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FACILE SYNTHESIS AND ANTIMICROBIAL SCREENING OF PYRAZOLE DERIVATIVES

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ABSTRACT

A series of novel and significant compounds containing pyrazole derivatives have been synthesized from base catalyzed reaction between N-acetyl-3-4-diphenylpyrazole and substituted benzaldehydes by grinding technique afforded 1-benzoaceto-3-5-diphenyldihydropyrazole (Ia-d) followed by reflux with different reagents like phenyl hydrazine ,Hydrazine hydrate in acetic acid and Hydrazine hydrate in sodium acetate gave corresponding N^1-(3,4-diphenyl,5'-dihydro-2,3-pyrazol)-3,5-diphenyl,4- diydro pyrazole(IIa-d),N^1-(4-phenyl,3-acetyl,5-dihydro,2,3-pyrazol)3,5-diphenyl-4-dihydropyrazole (III_{a-d}), N^1-(4-phenyl,5-dihydro-2,3-pyrazol)-3,5-diphenyl -4-dihydro pyrazole (IV_{a-d}) respectively. The structures of the newly synthesized compounds have been confirmed on the basis of elemental analysis and spectral data. Some of the synthesized compounds exhibit significant antibacterial activity.

KEY WORDS: Pyrazole, Grinding, Antibacterial activity.

INTRODUCTION

Pyrazole and its derivatives are among the important scaffolds possessing various biological activities and having prestigious position in medicinal and pharmaceutical chemistry. This mainly due to the easy preparation and important biological activity and therefore represents an interesting template for combinatorial as well as medicinal chemistry. Pyrazole framework plays an essential role in biological active compounds .The pyrazole nucleus is a ubiquitous feature of fertile source of medicinal agents such as antimicrobial[1], anticancer[2], antitumor[3], anticonvulsant[4], antihistaminic[5], analgesic[6], anti-inflammatory[7] etc. Many pyrazole have been found to be luminescent and fluorescent agents. In addition, pyrazoles have played a crucial

role in the development of theory in heterocyclic chemistry and also used extensively as useful synthon in organic synthesis. In addition, the pyrazole derivatives have many applications on crop protection chemistry such as insecticide and pesticide[8] and used as intermediates for the synthesis of new chemical entities[9]. As a consequence, much attention has been paid to the design and synthesis of pyrazole derivatives prompted us to synthesize some new pyrazole derivatives as per Scheme.

EXPERIMENTAL SECTION

Melting points were taken in open capillary tubes and are uncorrected. Purity of the compound was checked by silica gel G TLC plates 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 Schimadzu spectrophotometer. The ^{1}H NMR spectra were scanned on Perkin Elmer spectrophotometer in $CDCl_3$ using TMS as internal standard and chemical shift are expressed in δ ppm. Elemental analysis was performed on a Heracus CHN analyzer and was within the ±0.5% of the theoretical values.

Experimental Procedure

Synthesis of 1-benzoaceto-3-5-diphenyldihydropyrazole (Ia-d)

Equimolar quantities of substituted benzaldehyde (0.01mol) & N-acetyl-3-4-diphenylpyrazole were dissolved in minimum amount of alcohol. Sodium- hydroxide solution (0.02mol) was added slowly &the mixture is stirred for 2 hrs. until the entire mixture becomes very cloud. Then mixture was poured slowly into 400ml water with constant stirring & kept in a refrigerator for 24 hrs. The precipitate obtained was filtered, washed and recrystallized from ethanol. The completion of reaction was monitored by TLC. Ia: IR (KBr) : λ_{max},3015 (Ar-H str),1705 (>C=O str), 1614(>C=N str) ,1595(>C=< str) cm^{-1}. NMR : ($CDCl_3$):δ,1.83(2H, dd, -CH_2-), 2.03 (1H, t, -CH), 6.2-6.6(2H, d, -CH=), 6.9-7.8 (15H, m, Ar-H), 7.88-7.81 (1H, d,=CH-Ar) ppm. Ib: IR (KBr) : λ_{max}, 3060 (Ar-H str), 1700 (>C=O str), 1620 (-C=O str), 1620 (>C=N str), 1600(>C=C< str), 1020 (-C-N str), 1430 (-NO_2) cm^{-1}.NMR : ($CDCl_3$):δ ,2.2-2.7(2H, dd,-CH_2-), 3.2 (1H, dd, -CH), 6.6-6.9 (2H, d, -CH=), 6.9-7.8 (14H, m, Ar-H), 7.88-7.81 (1H, d,=CH-Ar) ppm Ic: IR (KBr) : λ_{max}, 3430(-OH br), 3099(Ar-H str), 1710(>C=O str), 1615(>C=N str), 1600(>C=C< str) cm^{-1} .NMR : ($CDCl_3$):δ 2.2-2.7(2H, dd, -CH_2-), 3.2 (1H, dd, -CH), 3.5(1H, s, -NH), 6.3-6.7(2H, dd, -CH-), 3.7(1H, s, -OH) 7.1-7.9 (14H, m, Ar-H), 7.88-7.81 (1H, d,=CH-Ar) ppm. Id: IR (KBr) : λ_{max}, 3055(Ar-H str), 1710(>C=O str), 1620 (>C=N str), 1600 (>C=C< str) cm^{-1}.NMR : ($CDCl_3$):δ ,2.2-

