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PPh_3 Promoted by an Efficient Synthesis of Series of 1-(2-methyl-1, 5-diphenyl-1H-pyrrol-3-yl) Ethanone Analogous and Bioevluation

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ABSTRACT:

In an attempt to find new class antibacterial agent of series 1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone(4a–4j)weresuccess fully synthesized from phenacyl bromide ,substituted aryl amine and Aetylacetone in the presence of organic base such as PPh3 promoted 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 aryl amines; PPh3; 1-(2-methyl-1, 5-diphenyl-1H-pyrrol-3-yl) ethanone. Antimicrobial activity.

I. INTRODUCTION

The Pyrrole derivatives and analogues are organic five membered heterocyclic compounds with an extensive and fascinating chemistry. Porphyria and porphyria 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 such as virus inhibition and specialized inhibition of HIV virus(5),antibacterial,antimycotic(6),cholesterol-lowering(7),antipsychotic,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].

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] . 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 analgueous Pyrrole is the heterocyclic compound constructed from phenacyl bromide, acetyl acetone with substituted aryl amine in presence of this is safest and abundantly available solvent. Now days, has focused to emerge as a promoter for synthesized derivatives in various organic reactions. It is an organic base which acts as Nucleophile, exceedingly soluble in water. The continuation our research works to develop environmentally friendly reactions.

Hence, we wish to report a simple, an efficient, practical and general one pot synthesis multi component reaction for the construction of 1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone derivatives by the reaction of substituted phenacyl bromide, substituted aryl amines with Aetylacetone in aqueous medium in the presence of This is safest and abundantly available solvent. Now days, has focused to emerge as a promoter

for synthesized derivatives in various organic reactions. It is an organic base which acts as Nucleophile, exceedingly soluble in water. The continuation our research works to develop environmentally friendly reactions and also study the antimicrobial activity as shown in (**Scheme-1**).

2.MATERIALS AND METHODS:

2.1. Experimental:

All reagents and starting materials were purchased from Sigma-Aldrich commercial suppliers and used without any further purification. All reactions and the purity of the newly synthesized derivatives were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel F254 plates (Merck) using ethyl acetate and n-hexane(4:6) as eluents. The spots of the desired product were detected either under UV light or by placing in an iodine chamber. All the compounds were routinely checked by 1H NMR and mass spectrometer. ^{1}H NMR spectra were recorded on a Bruker AVANCE II 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz The chemical shift were recorded in parts per million (ppm) with TMS as internal reference. Mass spectra were recorded on mass spectrometer using Argon/Xenon (6 kV,mB) gas. Column chromatography was performed on silica gel (Merck). Anhydrous sodium sulfate was used as a drying agent for the organic phase.

2.2. General Procedure

A mixture of phenacyl bromide (1mol), acetyl acetone (1mol), substituted aryl amine (1mol) and PPh_3catalyst(5mol%) was stirred in 15ml ethanol at 75°C for the appropriated time. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine solution and dried over Na_2SO_4. The organic layer was concentrated under vacuum and the resulting product was directly charged on a silica gel (Merck, 100 meshes) column and eluted with a mixture of ethyl acetate/n-hexane (4:6) to afford the corresponding pure product. All the products were characterized by mass and NMR spectroscopy.

Characterizationsof1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone derivatives :

2.2.1).1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone(4a):

Yellow oil; M.p-178-180^{0}CYeild-87%;^{1}HNMR(400MHz,$CDCl_3$)δppm:7.964-7.355 (m, 10H,Ar-H),6.214(s,1H,pyrrole), 1.487(s,3H,CH_3), 0.945(s,3H,CH_3), ^{13}CNMR(100MHz, $CDCl_3$)ppm:195.14,139.46,133.77,130.74,129.07,128.88,128.25,127.64,126.68, 125.16, 123.80,120.46, 118.45,109.54,28.91,13.87. LCMS(m/z): 274.75(M^+-H);Molecular formula: $C_{19}H_{17}NO$. Elemental analysis: calculated:C-82.88, H-6.22, N-5.09, Obtained: C-82.81, H-6.21, N-5.18.

