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Microwave Assisted Synthesis of 3,4-bis (Substituted Phenyl) -7-(4-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c′] dipyrazoles

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Abstract : A green and facile microwave supported synthesis of Bis-Pyrazoles defined with the successive cyclization of Bis-Chalcones with Hydrazine Hydrate as an ammonia derivative in presence of Neutral alumina the synthesized compounds exhibites good yields.
Keywords : Succinic anhydride, substituted pyridine amines, cyclic imides, Bis-chalcone.

Introduction:

Pyrazole belongs to the "diazole" class of heterocycles and is the most important moiety found in a large number of pharmaceutical agents.Pyrazole derivatives have attracted the attention of research scholars on account of their wide range of applications in medicine. Steroids containing pyrazole moiety are of interest as psychopharmacological agents. One of the most fundamental objectives of organic and medicinal chemistry is the design and synthesis of molecules having value as human therapeutic agents Due to the pyrazole moiety & unique in their chemical behaviour. A diversity of biological activities and pharmaceutical uses have been attributed to them, such as pyrazole is a part of many active molecules possessing activities such as antibacterial,[1][2][3]antifungal,[1][2][3]antimicrobial,[1][2][3]antiviral,[3] [4]anti-inflammatory, [4] [5] In vivo anti-inflammatory activity, [6] Anti-neurotoxic, [6]COXenzymatic activity,[6]Neuroprotective effects,[6]Ulcerogenic activity,[6] anticonvulsant,[7] in vitro antioxidant,[7] analgesic,[7] anti-angiogenic.[7]

Materials and Methods:

All research chemicals were purchased from Sigma-Aldrich and S.D. Fine Chemicals India Pvt. Ltd. and used as such for the reactions. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates. Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. IR spectra were recorded on Shimadzu 8400S FTIR spectrometer using KBr pellets. The 1H NMR were recorded on Bruker WM-300 (at 500 MHz) using DMSO as solvent. Chemical shifts are reported in δ ppm units with respect to TMS as internal standard. Purity of the compounds was checked on precoated TLC plates using silica gel plates.

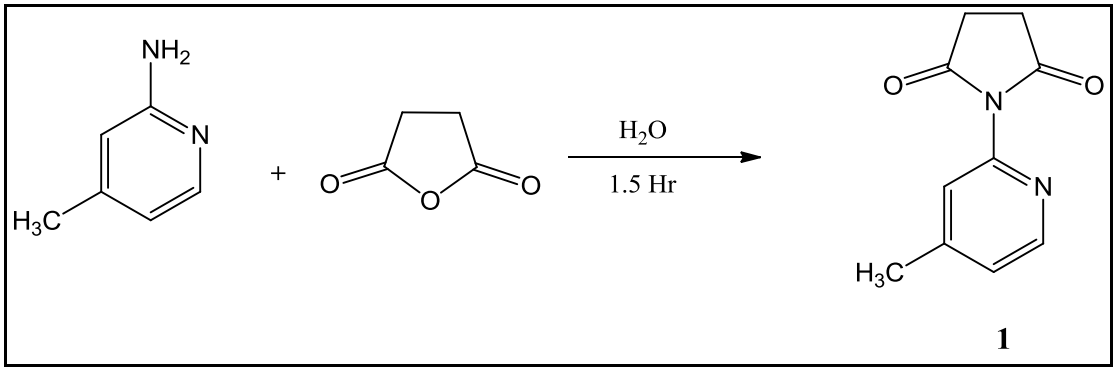
Experimental Section:

General Procedure of Synthesis:

***Preparation of 1-(4-Methylpyridin-2-yl) pyrrolidine-2, 5-dione: (1)**

0.01 mole of the appropriately 4-methyl 2-amino pyridine was dissolved in 20 ml of water and 0.01 mole of succinic anhydride was gradually added. The mixture was heated in oil bath with simultaneous distillation of water. The water complete removed, the temperature of the reaction mixture was maintained at 180^{o}Cabout 1.5 hr. the crude product was separated and recrystalised from isopropyl alcohol **(Scheme-1)**