2.7(2H, dd, -CH_2-), 3.4(1H, dd, -CH), 6.1-6.5(2H, d, -CH=), 7.1-7.8(14H, m, Ar-H), 7.88-7.81 (1H, d,=CH-Ar) ppm.

Synthesis of N^1-(3,4-diphenyl,5'-dihydro-2,3-pyrazol)-3,5-diphenyl,4- diydro pyrazole (IIa-d)

A mixture of (I) (0.01mol), phenylhydrazine (0.01mol) and 2-3 drops of glacial acetic acid was refluxed in absolute ethanol (50ml) for 6 hrs. The reaction mixture was concentrated in vaccum & the solid so obtained was filtered, washed, dried & recrystallised from ethanol. The completion of reaction was monitored by TLC IIa: IR (KBr) : λ_{max}, 3045 (Ar-Hstr), 1617 (-C=N-str) cm^{-1}.NMR : ($CDCl_3$):δ 1.57(4H, dd, -CH_2-), 2.13 (2H, t, -CH), 6.9-7.8(20H, m, Ar-H) ppm. IIb: IR (KBr) : λ_{max}, 3075(Ar-H str), 1619(-C=O str), 1023(-C=N str) cm^{-1}.NMR : ($CDCl_3$):δ 2.2-2.7(4H, dd, -CH_2-), 3.2 (2H, dd, -CH), 6.9-7.8(19H, m, Ar-H)ppm. IIc: IR (KBr) : λ_{max}, 3395(-OH br), 3066(Ar-H str), 1618(>C=O str), cm^{-1}. NMR : ($CDCl_3$):δ, 2.2-2.7(4H, dd, -CH_2-), 3.4 (2H, dd, -CH), 3.7(1H, s, -NH), 6.9-7.9 (19H, m, Ar-H)ppm. IId: IR (KBr) : λ_{max}, 3047(Ar-H str), 1613(-C=N str.) cm^{-1}.NMR : ($CDCl_3$):δ 2.4-2.7(4H, dd, -CH_2-), 3.1(2H, dd, -CH), 3.1 (2H, dd, -CH), 2.2(3H, s, -OCH_3) 7.2-7.9 (19H, m, Ar-H) ppm