2.2.2).**1-(1-(4-hydroxyphenyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl)ethanone (4b):**

Yellowoil;M.p-189-191^{0}C;Yeild-88%.^{1}HNMR(400MHz,$CDCl_3$)δppm:9.125(s,1H,-OH), 7.868-7.347(m,7H,Ar-H),6.251(s,1H,Pyrrole ring), 2.325(s,3H, CH_3), 1.896(s,3H,CH_3); ^{13}CNMR (100MHz, $CDCl_3$)δppm:192.54,142.37, 137.64,135.05,129.08, 128.71,127.37, 126.79,124.44,122.84,120.75,118.57,107.81,28.90,13.07:LCMS(m/z)=291.11[M^+];
Molecularformule:$C_{19}H_{17}NO_2$.Elementalanalysis:calculated:C-78.33H-5.88,N-4.81, Obtained:C-78.25,H-5.87,N-4.96.

2.2.3)1-(1-(4-methoxyphenyl)-2-methyl-5-phenyl-1H-pyrol-3-yl)ethanone(4c):

Yellow oil; M.p-194-196^{0}C;Yeil-90%;.^{1}HNMR(400MHz,$CDCl_3$)δppm:7.875-7.441(m, 7H,Ar-H),7.158-6.975(m,2H,Ar-H), 6.126 (s,1H,pyrrolering), 3.767(s,3H,OCH_3),1.562 (s,3H,CH_3),0.989(s,3H,CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm:194.51,136.78,132.16, 130.07,129.05,128.77,127.35,126.71,123.76,120.15,119.24,109.97,53.08,29.44.,14.18:
LCMS(m/z):306.17[M^++H];Molecularformule:$C_{20}H_{19}NO_2$.ElementalAnalaysis: calculated: C-78.66, H-627, N-4.59, Obtained: C-78.61, H-6.27, N-4.63.

2.2.4)1-(1-(4-Chlorophenyl)-2-methyl-5-phenyl-1H-pyrole-3-yl) ethanone(4d):

Yellow oil; M.p-198-200^{0}C;Yeild-88%;^{1}HNMR(400MHz,$CDCl_3$)δppm:97.70-7.332 (m, 9HAr-H),6.110 (s,1H,pyrole), 1.596 (s,3H,CH_3), 0.945(s,3H,CH_3);^{13}CNMR(100MHz, $CDCl_3$)δppm:192.78,141.56,137.91,135.32,129.54,128.79,128.19,127.28,125.57,121. 05,120.45,118.64, 30.02,14.35.:LCMS(m/z)=311.58[M+2];Molcularformulae: $C_{19}H_{16}ClNO$.Elementalanalysis:calculated:C-73.60,H-5.21,N-4.52, Obtained:C-73.56,H-5.20,N-4.58.

2.2.5).1-(1-(4-bromo-2-methylphenyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl)ethanone (4e):

Yellowoil;M.p-195-197^{0}C;Yeild-89%;^{1}HNMR(400MHz,$CDCl_3$):δppm:7.867-7.545(m,5H,Ar-H),7.437-7.274(s,2H,Ar-H),7.254(s,1H,Ar-H), 6.150 (s,1H,pyrrolering),1.575(s, 3H,CH_3),1.123(s,3H,CH_3),0.892(s,3H,CH_3);^{13}CNMR100MHz,$CDCl_3$)δppm:195.09, 137.57,134.49, 129.56,

129.07,128.78,128.21,127.55,125.74,123.41,120.77,118.64,116.94,109.45,30.14,18.73,12..84;LCMS(m/z)=367.87[M+H];Molecularformule: $C_{20}H_{18}BrNO$.:Elementalanalysis:calculated:C-65.23,H-4.93, N-3.80: Obtained: C-65.19, H-4.92, N-3.86.

