International Research Journal of Natural and Applied Sciences
ISSN: (2349-4077)
Impact Factor 5.46 Volume 5, Issue 5, May 2018
Website- www.aarf.asia, Email : editor@aarf.asia , editoraarf@gmail.com

Synthesis and biological evaluation of (4-substituted benzylidene)-3-methyl-1-(substituted phenyl sulfonyl and substituted benzoyl)-1H-pyrazol-5(4H)-one as anti-inflammatory agent

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Abstract

The Synthesis of 5-methyl -2,4-dihydro-3H-pyrazole-3-one is prepared by the cyclisation reaction between ethylacetoacetate and hydrazine hydrate in absolute alcohol**.(compound 1).** 5-methyl -2,4-dihydro-3H-pyrazole-3-one react with substituted benzaldehyde to prepare 4-(4-substituted benzylidene)-5-methyl-2,4-dihydro-3H-pyrazol-3-one **(compound 2)**. 4-(4-substituted benzylidene)-5-methyl-2,4-dihydro-3H-pyrazol-3-one and substituted benzoyl chloride and substituted benzene sulfonyl chloride and add Triethylamine1 to2 drops and stirring for 4 hr and evaporate Trietylamine on water bath and product of (4-Substituted benzylidene)-3-methyl-1-(Substituted Phenyl Sulfonyl and substituted benzoyl)-1H-pyrazol-5(4H)-one**(compound 3 and 4)** obtained

Keywords: Ethylacetoacetate**,** Hydrazine hydrate, Trietylamine, substituted benzaldehyde,p-toluene sulfonyl chloride, Benzoyl chloride

Introduction

The pyrazole ring is a prominent structure found in numerous pharmaceutically active compounds. This mainly due to the easy preparation and important biological activity.Pyrazole framework plays an essential role in biologically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemistry[1-5]. The pyrazole nucleus is a ubiquitous feature of fertile source of medicinal agents such as antibacterial, antifungal, antiviral, antitubercular, antiamoebic, antiandrogenic etc. Some of this compounds have also exhibited anti-inflammatory,antidiabetic,anaesthetic,analgesic and antiparasitic properties.Many pyrazole have been found to be luminescent and fluorescentagents.In addition pyrazoleshave played a crucial role in the development of theory in heterocyclic chemistry and also used extensively as useful synthon in organic synthesis.It is interesting to note that pyrazole are reported as well known pharmacophores.This has prompted as to synthesize some of the pyrazole derivatives by using substituted benzene sulfonyl chloride and benzoyl chloride. Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. The recent success of pyrazole COX-2 inhibitor has further highlighted the importance of these heterocycles in medicinal chemistry. A systematic investigation of this class of heterocyclic lead revealed that pyrazole containing pharmacoactive agents play important role in medicinal chemistry. The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead. The treatment of pain continues to be the subject of considerable pharmaceutical and clinical research. Microbial infections often produce pain and inflammation. Chemotherapeutic, analgesic and anti-inflammatory drugs are prescribed simultaneously in normal practice. The compound possessing all three activities

is not common. It has been reported that pyrazoline possess analgesic, anti-inflammatory [6-8]. The synthesis of pyrazole and its analogues has been a subject of consistent interest because of the wide range of applications for such heterocycles in the pharmaceutical and agrochemical industries[9].Therefore, extensive research efforts are continually directed at the discovery of new heterocycles with appropriate pharmacological effects. Among their range of properties, the compounds containing a pyrazole scaffold have been shown to exhibit HIV-1 reverse transcriptase and IL-1 synthesis inhibition, as well as antihyperglycemic, antibacterial, sedativehypnotic, anti-inflammatory, antipyretic and analgesic activity[10]. In part, the anti-inflammatory, antipyretic and analgesic properties of pyrazole derivatives have been associated with the inhibition of prostaglandin biosynthesis in the cyclooxygenase step. Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials. Hence, a practical method for the preparation of such compounds is of great interest in synthetic organic chemistry. Pyrazole and its derivatives, a class of well known nitrogen containing heterocyclic compounds, occupy an important position in medicinal and pesticide chemistry with having a wide range of bioactivities such as antimicrobial, anticancer,antiinflammatory, anticonvulsant,, antihyperglycemic, antipyretic, antibacterial, antifungal activities,CNSregulants, and selective enzyme inhibitory activities. It has beenfound that these compounds have hypoglycemic activity, and are also known as inhibitors and deactivators of liver alcohol dehydrogenase and oxidoreductases.