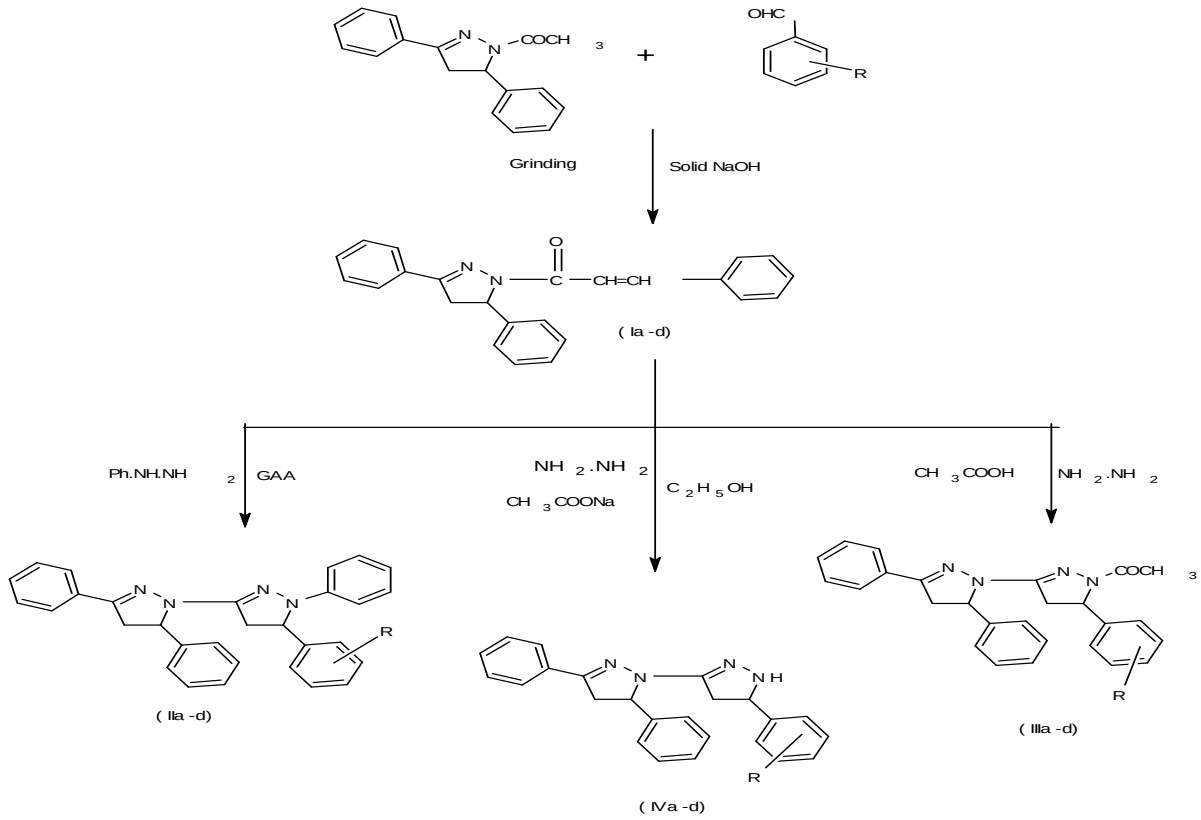
Synthesis of N^1-(4-phenyl, 3-acetyl, 5-dihydro, 2,3-pyrazol)3,5-diphenyl-4-dihydro pyrazole (IIIa-d)

The compound II (0.01 mol) was dissolved in glacial acetic acid (30 ml) and hydrazine hydrate (0.01 mol) was added to it. Then the reaction mixture was refluxed for 6 hrs. The reaction mixture was then cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from ethanol. The completion of reaction was monitored by TLC. IIIa: IR (KBr) : λ_{max}, 3024 (Ar-H str), 1715 (>C=O str), 1638 (-C=N str), 1610 (>C=C< str) cm^{-1}.NMR : ($CDCl_3$):δ 2.2-2.7(4H, dd, -CH_2-), 3.5 (1H, t, -CH), 1.5(3H, s, CH_3), 6.8-7.1(15H, m, Ar-H) ppm. IIIb: IR (KBr) : λ_{max}, 3027(Ar-H str), 1717(>C=O str), 1637(-C=N str), 1612(>C=C str) cm^{-1} ;NMR : ($CDCl_3$):δ 2.2-2.7(4H, dd, -CH_2-), 3.5 (1H, dd, -CH), 1.5(3H, s, -CH_3), 6.8-7.0(14H, m, Ar-H)ppm IIIc: IR (KBr) : λ_{max}, 3388(-OH br), 3076(Ar-H str), 1621(-C=O str), cm^{-1}.NMR : ($CDCl_3$):δ 2.2-2.7(4H, dd, -CH_2-), 3.6(2H, dd, -CH), 1.6(3H, s, -NH), 6.8-6.9 (14H, m, Ar-H), 3.2(1H, s, -OH) ppm.
IIId: IR (KBr) : λ_{max}, 3050(Ar-H str), 1623(-C=N str.), 1608(-C=C str) cm^{-1}.NMR : ($CDCl_3$):δ 2.4-2.7(4H, dd, -CH_2-), 3.5(2H, dd, -CH), 2.3(3H, s, -OH_3), 1.7 (3H, s, -CH_3), 7.2-7.9 (14H, m, Ar-H) ppm.