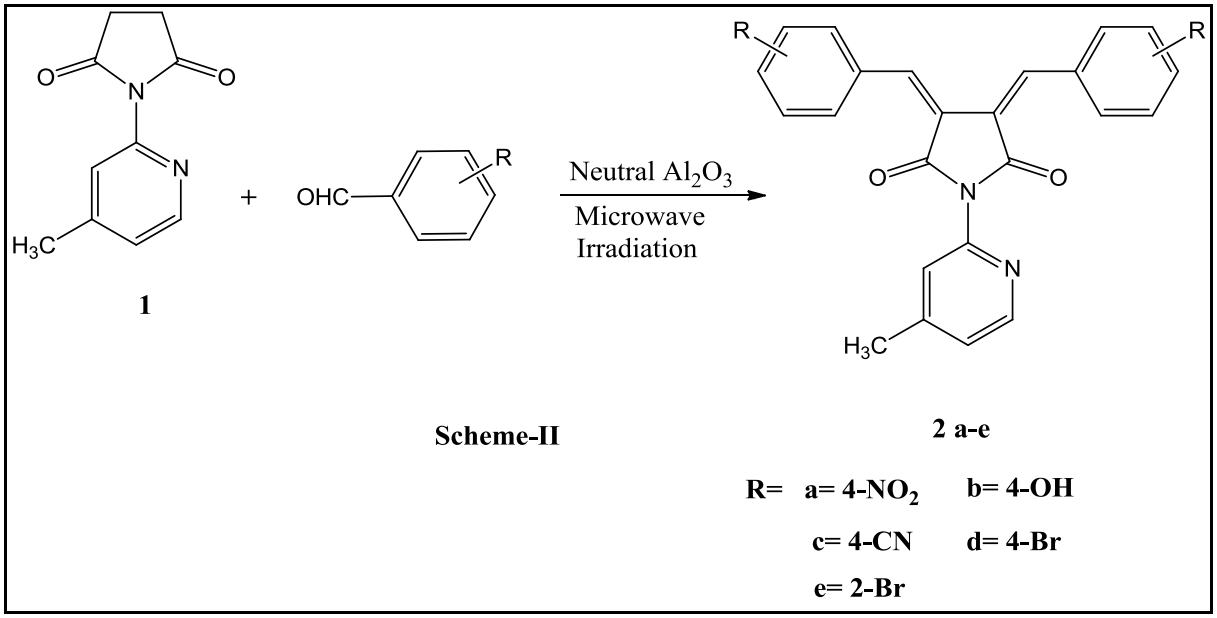
Reaction Scheme:



