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SYNTHESIS OF 3-CHLORO-1-PHENYL-4-(1,3-DIPHENYL-1H-PYRAZOL-4-YL)AZETIDIN-2-ONE

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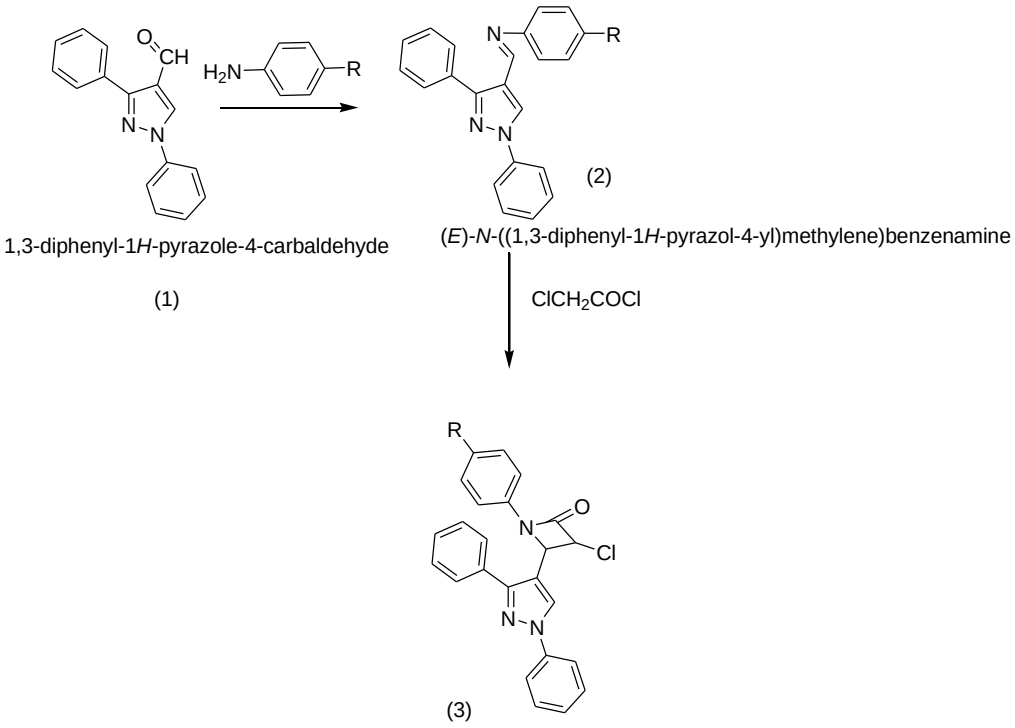
ABSTRACT
Schiff base synthesis of 3-chloro-1-phenyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)azetidin-2-one were carried out by the condensation of (1,3-diphenyl-1H-pyrazole-4-carbaldehyde with schiff base to obtain (E)-N-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)benzenamine. This reaction was subjected in Chloroacetyl chloride. .The structure of these newly synthesized compounds were characterised by ^{1}H NMR,^{13}CNMR ,Mass ,IR, and elemental analysis.

KEYWORDS;- *Azetidinones, Schiff base,* β- *Lactam, pyrazol*

INDRODUCTION
Heterocyclic compounds represents an important class of biological molecules. The heterocyclic molecules which possess pyrazole and azetidine moieties exhibit wide range of biological activities. Pyrazole derivatives found to possess high range of biological activities which includes antibacterial [I,II] analgesic[1], antipyretic[ii], antifungal[iii], antiflamatory [iv,viii] anthelmintic [vii],cardiovascular[viii] ,anticonvalsant[ix], and selective COX-2 inhibitary activities[xiii,xvi], anticonvalsant[ix], and selective COX-2 inhibitory activities [xiii,xvi]
The chemistry of pyrazolone and its derivatives were found to play an important role in medicinal chemistry herbicidal [x], fungicidal [xi], bactericidal [xii], anti-flammatory [xiii], antipyretic [xiv] antiviral [xv], bloodpressure [xvi] lowering [x]and protease inhibitors [xvii]agents.
Azetedine skleton was found in β-lactam antibiotics, which were the most widely employed class of antibiotics. Azetidine derivatives were reported to show a variety of antimicrobial , antitubercular, anticonvulsant, antitlammatory [xvii,xviii,xxii] and cardiovascular activities. In view of above observations found in literature, we have reported an efficient synthesis for indole derivatives containing pyrazolone moiety besides β-lactam ring.

MATERIALS AND METHODS

Melting points were determined on open capillaries using a cintex melting point apparatus . T.L.C. analysis were performed on precoated silica gel (E-Merck Kieselgel 60 F_{254}) plates and visualisation was done by exposing to iodine vapour. Solvent were purified by standard procedures before use. Column chromatography was conducted by using Silica gel with different solvent systems as elutes. IR Spectra were recorded KBr on perkin –elmer spectrum BX series FTIR spectrometer.H^1-NMR spectrum were recorded on varian zemini 300MHz and 200MHz spectrometers using TMS as internal standard(chemical shifts in & ppm) C^{13}NMR spectra were recorded on a brucker 75MHz spectrometer . Mass spectra were scanned on a varian MATCH -7 and jeol JMSD-300 mass spectrometer at 70 ev. Elemental analysis were carried out on carloerba 106 and perkin –analyser . All the chemicals used in the present investigation were purchased from Aldrich chemicals .