Synthesis of N^1-(4-phenyl,5-dihydro-2,3-pyrazol)-3,5-diphenyl -4-dihydro pyrazole (IVa-d)

A mixture of II (0.02 mol) hydrazine hydrate (0.02mol) & sodium acetate in ethanol (25 ml) was refluxed for 6 hrs. The mixture was concentrated by distilling out the solvent under reduced pressure, & poured into ice water. The precipitate obtained was filtered, washed & recrystallized from ethanol. The completion of reaction was monitored by TLC. IVa: IR (KBr) : λ_{max}, 3275 (-N-H str), 3027 (Ar-H str), 1640) (>C=N str), 1605 (>C=C str) cm^{-1}NMR : ($CDCl_3$):δ 2.2-2.7(4H, dd, -CH_2-), 3.5 (1H, t, -CH), 5.8 (1H, s, N-H), 6.8-6.9 (1H, m, Ar-H)ppm. IVb: IR (KBr) : λ_{max}, 3227(N-H str), 3025(Ar-H str), 1639(-C=N str), 1606(>C=C str) cm^{-1}. NMR : ($CDCl_3$):δ 2.2-2.7(4H, dd, -CH_2-), 3.6 (1H, dd, -CH), 5.7(1H, s, -NH), 6.8-6.9(14H, m, Ar-H)ppm. IVc: IR (KBr) : λ_{max}, 3274(-OH br), 3019(Ar-H str), 1643(-C=N str), 1643 (-C=N str), 1602 (>C=C< str) cm^{-1}, NMR : ($CDCl_3$):δ 2.2-2.7(4H, dd, -CH_2-), 3.5(1H, dd, -CH), 3.7(1H, s, -OH), 5.6(1H, s, NH), 6.8-6.9) (4H, m, Ar-H) ppm IVd:IR (KBr) : λ_{max}, 3276(N-H str), 3021(Ar-H str), 1647(-C=N str), 1607 (>C=C<) cm^{-1}. NMR : ($CDCl_3$):δ 2.2-2.7(4H, dd, -CH_2-), 3.5(2H, dd, -CH), 2.4 (3H, s, -OCH_3), 5.7 (1H, S, -HN), 2.2 (3H, s, -OCH_3) ppm .

SCHEME



R= -H, -NO_2, -OH, -OCH_3

Table- 1: Physical and Analytical data of substituted pyrazole derivatives (Ia – IVd)

Compound No.	- R	M.P. ^{0}C	Yield %	Mol. Formula	Elemental Analysis Calc./ (Found) %		
					C	H	N
I_a	-H	98	87	$C_{24}H_{20}ON_2$	81.82 (81.80)	5.68 (5.60)	7.95 (7.91)
II_a	-H	78	76	$C_{30}H_{26}N_4$	81.45 (81.46)	5.88 (5.88)	12.67 (12.65)
III_a	-H	95	65	$C_{26}H_{24}ON_4$	76.47 (76.47)	5.88 (5.80)	13.73 (13.74)
IV_a	-H	63	72	$C_{24}H_{22}N_4$	78.89 (78.87)	6.01 (6.00)	19.44 (19.40)
Ib	$-NO_2$	94	73	$C_{24}H_{19}O_3N_3$	72.54 (72.53)	4.79 (4.75)	10.58 (10.59)
IIb	$-NO_2$	80	68	$C_{30}H_{25}O_2N_5$	73.92 (73.90)	5.13 (5.11)	14.37 (14.37)
IIIb	$-NO_2$	100	80	$C_{26}H_{23}O_3N_5$	68.87 (68.85)	5.08 (5.00)	15.45 (15.41)
IVb	$-NO_2$	124	75	$C_{24}H_{21}O_2N_5$	70.07 (70.01)	5.11 (5.10)	17.03 (17.00)
Ic	-OH	116	78	$C_{24}H_{20}O_2N_2$	78.26 (78.25)	5.43 (5.42)	7.61 (7.62)
IIc	-OH	102	65	$C_{30}H_{26}ON_4$	78.60 (78.58)	4.37 (4.38)	12.23 (12.19)
IIIc	-OH	118	68	$C_{26}H_{24}O_2N_4$	73.58 (73.56)	5.66 (5.66)	13.21 (13.20)
IVc	-OH	100	63	$C_{24}H_{22}ON_4$	75.39 (75.32)	5.76 (5.75)	14.66 (14.65)
Id	$-OCH_3$	85	69	$C_{25}H_{22}O_2N_2$	78.53 (78.51)	5.76 (5.75)	7.33 (7.34)
IId	$-OCH_3$	104	63	$C_{31}H_{28}ON_4$	78.81 (78.80)	5.93 (5.90)	11.86 (11.85)
IIId	$-OCH_3$	85	66	$C_{27}H_{26}O_2N_4$	73.97 (73.93)	5.94 (5.90)	12.79 (12.75)
IVd	$-OCH_3$	96	70	$C_{25}H_{24}ON_4$	75.76 (75.75)	6.06 (6.02)	14.14 (14.11)