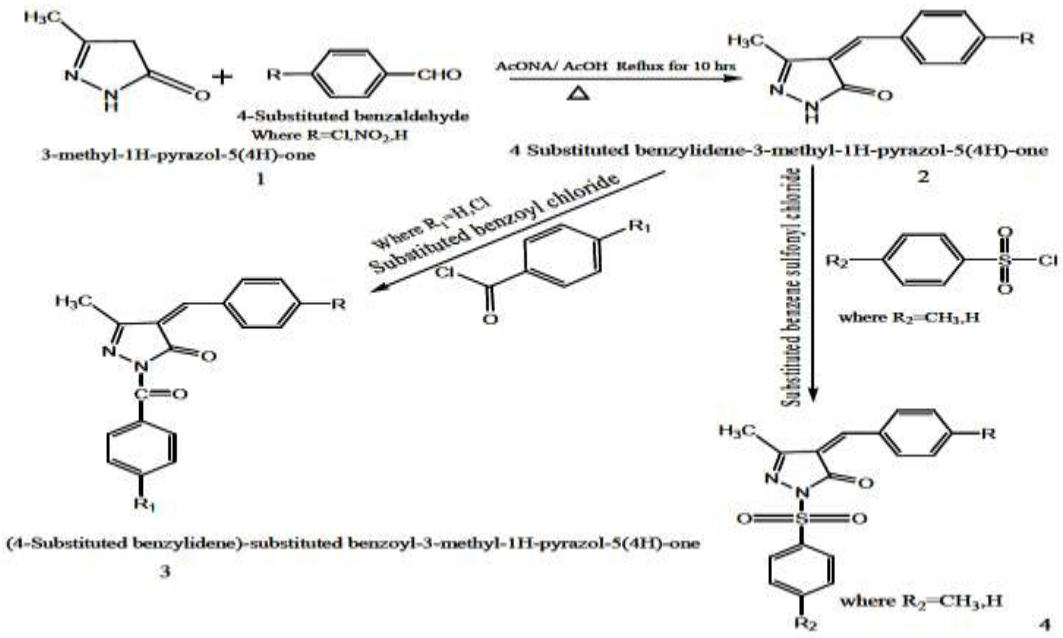
Experimental Section

Melting points were taken in open capillary takes and are therefore uncorrected. Purity of the compound was checked on silica gel GTLC plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system, The visualization of spot was carried out in an iodine chamber.The IR spectra were recorded on Perkin-Elmer spectrometer.The ^{1}H NMR spectra were scanned on a Bruker DRX-300 MHz.Spectrometer (300 MHz) in $CDCL_3$ using TMS as Internal standard and chemical shift are expressed in *δPpm.*

Result and Discussion

In the present work the synthesis of benzene sulfonyl derivatives of some pyrazole from series of reactions was carried out. In order to achieve this aim,5-methyl-2,4-dihydro-3H-pyrazole-3-one was used as starting material, which was prepared by the reaction between etylacetoacetate and hydrazine hydrate in absolute alcohol. Compound 1 on condensation with substituedbenzaldehydes in presence of sodium acetate as a base furnished 5-methyl-4-substituted benzylidene-2,4-dihydro-3H-pyrazole-3-one.Their structure were confirmed by means of IR and ^{1}H NMR spectral analysis

Scheme



((4-Substituted benzylidene)-3-methyl-1-(Substituted Phenylsulfonyl)-1H-pyrazol-5(4H)-one

Table 1-Physical and analytical data of synthesized compound

Compound	Mol.Formula	Mol.wt	R	R_1	R_2	M.P	Yield(%)
1	$C_4H_5N_2O$	98	-	-	-	222^0c	91%
2a	$C_{11}H_9N_2OCl$	220	Cl	-	-	156^0c	70%
2b	$C_{11}H_{10}N_2O$	186	H	-	-	171^0c	68%
2C	$C_{11}H_9N_3O_3$	231	NO_2	-	-	180^0c	69%
3a	$C_{18}H_{13}ClN_2O_2$	324	Cl	H	_	156^0c	60%
3b	$C_{18}H_{13}N_3O_4$	335	NO_2	H	-	168^0c	65%
3c	$C_{18}H_{14}N_2O_2$	290	H	H	-	180^0c	68%
4a	$C_{18}H_{15}ClN_2O_3S$	374	Cl	-	CH_3	200^0c	58%
4b	$C_{18}H_{15}N_3O_5$	385	NO_2	-	CH_3	230^0c	56%
4c	$C_{18}H_{16}N_2O_3S$	340	H	-	CH_3	235^0c	52%

