



SYNTHESIS OF BIS-PYRAZOLES USING 1-(4-METHYLPYRIDIN-2-YL) PIPERIDINE-2,6-DIONE

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ABSTRACT

The green and efficient synthesis of new series of bis pyrazoles derivatives from 1-(4-methylpyridin-2-yl) piperidine-2,6-dione under microwave irradiation. The 1-(4-methylpyridin-2-yl) piperidine-2,6-dione, was synthesized from Glutaric anhydride and 4-methyl pyridine-2-amine. This cyclic imides condensed with substituted aromatic aldehydes using solid support neutral Al_2O_3 in microwave. The resultant bis-chalcone underwent ring closer with hydrazine hydrate in presence of neutral Al_2O_3 under microwave irradiation offer bis-pyrazoles derivatives.

KEYWORDS: Glutaric anhydride, substituted pyridine amines, cyclic imides, Bis-chalcone.

INTRODUCTION

Chalcones having an α , β unsaturated carbonyl group are one of the important biocides and useful synthons for various chemical transformations. Most of the chalcones are highly biologically active with a number of pharmacological and medicinal applications.

The custom of microwave energy to accelerate the organic reactions is of increasing attention and offers several benefits over conventional heating techniques. Synthesis of the molecules which normally involves a long time can be completed conveniently and rapidly in microwave oven. Less reaction time, easy work up and cleaner products are the major benefits of microwave heating.^[1] Furthermore the reactions can be carried out under solvent free conditions which holds a planned position as the solvents are often very toxic, expensive, problematic to use. Solvent free condition is especially suitable for microwave activation. Thus the use of microwave energy for the synthesis of organic compounds forms a part of green chemistry.^[1]

Pyrazole belongs to the "diazole" class of heterocycles and is the most significant moiety found in a large number of pharmaceutical agents. Pyrazole products have attracted the attention of research scholars on account of their extensive range of applications in medicine.^[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.^[3] One of the most fundamental purposes 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.^[4] It possess different biological and pharmacological activities, which exhibit an antibacterial^[5], antifungal^[5], anti-inflammatory^[6], herbicidal, plant growth regulating, fungicidal, bactericidal, anti-pyretic.^[7] Pyrazole and its derivatives possess Monocytic cell viability and chemokine secretion, Anti-neurotoxic effects, COX enzymatic activity, Neuroprotective effects, Anti-neurotoxic activity, Ulcerogenic activity, Acute toxicity.^[8]

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

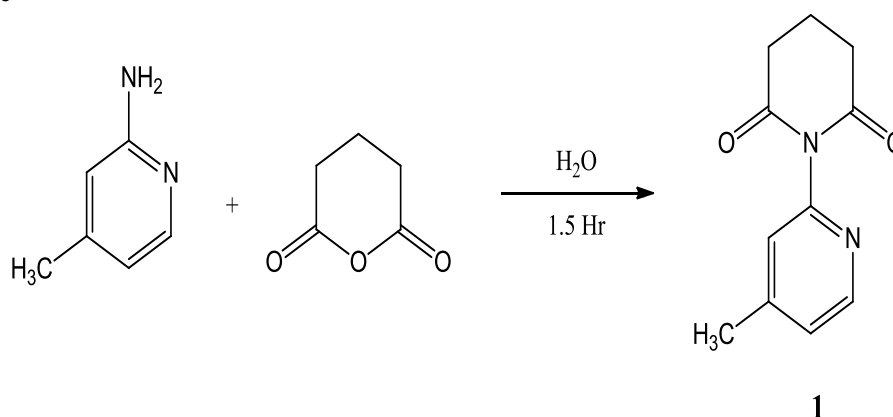
General Procedure of Synthesis

*Preparation of 1-(4-methylpyridin-2-yl) piperidine-2,6-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 glutaric 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°C about 1.5 hr. the crude product was separated and recrystallised from isopropyl alcohol (**Scheme-1**).

Reaction Scheme

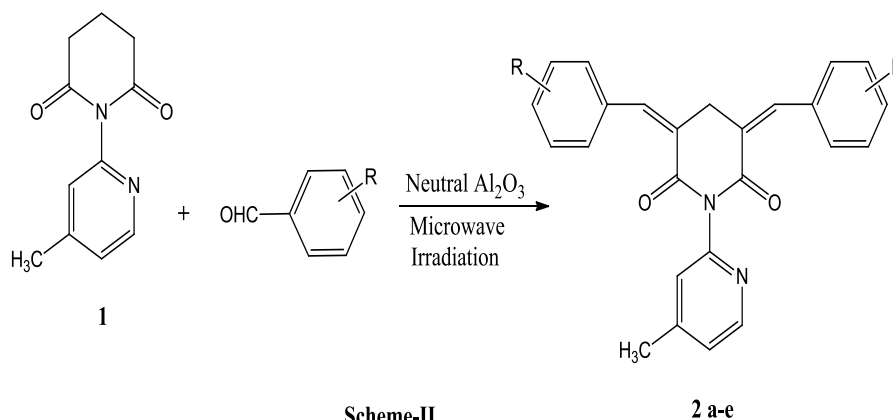


Scheme-1.

