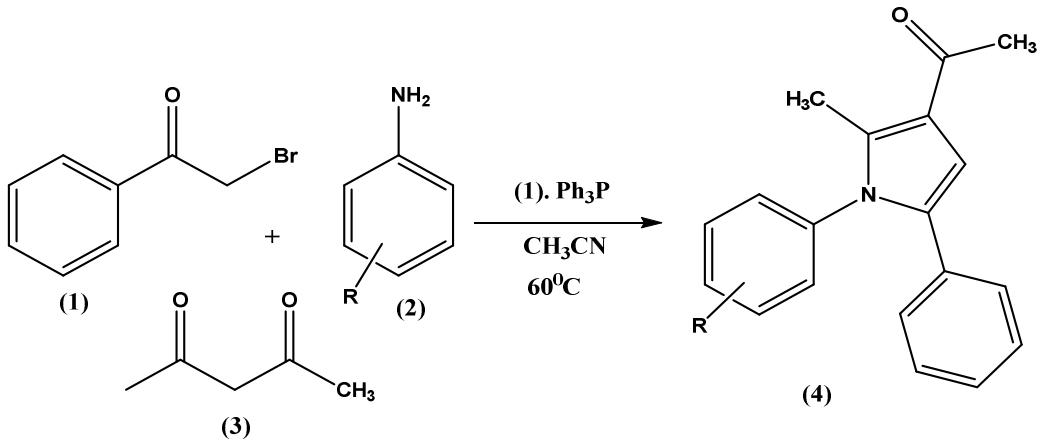
The antimicrobial activity of titled derivatives **(4a-4h)** compounds tested by the diffusion method against various bacteria such as B. subtilis, S. aureus, E. coli, P. aeruginosa. For the detection of antibacterial activities, the filter paper disc diffusion method was used. Cifrafloxin was used as standard antibiotic for antibacterial activities. Nutrient agar (NA) was used as as basal medium for test bacteria. The agar media were inoculated with 0.5ml of 24h liquid cultures containing 10^7 microorganisms/ml. Diffusion time was 24 h at 25^{o}C for all bacteria, and incubation time was 36 h at 37^{o}C. Discs with only DMSOwere used as control. The results of our tested derivatives were presented as the inhibition zones, given in millimeters (mm). The compound that exhibited best antimicrobial activity was further tested by the dilution method.

Antifungal screening:

Antifungal activities of titled compounds were studied (**4a-4h)** towards one human pathogenic and mould fungi. *Candida albicans* (human pathogen), *Aspergillus niger* (mould) and *Aspergillus flavus* (mould). Antifungal activity was assessed by the poisoned food technique in a modified condition**.** Fluconazole was used as standard fungicide. Potato dextrose agar (PDA) was used as basal medium fungi. Glass Petri dishes were sterilized. Sterilized melted PDA medium (45^0C) was poured at the rate of 15 ml into each Petridis (90 mm). After solidification of the medium, small portions of the mycelium of each fungus were spread carefully over the centre of each PDA plate with the help of sterilized needles. Therefore, each fungus was transferred to number of PDA plates, which were then incubated at (25 ± 2)^{o}C and ready for use after five days of incubation. Prepared discs of samples were placed gently on solidified agar plates, freshly seeded with the test organisms with sterile forceps. A control disc was placed on the test plates to compare the effect of the test derivatives and to nullify the effect of solvent respectively. Then the plates were kept in refrigerator at 4^{o}C for 24 h so that the materials had sufficient time to diffuse over a considerable area of the plates. After this, the plates were

incubated a 37^0C for 72 h. Dimethyl sulphoxide (DMSO) was used as solvent to prepare desired solutions (10 mg/ml) of the derivatives initially and maintain proper control.

4. Results and Discussions:



(4a-4h)

R= H, 2-OH, 4-OH,4-CH_3, 4-OCH_3,4-Cl,4-Br,4-NO_2,

(Scheme-1)

Chemistry:

The initial reaction of phenacyl bromide (1 mol), phenyl ethylamine (1 mol) andacetylactone (1mol) in ethanol (15ml) at room temperature acquired low yield (40%) of corresponding pyrrole derivatives even after stirring for extended time (8 hr). Even after heating the reaction mixture at 76°C for 5 hr did not increase yield of the derivatives. However, the reaction was forced to completion by the addition of catalytic amount Ph_3P (5mol %) and desired derivatives of pyrrole were isolated in high yield (87%). After extensive evaluated of the

mole ratio (3mol,5mol,10mol %) of Ph_3P, we observed that 5 mol% was suitable for maximum conversion of product.

The improved in the mole ratio of Ph_3P did not improve the yield. Among the solvents like, water, Toluene, Acetonitrile, DCM, Ethanol, methanol, Ethanol appears to acquire the best result. This remarkable development for the catalytic activity of DBU give an incentive for further study of reactions with other substituted aryl amines, Ph_3P has been found to be superior to other tertiary amines as catalyst for a variety of organic reactions in recent years [20-23]. DBU is one of the strongest organic neutral base and mesmeric +M effect of the adjacent nitrogen stabilizes the protonated species.