Table II : Antibacterial activity of Synthesized compounds (IIa-IVc)

Compound No.	Zone of inhibition in mm		
	Gram Positive		Gram Negative
	S. aureus	B. substilus	E. Coli
IIa	06	05	04
IIIa	06	07	05
IVa	07	08	07
IIb	06	07	06
IIIb	09	10	08
IVb	04	06	04
IIc	05	06	05

IIIc	03	04	04
IVc	11	13	11
Standard Drug **1. Streptomycin** **2. Amphicilin**	 12 10	 13 09	 12 11
Duration 24 hours			

RESULTS AND DISCUSSION

The synthesis of 1-(sub.) benzoaceto-3,5-diphenyldihydropyrazole Ia-d Were carried out by the reaction of substituted benzaldehyde and N-acetyl-3-4-diphenylpyrazole by grinding technique as a key intermediate which further on treatment with phenyl hydrazine , hydrazine hydrate in glacial acetic acid and hydrazine hydrate in sodium acetate targeted corresponding N^1-(3,4-diphenyl,5'-dihydro-2,3-pyrazol)-3,5-diphenyl,4- diydropyrazole (IIa-d), N^1-(4-phenyl, 3-acetyl, 5-dihydro, 2,3-pyrazol)3,5-diphenyl-4-dihydro pyrazole (IIIa-d) and N^1-(4-phenyl,5-dihydro-2,3-pyrazol)-3,5-diphenyl -4-dihydro pyrazole (IVa-d) respectively. The structures of the newly synthesized compounds were confirmed on the basis of elemental analysis (Table-I) and spectral data. The completion of reaction was monitored by TLC by using n-hexane and ethyl acetate as solvent system (2:8).The reagents utilized in the proposed method are readily available and does not involve any critical reaction conditions or tedious sample preparation.

Anti-microbial screening

In the present study, all the newly synthesized compounds were screened for their antibacterial activity using cup plate method against various gram positive i.e. *Staphylococcus aureus* and *Bacillus Substilus* while gram negative i.e. *E. Coli* using Streptomycin and Amphicilin as standard drug**.** All the compounds were tested at the concentration of 100mg/mL .The zone of inhibition was measured in mm and DMF was used as a solvent**.** Most of the compounds were found to be more active against gram positive than gram negative bacterial species**.** Among the screened compounds IIIb and IVc were exhibited more activity against *B. substilus* and *S.aureus*. While no activity was noticed against rest of the species. The compound IVa was found to be moderately active against S. aureus, B. substilus and E. coli . The remaining pyrazole derivatives were found to be less activity against gram positive and gram negative bacterial species as per Table-II.

CONCLUSION

We have demonstrated eco-friendly, operationally simple and time efficient protocol for the synthesis of pyrozolidine derivatives of pyrrozole . Reaction procedures are very simple and yield of products are also excellent. The reagents utilized in the proposed method are readily available without the need for expensive instrumentation. All synthesized compounds were screened for antimicrobial activities and found to be moderate to excellent activity as compare to standard drug. A few exhibited activities comparable to those of a standard drug while one of them showed antibacterial activity more pronounced than that of the standard drug.

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