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Synthesis and Characterization of Bis-Pyrazoles Using 1-(5-Methyl Pyridine-2-yl) Pyrrolidine-2,5Dione Under Microwave Irradiation

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Abstract : The current study shows that the green and efficient synthesis of new series of bis-pyrazoles derivatives from 1-(5-methyl pyridine-2-yl) pyrrolidine-2,5dione under microwave irradiation. The 1-(5-Methylpyridin-2-yl) pyrrolidine-2,5-dione, was synthesized from succinic anhydride and 5-methyl pyridine-2-amine. This cyclic imides condensed with substituted aromatic aldehydes using solid support neutral Al_2O_3in microwave. The resulting bis-chalcone derivatives underwent ring closer with hydrazine hydrate in presence of neutral Al_2O_3 under microwave irradiation offer dedbis-pyrazoles derivatives.
Keywords : Succinic anhydride, 5-methyl pyridine-2-amine, bis-chalcone, bis-pyrazole.

Introduction:

Cyclic Imides such as Succinimides & Glutarimides are an important class of heterocyclic compounds with numerous pharmacological applications in different fields such as irreversible protease inhibitors[1]. Succinimide-based pseudopeptides[1] have been shown to stabilize β-turn conformations and good potent anticonvulsant,[2][3][4] antiepileptic, [2][3][4] anti-seizure activity,[2][3][4]and neutotoxic properties[2]. Development of new methods for the synthesis of biologically important organic compounds from readily and easily available starting materials is a key task in synthetic organic chemistry. N-aryl and N-alkyl imides have attracted much more attention of organic and medicinal chemists, due to their biological activities, synthetic utility as intermediates[5], and applications in polymer science[5].

Bis-chalcones are the innovator flavonoids of heterocycle precursor containing carbon stuck between α, β-unsaturated aromatic rings and carbonyl carbons. [6] The chalcones are synthesized by using the several types of synthetic routes like solid phase claisenschemdit, cross aldol condensation, acid catalyst, coupling reaction, knoevanogel condensation and microwave assisted synthesis.[6]Chalcones are very interesting molecules due to their diverse applications in different fields. They display a wide range of pharmacological properties, including antimutagenic and antitumor-promoting activities [6],antibacterial[6].

Pyrazoles are also useful in numerous pharmacological applications in different fields such as Antibacterial,[6][7][8] Antifungal,[6][7][8]Analgesic,[9] Anti-inflammatory,[9] Antiplatelet Activity,[9]Anti-Oxidant,[10] and shows variety of Anti-neurotoxic, [11]COX enzymatic activity, [11]Neuroprotective effects, [11]Ulcerogenic activity[11].

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.

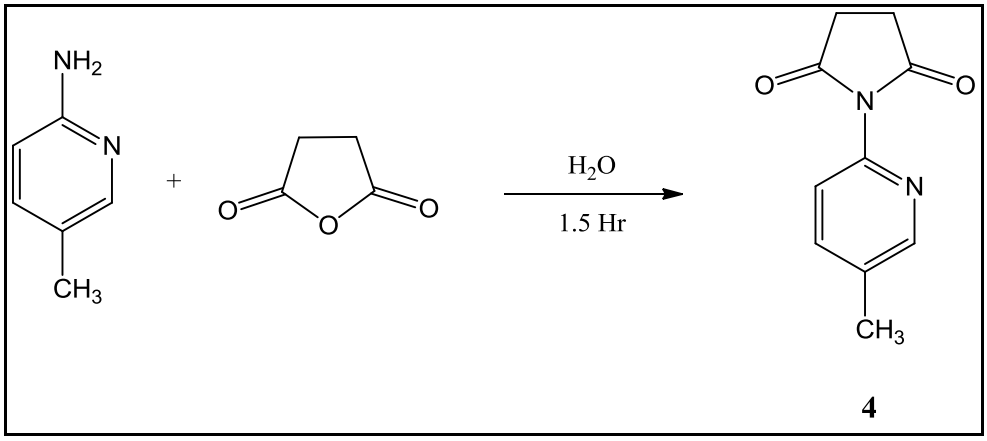
Experimental Section:

General Procedure of Synthesis:

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

0.01 mole of the appropriately 5-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 180^0C about 1.5 hr. the crude product was separated and recrystalised from isopropyl alcohol **(Scheme-1)**