2.2.6).1-(1-(4-bromophenyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl)ethanone(4f):

Yellowoil;M.p201203^{0}C;Yeild90%;1HNMR(400MHz,CDCl3)δppm:8.0127.484(m,9H),6.190(s,1H),1.688(s,3H,CH_3),0.954(s,3H,CH_3);^{13}CNMR(100MHz,$CDCl_3$)δppm ppm:195.40,137.09,133.95,130.46,129.19,128.87,128.44,127.41,126.47,124.26,123.07,120.39,108.58,29.46,13.27;

Molecular formulae: $C_{19}H_{16}BrNO$;LCMS(m/z)- 354.25, [M+1]+;ElementalAnalaysis:calculated:C-64.42,H-4.55,N-3.95,Obtained:C-64.38,H-4.54,N-4.04.;

2.2.7) 1-(2-metyl-1-(4-nitrophenyl)-5-phenyl-1H-pyrole-3-yl) ethanone (4g):

Yellowoil;M.p-205-207^{0}C;Yeild-84%;^{1}HNMR(400MHz,$CDCl_3$)δppm:8.215-8.027(m,2H,Ar-H),7.871-7.445(m,7H,Ar-H),6.020 (s,1H,pyrrolering);1.489(s,3H,CH_3),0.948 (s,3H,CH_3),^{13}CNMR(100MHz,$CDCl_3$)δppm:196.27,144.92,138.45.133.76,129.06,128.90,128 .25,126. 58,125.01,122.72,121.04,120.75,118.24,109.62,29.74,14.46;.LCMS(m/z):318.77[M+-H)(fig-12);Moleculerformule:$C_{20}H_{17}NO_3$Elemental Analysis: Calculated: C-71.24, H-5.03, N-8.74, Obtained: C-71.18, H-5.02, N-8.81.

3.BIOLOGICAL EVALUATION:

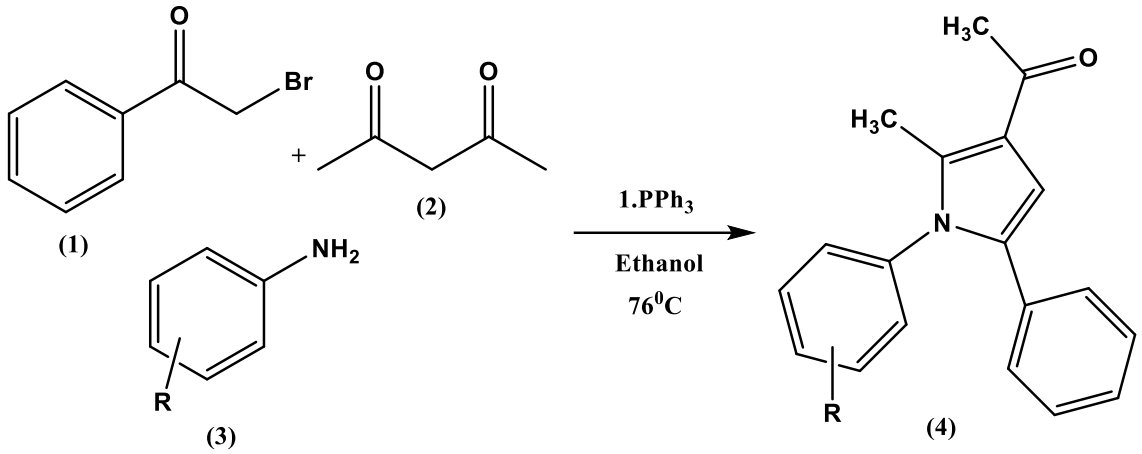
ANTIBACTERIAL SCREENING:

The antimicrobial activity of 1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone**(4a-4g)** compounds tested by the diffusion method against various bacteria such as B.subtilis , S.aureus, Escherichia coli , P.aeruginosa .For the identification of antibacterial activities, the filter paper disc diffusion method **(14, 15)** was used. Cifraflaxin 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 25ºC for all bacteria, and incubation time was 36 h at 37ºC. 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-4g)** towards one human pathogenic and mould fungi. *C. albicans* , *A. niger* and *A. flavus*. Antifungal activity was assessed by the poisoned food technique,(**17)** in a modified condition**.(18)** 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^{0}C) 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)ºC 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 4ºC 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^{0}C 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-4g)