Synthesis of 5-Methyl-2,4-dihydro-3H Pyrazol-3-one

Ethyl acetoacetate (0.1mole) was taken in conical flask and hydrazine hydrate (0.2 mole) in ethanol (20 ml) was added dropwise to it with stirring. The temperature raised during this addition and it was maintained at 60^0C when a crystalline solid separated.The reaction-mixture was further stirred for 1 hr at room temperature then cooled in an ice bath to complete the crystallization.Separated solid was washed with ice cold ethanol.

Synthesis of 4-(4-substituted benzylidene)-5-methyl-2,4-dihydro-3H-pyrazol-3-one[11]

5-Methyl-2,4-dihydro-3H Pyrazol-3-one (**1**,0.01 mole), 4-substituted benzaldehyde(0.01 mole) and anhydrous sodium acetate (0.02 mole) were dissolved in acetic acid and reflux for 10 hr.The reaction mixture was filtered and the filtrate was poured on crushed ice.The solid obtained was recrystallized from ethanol.

Synthesis of (4-substituted benzylidene)-3-methyl-1-(substituted benzoyl)-1H-pyrazol-5(4H)-one

4-(4-substituted benzylidene)-5-methyl-2,4-dihydro-3H-pyrazol-3-one (0.1 mole) and substituted benzoyl chloride (0.1 mole) and add Triethylamine1 to2 drops and stirring for 4 hr and evaporate Trietylamine on water bath and product was obtained, then recrystallized from methanol.

Synthesis of (4-substituted benzylidene)-3-methyl-1-(substituted phenyl sulfonyl)-1H-pyrazol-5(4H)-one

4-(4-substituted benzylidene)-5-methyl-2,4-dihydro-3H-pyrazol-3-one (0.1 mole) and substituted benzene sulfonyl chloride (0.1 mole) and add Triethylamine1 to2 drops and stirring for 4 hr and evaporate Triethylamine on water bath and product was obtained .Then recrystallized from methanol.

Table-2. Spectral data of the Synthesized Compounds

Compound	Mass (m/z)	IR (v,cm^{-1})	^{1}H NMR(δ,Ppm) (Dmso)
3b	335(M^+)(100) 336.5 (M+1)(21)	-NO_2 (Asy 1500 sym 1450) C=O(1700) CH_3 (1450)	7.5(m,4H,Ph) 8.1(t,2h,Ph(2H)) 2.1(s,3H,CH_3)
3c	290(M^+)(100) 290.1(M^+)(99.9)	C=O(1700) CH_3 (1423) C=N (1683.74)	7.5(m,5H,Ph) 8.2(q,2H,Ph(2H)) 2.1(s,3H,CH_3)
4a	374(M^+)(100) 375(M+1)(39.3)	C=O(1700) C=N (1600) C-Cl (1012.35) -SO2- (Antisymmetric1355,Symmetric 1150)	7.3(q,4H,Ph) 1.2(t,3H,CH_3) 3.2(m,1H,=CH-)
4b	385(M^+)(100) 386(M+1)(39.3)	-No2(Asy 1544 sym 1390) C=O(1700) C=N (1600), -SO2- (Antisymmetric1350,Symmetric 1145)	2.1(t,3H,CH_3) 3.2(m,1H,=CH-) 7-8(m,4H,Ph)

Conclusion:

The present work of the synthesis of pyrazole derivative in solid phase **(**4-Substituted benzylidene)-3-methyl-1-(substituted benzoyl)-1H-pyrazol-5(4H)-one compound is better yield compare to the **(**4-Substituted benzylidene)-3-methyl-1-(Substituted Phenyl Sulfonyl)-1H-pyrazol-5(4H)-one.

Acknowledgements

The authors wish to thank Prof. B.G.Thakur , Department of Chemistry, C.M.Science College, Darbhanga for providing their valuable suggestions to carry out this work.The authors gratefully acknowledge to Professor L. K. Mishra, Science College, Patna University for providing valuable suggestions for carrying out this work. Authors also expresses their heartiest thankful to Prof. S. Jha, University PG Dept. of Chemistry, L.N.M.U Darbhanga for fruitful discussion of the results.

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