Reaction Scheme:



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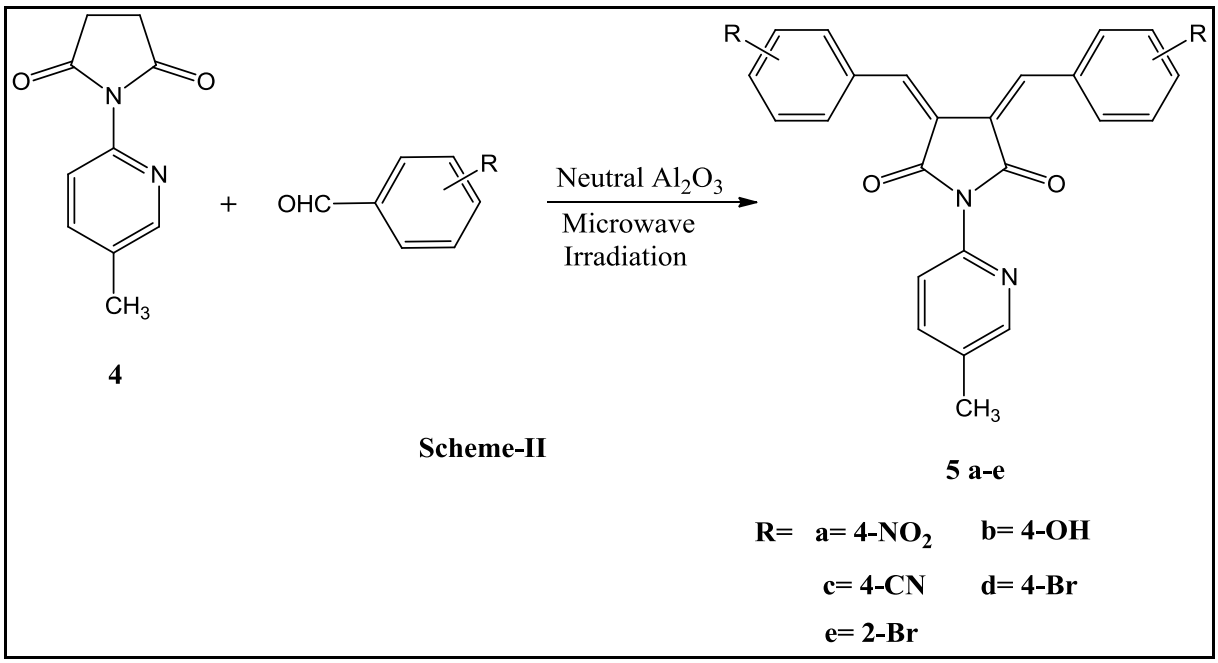
Scheme-1