Scheme-1

***Preparation of 2-((3E, 4E)-3, 4-bis (Substituted benzylidenePyrrolidin-1-yl)-4-Methyl Pyridines (2 a-e) :**

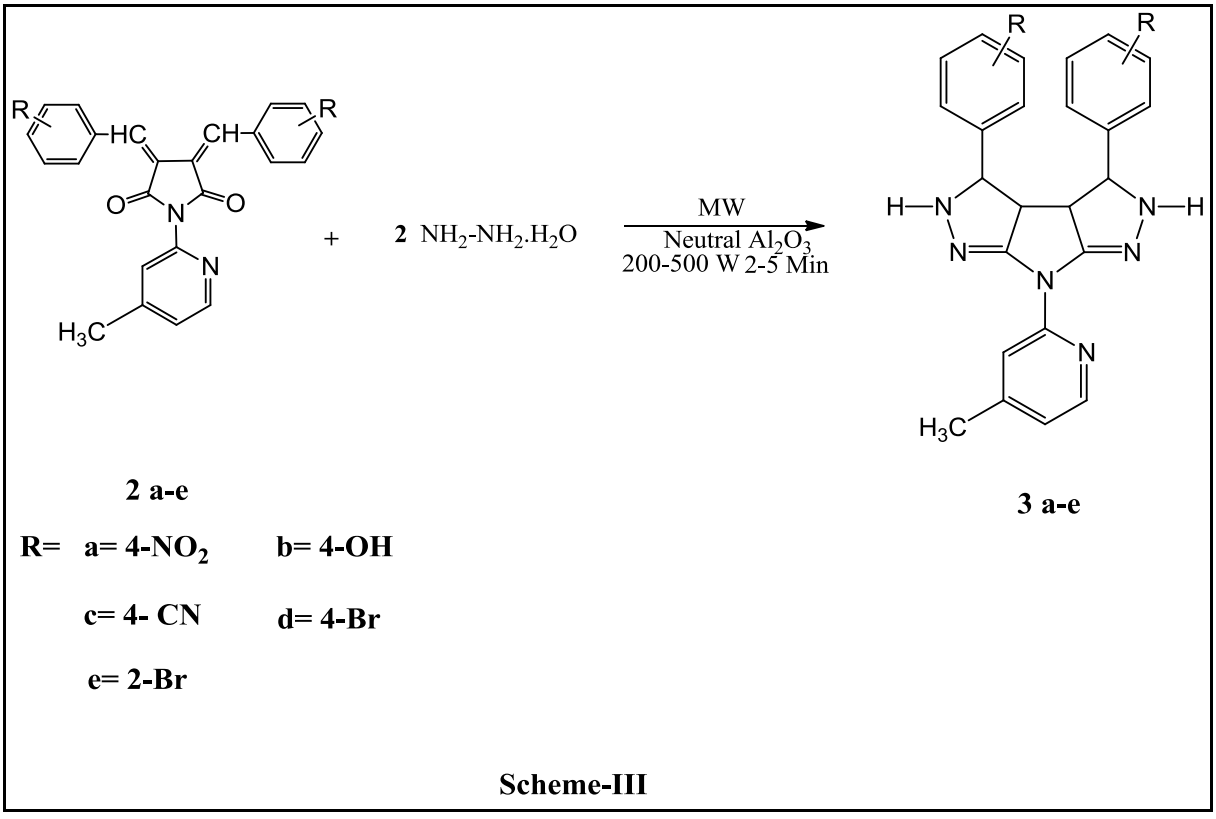
The bis-chalcones (II a-e) derivatives were synthesized by the mixture of 0.01 moles N-4-Methyl pyridine succinimide and 0.02 mole of substituted benzaldehyde in 1 gm. of Neutral Al_2O_3 with the help of microwave irradiations. This mixture is kept in microwave at 800 W power for 3-5 min. in solvent free conditions. The bis-chalcone derivatives were separated. The crude product was washed with hot water for removel of neutral Al_2O_3. **(Scheme-2)**



Scheme-II

***Preparation of 3, 4-bis (Substituted Phenyl) -7-(4-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (3 a-e):**

The bis-pyrazole (3 a-e) derivatives were synthesized by mixture of 1 moles of bis-chalcone (2 a-e) and 2 moles of hydrazine hydrate in 1 gm of neutral Al_2O_3 under microwave supported solvent less condition on 800 W power for 4-7 min. The separated compounds were recrystalised from ethanol. **(Scheme-III)**



2 a-e

3 a-e

R= a= 4-NO_2 b= 4-OH

c= 4- CN d= 4-Br

e= 2-Br

Scheme-III

Physiochemical and Analytical data for Compounds:

1-(4-Methylpyridin-2-yl) pyrrolidine-2, 5-dione: (1)

Whitish Solid, Yield (70%) M.P. 142-144^{0}C M.F. $C_{10}H_{10}O_2N_2$ M.W= 190.20, **Elemental Analysis: Calculated** C (63.15%); H (5.30%); N (14.73%). Found C (63.01%); H (5.12%); N (14.80%). **IR (KBr):** 1709, 2487, 1334, 1301, 3044, 2967, 2924, 1551, 1598, 2759 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):** 2.35(S, 3H, CH_3-Pyridine), 2.90(S, 4H, imide), 7.85-8.47(m, 2H, pyridine), 8.23(d, 1H, pyridine).