3-chloro-1-phenyl-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)azetidin-2-one

COMPOUND	**3(a)**	**3(b)**	**3(c)**	**3(d)**	**3(e)**	**3(f)**
R	**H**	**CH_3**	**OCH_3**	**Br**	**CF_3**	**NO_2**

Synthesis of (E)-N-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)benzenamine(2)

Equimolar quantity of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde were dissolved in absolute alcohol, to this three drops of aceticacid is added then heated on a steam bath for 5-6 hrs at 100^0C. After standing for 24hrs at room temperature, the product was dried and recrystalised from warm absolute alcohol. The separated solid was identified as (E)-N-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)benzenamine Yield 70%,m.p.:150-156^0C

IR Spectra (√, cm^{-1}):

IR (KBr) spectrum of (E)-N-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)benzenamine was recorded in the range 4000-667cm^{-1} and IR absorption signals were found at 3032 (√ Ar-H),

2980 and 2960 (√ aliphatic CH_2 and CH_3), 1760 (√ CO of ester group), 1610(√ C=N group) and 1182(√ C-O-C of ester group).

^{1} H NMR spectra(300MHZ,$(CD)_2$ SO,TMS):δ;

^{1}H NMR Spectra (E)-N-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)benzenamine was recorded in DMSO-d6 solvent. The NMR signal of ethyl 2-(3-phenyl imino)metyl was found at $\delta_{PPm,}$ 1.29(t,3H, J=13.2Hz, CH_3 of ethyl group), 4.13 (q, 2H, J=13.2Hz, CH_2 of ethyl group), 4.78(s, 2H, N-CH_2 group) and 6.92 , 7.58 (m, 10H, C_8H_5N nucleus and C_6H_5 phenyl nucleus) and 8.44(s, 1H, N=CH group).

Synthesis of 3-chloro-1-phenyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)azetidin-2-one(3)

The compound (2) was converted into azetidine-2-one on treatement with chloroacetyl hloride. The formation compound was conformed by IR,NMR data.

IR spedtra ; The compound (3) shows signals at, 1610(C=N), 1760 (ester –C=O), 3032(Ar-H),1182(-C-O-C)

^{1}HNMR spectra ;1.29(t,3H,CH_3 of C_2H_5), 4.78(s,2H N-CH_2-C =O), 4.13(q,2H,-O-CH_2 Of OC_2H_5), 6.92-7.58(m,10H,Ar-H,8.44(N=CH).Table: 2.2 1H NMR spectra of 3-chloro-1-phenyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)azetidin-2-one(3)

Anti-Bacterial Activity:

The antibacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacteria screened were staphylococcus aureus NCCS 2079 . The gram negative bacteria screened were Escherichia coli NCCS 2065 and pseudomonas aeruginosa NCCS 2200.

The synthesized compounds were used at the concentration of 250µglml and 500µglml using DMSO as a solvent, the Ciprofloxacin 10µglml disc was used as a standard .(Himedia, Laboratories Ltd, Mumbai).

The test results presented in the table -1,suggest that 4b,4d,4e exhibit high activity against the tested bacteria, the rest of the compounds were found to be moderate active against the tested microorganisms.

Antifungal activity

The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of Penicillium and Trichophton.

Compounds were treated at the concentrations of 500µglm and 1000µglml using DMSO as solvent. The standard used was Cyclopiroxolamine 50µglml against both organisms.The test results were presented in the table-2.

TABLE.- 1 Antibacterial activity by disc diffusion method of pyrazole linked azetedene. 3(a.f)

Compound	Zone of inhibition (mm)			
	E.Coli	Staphylococcus	Klebsiella	Pseudomonas aeruginosa
3a	7.5(18)	6.5(20)	7.0(18)	7.5(18)
3b	12(15)	11(15)	14(18)	11(18)
3c	12(10)	-	-	13.5(15)
3d	11(14)	-	8.5(12)	-

3e	14(15)	-	7.5(11)	-
3f	9(18)	9(16)	7.5(18)	-
Ciprofloxacin	6.25(30)	6.25(30)	6.25(27)	6.25(28)

Table-;2 Antifungal activity by disc diffusion method for pyrazole linked azetedine. 3(a.f)

Compound	Zone of inhibition (mm)	
	Penicillium	Trichophton
3a	9.5(18)	7.5(18)
3b	13(15)	12(11)
3c	12(10)	-
3d	14(15)	-
3e	10(12)	-
3f	8.5(16)	7.5(18)
Cyclopiroxolamine	7.5(27)	3.12(30)

Conclusions:

1. Further more the substitution with phenyl group having a chloro group at p-position showed better activities.
2. The azidines showed better anti-inflammatory and analgesic activities.
3. Pyrazolone and its derivatives were found to play an important role in medicinalchemistry as herbicidal, fungicidal, bacterial, antiflammatory.

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