***Preparation of 2-((3E, 4E)-3, 4-bis (Substituted benzylidenePyrrolidin-1-yl)-5-Methyl Pyridines (5 a-e) :**

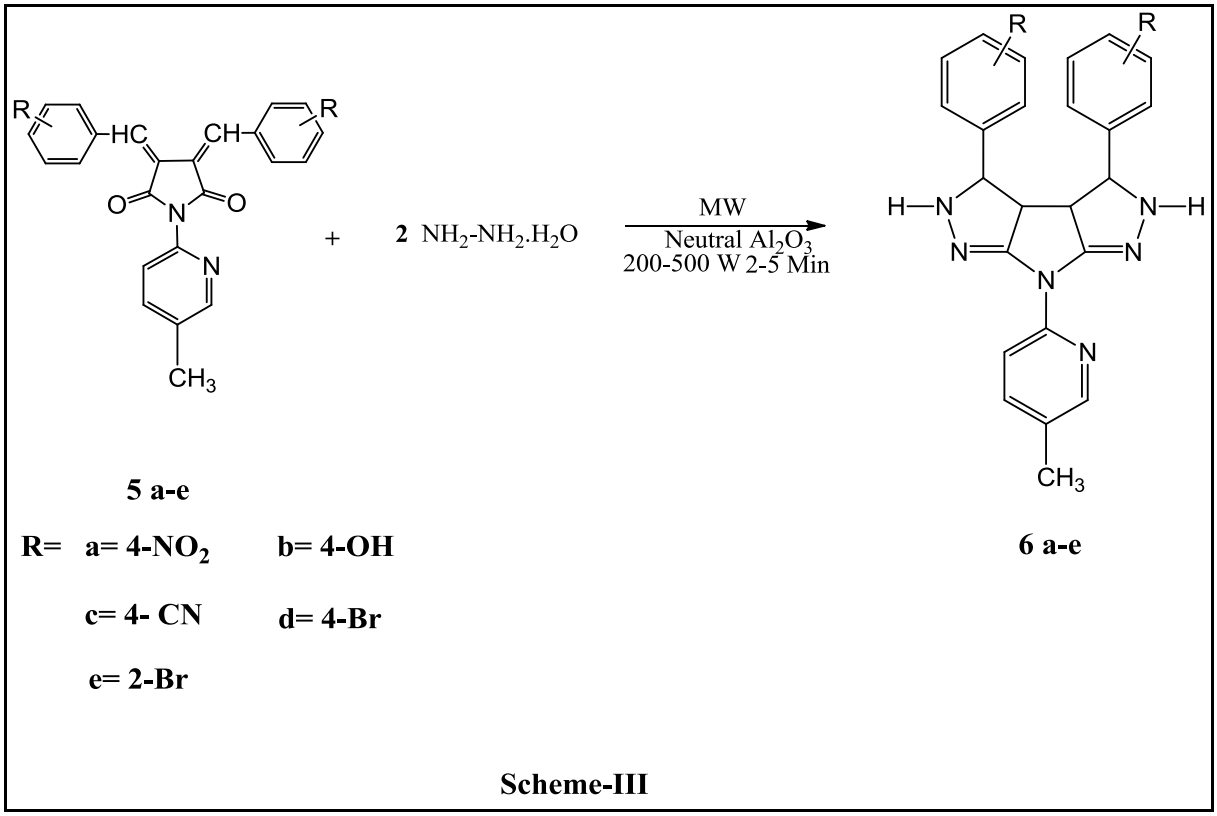
The bis-chalcones (5 a-e) derivatives were synthesized by the mixture of 0.01 moles N-5-Methyl pyridine succinimide and 0.02 mole of substituted benzaldehyde in 1 gm. of Neutral Al_2O_3 with the help of microwave irradiations. This mixture is kept in microwave at 800 W power for 3-5 min. in solvent free 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-(5-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (6 a-e):**

The bis-pyrazole (6 a-e) derivatives were synthesized by mixture of 1 moles of bis-chalcone (5 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)**



Scheme-III

Physiochemical and Analytical data for Compounds:

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

Whitish Solid, Yield (75%) M.P. 146-148^{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 (63.10%); H (5.20%); N (14.76%). **IR (KBr):** 1709, 2487, 1334, 1301, 3044, 2967, 2924, 1551, 1598, 2759 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):** 2.32 (S, 3H, CH_3-Pyridine), 2.95 (S, 4H, imide), 7.82-8.40 (m, 2H, pyridine), 8.21 (d, 1H, pyridine).

(3Z,4Z)-3,4-bis(4-Nitrobenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione (5a) : Brown solid, Yield (81%) M.P. 112-114^{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 (63.10%); H (3.20%); N (12.76%). **IR (KBr):** 740, 850, 1352, 3041, 2965, 2924, 1551, 1598, cm^{-1}.

^{1}HNMR (500 MHz, DMSOd^6,δ ppm):8.10-6.50 (m, 7H, Ar-H and =CH), 2.41 (S, 3H, -CH_3)

(3Z,4Z)-3, 4-bis (4-Hydroxybenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione**(5b)**Orange solid, Yield (60%) M.P. 118-120^{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 (72.20%); H (4.30%); N (7.16%). **IR (KBr):** 732, 826, 3180, 1334, 1301, 3044, 2900, 2924, 1551, 1598, cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.22-7.12 (m, 7H, Ar-H and =CH), 2.31 (S, 3H, -CH_3)

(3Z,4Z)-3,4-bis(4-Cyanobenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione (5c)

LightYellow solid, Yield (88%) M.P. 142-146^{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 (74.90%); H (3.70%); N (13.76%). **IR (KBr):** 751, 823, 2287, 1325, 3154, 2967, 1551, 1598, cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):** 8.12-6.18 (m, 7H, Ar-H and =CH), 2.46 (S, 3H, -CH_3)