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

(Scheme-1)

Chemistry:

The initial reaction of phenacyl bromide (1 mol), phenyl ethylamine (1 mol) and Aetylacetone (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 PPh_3(5mol %) and desired derivatives of Pyrrole were isolated in high yield (87%). After extensive evaluated of the mole ratio (3mol, 5mol, 10mol %) of PPh3, we observed that 5 mol% was suitable for maximum conversion of product. The improved in the mole ratio of PPh_3did 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 PPh3 give an incentive for further study of reactions with other substituted aryl amines. 1,8-diazabicyclo[5.4.0]undec-7-ene PPh_3 has been found to be superior to other tertiary amines as catalyst for a variety of organic reactions in recent years [20-23]. PPh_3 is one of the strongest organic neutral bases 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 and Substituted aryl amines possessing electron releasing substituent's like, hydroxyl (entries 4b and 4c), methoxy (entries 4d), are smoothly reacted with phenacyl bromides to gave desired high yield product. Similarly, halogen substituted aryl amines (entries 4e, 4f, 4g) reacted with phenacyl bromides and resulted into expected Pyrrole in good yield. In addition to this, the reaction of electron attracting substituted aryl amines (entries 4e, 4f,4g) 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 –COOH group showed at 11.49ppm of the derivative (4b).The –OH protons at 8.93 and 8.87 ppm of the derivatives "4b" and "4c"respectively.The–OCH_3protons showed at3.674ppmofthe derivative "4d".The ^{13}CNMR values of carbonyl carbon showed at 194.27ppm of derivative.

4.2. BIOLOGICAL EVALUATION:

ANTIBACTERIAL ACTIVITIES:

The antibacterial activities of newly synthesized compounds (**4a-4g)** 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-4g)** 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) are of a particular interest since the strong electron-withdrawing effect of chlorine and bromine groups contributes to molecule's biological properties. The isosteric substitution of hydrogen by chlorine, bromine in 1-(2-methyl-1,5-diphenyl-1H-pyrrol-3-yl)ethanone 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 bacteria 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 1-(2-methyl-1, 5-diphenyl-1H-pyrrol-3-yl) ethanone (4a-4g).

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

Entry	**Anti-Bacterial Activity**			
	E. coli	***P. aeruginosa***	***B. subtilis***	***S. aureus***
4a	04	06	08	07
4b	15	17	14	15
4c	15	13	12	16
4d	12	15	16	15
4e	21	20	18	18
4f	20	22	19	18
4g	10	08	08	09
Cifraflaxin	25	25	22	22
DMSO	-	-	-	-

Antifungal activities:

The antifungal activities of newly synthesized compounds **(4a-4g)** 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 showed low antifungal activities and the derivatives of titled compound such as 4b,4c,4d and 4e exhibited goof activity against the three pathogens while the compound 4e,4f showed excellent 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 A.niger and A 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 4e and ,4f derivatives containing electron withdrawing groups nature but having lone pair of elections.

Table-II: Antifungal activity of the 1-(2-methyl-1, 5-diphenyl-1H-pyrrol-3-yl) ethanone derivatives. Zones of inhibition (mm) of compounds (4a–4j) against tested fungal strains:

Entry	**Anti-Fungal Activity**		
	A.Niger	**A. flavus**	**C. albicans**
4a	05	06	05
4b	14	14	15
4c	13	14	10
4d	11	12	14
4e	15	16	18
4f	17	17	16
4g	08	05	08

Fluconazole	20	20	20
DMSO	-	-	-

5. CONCLUSION*:*

The present work describes a rapid, convenient and highly an efficient synthesis of biologically valued 1-(2-methyl-1, 5-diphenyl-1H-pyrrol-3-yl) ethanone analogous is achieved utilizing base by PPh_3catalyzed 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 derivatives

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