We have studied the reaction of various substituted aryl amines and phenacyl bromides to describe the generality of method and the results are summarized in **Figure-I**. Substituted aryl amines possessing electron releasing substituent's like, hydroxyl (entries 4b and 4c), methoxy (entries 4d), are smoothly reacted with phenacyl bromides to give desired high yield product. Similarly, halogen substituted aryl amines (derivatives 4e, 4f, 4g and4h) reacted with phenacyl bromides and resulted into expected pyrrole in good yield. In addition to this, the reaction of electron attracting substituted aryl amines (derivatives 4e, 4f,4g and 4h) with phenacyl bromides and resulted into pyrrole in moderate yield of expected product. The evaluation of titled derivatives by spectral analysis reveals that the proton values of the –OH protons at 8.935 and 8.874 ppm of the derivatives "4b" and "4c" respectively. The–OCH_3protons showed at 3.674ppmofthe derivative "4d". The ^{13}CNMR values of carbonyl carbon showed at 197.27ppm of derivative "4h".

Biological evaluation:

Antibacterial activities:

The antibacterial activities of newly synthesized compounds (**4a-4j)** have been assayed against four pathogenic bacteria. Among these pathogens, two were gram-negative and other two were gram-positive. Inhibitory effects of compounds (**4a-4j)** against these organisms are given in **table -I**. The screening results evidenced that the compounds 4i and 4j did not show any antibacterial activity to the bacteria tested. We observed experimental data and also found that the titled compounds with halogen substituent are the most efficient against Gram-positive

bacteria and Gram negative bacteria, particularly against E.coli and P.aeruginosa. The bromoderivatives (4e, 4f, 4g, 4h) are of a particular interest since the strong electron-

withdrawing effect of chlorine and bromine groups contributes to molecule's biological properties. The iso steric substitution of hydrogen by chlorine, bromine in 1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl) ethenone compounds increases the lipophilicity and thus improve the rate of cell penetration, which is a very importance of drug efficiency. The compounds such as 4b, 4c, 4d and 4e exhibited moderate active potential towards every bacterium tested due electron donating groups and low lipophilicity and slowly increases the rate of cell penetration while compound 4a showed very low active potent against E. coli, P. aeruginosa, B. subtilis, S. aureus due it does not possess electron donating groups and electron withdrawing groups.

Table-I: Antibacterial activity of the Titled derivatives (4a-4h).

Zones of inhibition (mm) of compounds against tested bacterial strains:

Entry	Anti-Bacterial Activity			
	E. coli	***P. aeruginosa***	***B. subtilis***	***S. aureus***
4a	06	10	08	09
4b	14	16	12	15
4c	15	13	12	16
4d	12	15	16	15
4e	21	20	16	17
4f	20	21	19	18
4g	21	20	18	16
4h	19	21	21	14
Cifrafloxin	27	27	25	25
DMSO	**-**	**-**	**-**	**-**

Antifungal activities:

The antifungal activities of newly synthesized compounds (**4a-4j)** have been assayed against three pathogens mould fungi. The inhibitory effects of these compounds against above organisms are given in **table –II.** The screening results reveals that the compounds **4a, 4i** and **4j** showed low antifungal activities and the derivatives of titled compound such as **4b,4c,4d and 4e** exhibited moderate activity against the three pathogens while the compound **4f,4g, and 4h** showed good antifungal activities at high concentration against three pathogens as compared to standard drug viz;Fluconozole. The antifungal activity of the tested compounds indicated that the value of inhibition zone of all the derivatives exhibited lower in ***C. albicans*** than the **Aspergillus Niger and Aspergillus flavus.** We observed the these results, the compounds possessing hydroxyl group and methoxy group which showed moderate values due partially activate potato molecules. The derivatives "4i and 4j" having electron withdrawing groups which inactive nature of biological active potential where as 4f,4g,and 4h derivatives containing electron withdrawing groups nature but having lone pair of elections.

Table-II: Antifungal activity of the Titled derivatives.

Zones of inhibition (mm) of compounds (4a–4h) against tested fungal strains:

Entry	Anti-Fungal Activity		
	A. Niger	**A. flavus**	**C.albicans**
4a	07	05	06
4b	11	13	13
4c	12	10	10
4d	10	12	10
4e	10	08	11
4f	18	18	15
4g	15	16	11

4h	10	09	08
Fluconazole	22	22	22
DMSO	**-**	**-**	**-**

CONCLUSION*:*

The present work describes a rapid, convenient and highly efficient synthesis of biologically valued 1-(2-methyl-1, 5-diphenyl-1H-pyrrol-3-yl) ethanone derivatives is achieved utilizing organ base by Ph3P base -catalyzed reaction of in ethanol under conventional refluxing conditions. The operational simplicity, good yields short reaction times and use of safe and readily available base catalyst and it a preferred procedure for the synthesis of these compounds. In additionally the evaluation of antimicrobial activity of the titled compounds.

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