(3Z,4Z)-3,4-bis(4-Bromobenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione(5d)

Yellow solid, Yield (84%) M.P. 90-94^{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 (54.90%); H (3.20%); N (5.40%). **IR (KBr):**740, 850,1334, 3134, 2961, 1548, 1590, cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.40-6.31 (m, 7H, Ar-H and =CH), 2.41 (S, 3H, -CH_3)

(3Z,4Z)-3,4-bis(2-Bromobenzylidene)-1-(5-methylpyridin-2-yl)pyrrolidine-2,5-dione (5e)

Yellow solid, Yield (76%) M.P. 96-98^{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 (54.80%); H (3.25%); N (5.60%). **IR (KBr):**750, 855,1328, 3145, 2960, 1541, 1560, cm^{-1}.**^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.32-6.25 (m, 7H, Ar-H and =CH), 2.63 (S, 3H, -CH_3)

3,4-bis (4-Nitro Phenyl) -7-(5-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (6a):

Dark Yellow solid, Yield (82%); M.P. 230-232^{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 (59.20%); H (4.22%); N (23.12%)**IR (KBr cm^{-1}):** 750, 850, 1358, 1550-1560, 1500-1600, 3150, 2900-3000cm^{-1}

^{1}HNMR (500 MHz, DMSOd^6,δ ppm):8.61-7.56 (m, 5H, Ar-H); 3.58(d, 1H, -CH), 2.62-2.60(d, 1H, -CH), 2.16 (S, 3H, CH_3), 10.51(S, 1H, N-H)

3,4-bis (4-HydroxyPhenyl) -7-(5-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (6b):

Orange solid, Yield (56%); M.P. 180-184^{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 (67.62%); H (5.21%); N (19.55%)**IR (KBr cm^{-1}):** 730, 840, 3280, 1555-1565, 1500-1600, 3180, 1280, 2950 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-(5-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (6c):

Yellow solid, Yield (86%); M.P. 184-186^{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 (70.28%); H (4.65%); N (25.38%)**IR (KBr cm^{-1}):** 745, 856, 2180, 1560-1570, 1500-1600, 3260, 2960 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-(5-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (6d):

Brown solid, Yield (84%); M.P. 216-220^{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 (52.28%); H (3.68%); N (15.36%)**IR (KBr cm^{-1}):** 730, 846, 1545-1555, 1500-1600, 2976, 3210, 1980 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-(5-Methyl Pyridin-2-yl)-3,3a,3b, 4,5,7-hexahydro-2H-Pyrrolo [2,3-(c:5,4-c')] dipyrazoles (6e):

Brown solid, Yield (79%); M.P. 144-146^{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}):** 735, 842, 1552-1563, 1500-1600, 2986, 3202 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)

Table: 1: It shows Physical Data of the synthesized compounds (5a-5e) and (6a-6e):

Compound code	Molecular Formula	Molecular Weight	% Yield	M.P (^{0}C)	Colour
4	$C_{10}H_{10}O_2N_2$	190.20	75	146-148	White solid
5a	$C_{24}H_{16}N_4O_6$	456	81	112-114	Brown solid
5b	$C_{24}H_{18}N_2O_4$	398	60	118-120	Orange solid
5c	$C_{26}H_{16}N_4O_2$	416	88	142-146	LightYellow solid
5d	$C_{24}H_{16}Br_2N_2O_2$	524	84	90-94	Yellow solid
5e	$C_{24}H_{16}Br_2N_2O_2$	524	76	96-98	Yellow solid
6a	$C_{24}H_{20}N_8O_4$	484	82	230-232	Dark Yellow solid
6b	$C_{24}H_{22}N_6O_2$	426	56	180-184	Orange solid
6c	$C_{26}H_{20}N_8$	444	86	184-186	Yellow solid
6d	$C_{24}H_{20}Br_2N_6$	551.8	84	216-220	Brown solid
6e	$C_{24}H_{20}Br_2N_6$	551.8	79	144-146	Brown solid

Results and Discussion:

The study concluded that all synthesized compounds (5a - 6e).in microwave assisted solvent free synthesis using neutral Al_2O_3 as a solid supportexhibited good yield. The Method is green and efficient and the product obtained in very short time. With high Percentage and purity also better than other conventional

method. The resulting compounds are bis-chalcones and bis-pyrazoles are expected to show good microbial activity

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