2-((3E, 4E)-3,4-bis(4-NitrobenzylidenePyrrolidin-1-yl)-4-Methyl Pyridines (2a) :

Brown solid, Yield (84%) M.P. 120-124^{0}C M.F. $C_{24}H_{16}N_4O_6$ M.W= 456, **Elemental Analysis: Calculated** C (63.16%); H (3.53%); N (12.28%). Found C (63.12%); H (3.30%); N (12.65%). **IR (KBr):** 1705, 1334, 1301, 3044, 2967, 2924, 1590, 2759 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.14-7.17 (m, 7H, Ar-H and =CH), 2.48 (S, 3H, -CH_3)

2-((3E,4E)-3,4-bis(4-HydroxybenzylidenePyrrolidin-1-yl)-4-MethylPyridines (2b): Orange solid, Yield (65%) M.P. 145-148^{0}C M.F. $C_{24}H_{18}N_2O_4$ M.W= 398, **Elemental Analysis: Calculated** C (72.35%); H (4.55%); N (7.03%). Found C (72.50%); H (4.60%); N (7.60%). **IR (KBr):** 1702, 1330, 1300, 3100, 2910, 1551, 1598, 2755 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.11-7.01 (m, 7H, Ar-H and =CH), 2.38 (S, 3H, -CH_3), 10.01 (S, 1H, OH)

2-((3E,4E)-3,4-bis(4-CyanobenzylidenePyrrolidin-1-yl)-4-MethylPyridines (2c) :

LightYellow solid, Yield (81%) M.P. 128-130^{0}C M.F. $C_{26}H_{16}N_4O_2$ M.W= 416, **Elemental Analysis: Calculated** C (74.99%); H (3.87%); N (13.45%). Found C (74.80%); H (3.90%); N (13.20%). **IR (KBr):** 1700, 2481, 2210, 1303, 3044, 2955, 2924, 1551, 1598, 2749 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.09-6.27 (m, 7H, Ar-H and =CH), 2.42 (S, 3H, -CH_3),

2-((3E,4E)-3,4-bis(4-BromobenzylidenePyrrolidin-1-yl)-4-MethylPyridines (2d) :

Yellow solid, Yield (88%) M.P. 130-132^{0}C M.F. $C_{24}H_{16}Br_2N_2O_2$,M.W= 524, **Elemental Analysis: Calculated** C (54.99%); H (3.08%); N (5.34%). Found C (54.78%); H (3.18%); N (5.28%). **IR (KBr):** 1702, 740, 856, 1334, 1301, 3041, 2967, 2935, 1540, 1600, 2720 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.42-6.38 (m, 7H, Ar-H and =CH), 2.51 (S, 3H, -CH_3)

2-((3E,4E)-3,4-bis(2-BromobenzylidenePyrrolidin-1-yl)-4-MethylPyridines (2e) :

Yellow solid, Yield (85%) M.P. 80-84^{0}C M.F. $C_{24}H_{16}Br_2N_2O_2$,M.W= 524, **Elemental Analysis: Calculated** C (54.99%); H (3.08%); N (5.34%). Found C (54.78%); H (3.20%); N (5.20%). **IR (KBr):** 1715, 735, 856, 2487, 1330, 3044, 2964, 2924, 1551, 1598 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.50-6.76 (m, 7H, Ar-H and =CH), 2.48 (S, 3H, -CH_3)

3,4-bis (4-Nitro Phenyl) -7-(4-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (3a):

Dark Yellow solid, Yield (80%); M.P. 240-242 ^{0}C, M.F. $C_{24}H_{20}N_8O_4$, M.W. 484, Elemental analysis calculated C (59.50 %); H (4.16%); N (23.13%) Found C (59.22%); H (4.20%); N (23.10%)**IR (KBr cm^{-1}): 740, 850, 1356, 1500-1600, 3210, 2960, 1555, 1980 cm^{-1}**

^{1}HNMR (500 MHz, DMSOd^6,δ ppm): 8.60-7.58 (m, 5H, Ar-H); 3.61(d, 1H, -CH), 2.68-2.61(d, 1H, -CH), 2.15 (S, 3H, CH_3), 10.53(S, 1H, N-H)

3,4-bis (4-HydroxyPhenyl) -7-(4-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (3b):

Orange solid, Yield (68%); M.P. 210-214^{0}C, M.F. $C_{24}H_{22}N_6O_2$, M.W. 426, Elemental analysis calculated C (67.59%); H(5.20%); N(19.71%) Found C (67.60%); H (5.23%); N (19.50%)**IR (KBr cm^{-1}): 748, 852, 3260, 1500-1600, 3240, 2980, 1550, 1978 cm^{-1}**

^{1}HNMR (500 MHz, DMSOd^6,δ ppm):8.58-7.56 (m, 5H, Ar-H); 3.59(d, 1H, -CH), 2.65-2.63(d, 1H, -CH), 2.11 (S, 3H, CH_3), 10.50(S, 1H, N-H)

3,4-bis(4-CyanoPhenyl) -7-(4-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (3c):

Yellow solid, Yield (88%); M.P. 178-178^{0}C, M.F. $C_{26}H_{20}N_8$, M.W. 444, Elemental analysis calculated C (70.26 %); H(4.54%); N(25.21%) Found C (70.30%); H (4.70%); N (25.34%)**IR (KBr cm^{-1}): 752, 855, 2260, 1500-1600, 3230, 2970, 1562, 1971 cm^{-1}**

^{1}HNMR (500 MHz, DMSOd^6,δ ppm):8.62-7.60 (m, 5H, Ar-H); 3.58 (d, 1H, -CH), 2.66-2.65(d, 1H, -CH), 2.18 (S, 3H, CH_3), 10.56(S, 1H, N-H)

3,4-bis(4-BromoPhenyl) -7-(4-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (3d):

Brown solid, Yield (85%); M.P. 206-210^{0}C, M.F. $C_{24}H_{20}Br_2N_6$, M.W. 551.8, Elemental analysis calculated C (52.20%); H (3.65%); N (15.22%) Found C (52.34%); H (3.60%); N (15.30%)**IR (KBr cm^{-1}): 758, 860, 1500-1600, 3260, 2950, 1552, 1974 cm^{-1}**

^{1}HNMR (500 MHz, DMSOd^6,δ ppm):8.62-7.60 (m, 5H, Ar-H); 3.66(d, 1H, -CH), 2.70-2.68 (d, 1H, -CH), 2.18 (S, 3H, CH_3), 10.60 (S, 1H, N-H)

3,4-bis(2-BromoPhenyl) -7-(4-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (3e):

Brown solid, Yield (78%); M.P. 180-184^{0}C, M.F. $C_{24}H_{20}Br_2N_6$, M.W. 551.8, Elemental analysis calculated C (52.20%); H (3.65%); N (15.22%) Found C (52.34%); H (3.60%); N (15.30%)**IR (KBr cm^{-1}): 756, 862, 1500-1600, 3277, 2990, 1562, 1969 cm^{-1}**

^{1}HNMR (500 MHz, DMSOd^6,δ ppm):8.62-7.58 (m, 5H, Ar-H); 3.62(d, 1H, -CH), 2.62-2.60(d, 1H, -CH), 2.12 (S, 3H, CH_3), 10.56 (S, 1H, N-H)

Physical Data of the Synthesized compounds:

Compound code	Molecular Formula	Molecular Weight	% Yield	M.P (^{0}C)	Colour
1	$C_{10}H_{10}O_2N_2$	190.20	70	142-144	White solid
2a	$C_{24}H_{16}N_4O_6$	456	84	120-124	Brown solid
2b	$C_{24}H_{18}N_2O_4$	398	65	145-148	Orange solid
2c	$C_{26}H_{16}N_4O_2$	416	81	128-130	LightYellow solid
2d	$C_{24}H_{16}Br_2N_2O_2$	524	88	130-132	Yellow solid
2e	$C_{24}H_{16}Br_2N_2O_2$	524	85	80-84	Yellow solid
3a	$C_{24}H_{20}N_8O_4$	484	80	240-242	Dark Yellow solid
3b	$C_{24}H_{22}N_6O_2$	426	68	210-214	Orange solid
3c	$C_{26}H_{20}N_8$	444	88	176-178	Yellow solid
3d	$C_{24}H_{20}Br_2N_6$	551.8	85	206-210	Brown solid
3e	$C_{24}H_{20}Br_2N_6$	551.8	78	180-184	Brown solid

Result and Discussion:

The target molecules of bis-pyrazoles (3a-e) were synthesized by the reaction of bis-chalcones (2 a-e) with Hydrazine hydrate in presence of neutral alumina. IR, 1HNMR spectra of the afforded derivatives were confirmed. IUPAC naming of the final compounds were determined by Perkins Elmer Chemdraw software.

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