*preparation of (3Z, 5Z)-1-(4-methylpyridin-2-yl)-3,5-bis (benzylidene) piperidine-2,6-dione (2 a-e)

The bis-chalcones (2 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 Al₂O₃ 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 removal of neutral Al₂O₃. (**Scheme-2**)



Scheme-II

R= a= 4-NO₂ b= 4-OH

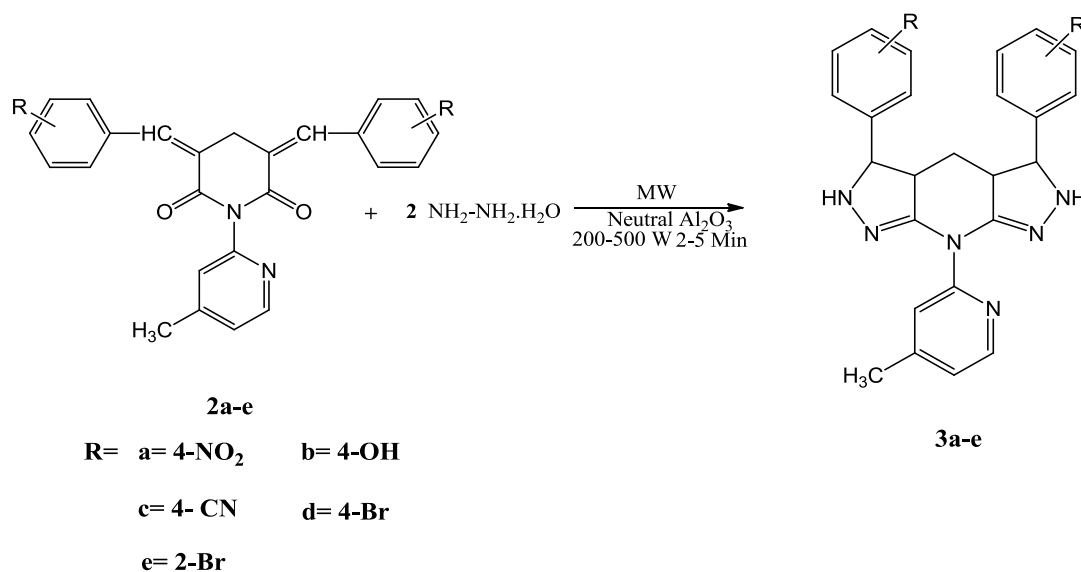
c= 4-CN d= 4-Br

e= 2-Br

*Preparation of 8-(4-methylpyridin-2-yl)-3,5-bis (Substituted Phenyl)-2,3,3a,4,4a,5,6,8-octahydrodipyrzolo[3,4-b:4',3'-e]pyridine (3 a-e)

The bis-pyrazole (3a-e) derivatives were synthesized by mixture of 1 moles of bis-chalcone (2a-e) and 2 moles of

hydrazine hydrate in 1 gm of neutral Al₂O₃ under microwave supported solvent less condition on 800 W power for 5-8 min. The separated compounds were recrystallised from ethanol. (**Scheme-III**).



Scheme-III

Physiochemical and Analytical data for Compounds 1-(4-methylpyridin-2-yl) piperidine-2,6-dione : (1)

Whitish Solid, Yield (80%) M.P. 150-154^oC M.F. C₁₁H₁₂O₂N₂ M.W= 204, **Elemental Analysis:** Calculated C (64.69%); H (5.92%); N (13.72%). Found C (64.01%); H (5.72%); N (13.80%). **IR (KBr):** 1705, 1610, 1375, 3150 cm⁻¹. **¹HNMR (500 MHz, DMSO-d₆, δ ppm):** 2.60 (s, 3H, CH₃-Pyridine), 1.6(m, 2H, CH₂), 2.3(t, 2H, CH₂), 8.3-7.20 (m, 3H, pyridine).

(3Z, 5Z)-1-(4-methylpyridin-2-yl)-3,5-bis(4-Nitrobenzylidene)piperidine-2,6-dione(2a)

Brown solid, Yield (88%) M.P. 136-138^oC M.F. C₂₅H₁₈N₄O₆ M.W= 470, **Elemental Analysis:** Calculated C (63.83%); H (3.86%); N (11.91%). Found C (63.72%); H (3.70%); N (11.65%). **IR (KBr):** 1701, 1344, 1310, 3044, 2977, 2920, 1580, 2750 cm⁻¹. **¹HNMR (500 MHz, DMSO-d₆, δ ppm):** 8.12-7.07 (m, 7H, Ar-H and =CH), 2.45 (s, 3H, -CH₃), 1.80 (s, 2H, -CH₂).

(3Z,5Z)-1-(4-methylpyridin-2-yl)-3,5-bis(4-Hydroxybenzylidene)piperidine-2,6-dione (2b)

Orange solid, Yield (61%) M.P. 135-138^oC M.F. C₂₅H₂₀N₂O₄ M.W= 412, **Elemental Analysis:** Calculated C (72.80%); H (4.89%); N (6.79%). Found C (72.50%); H (4.62%); N (6.60%). **IR (KBr):** 1699, 1335, 1303, 3110, 2911, 1580, 1590, 2740 cm⁻¹. **¹HNMR (500 MHz, DMSO-d₆, δ ppm):** 8.11-7.05 (m, 7H, Ar-H and =CH), 2.35 (s, 3H, -CH₃), 1.85 (s, 2H, -CH₂), 10.01 (s, 1H, OH).

(3Z,5Z)-1-(4-methylpyridin-2-yl)-3,5-bis(4-Cyanobenzylidene)piperidine-2,6-dione(2c)

Light Yellow solid, Yield (84%) M.P. 165-168^oC M.F. C₂₇H₁₈N₄O₂ M.W= 430, **Elemental Analysis:** Calculated C (75.34%); H (4.21%); N (13.02%). Found C (75.80%); H (4.10%); N (13.20%). **IR (KBr):** 1710, 2470, 2230, 1311, 3035, 2930, 2921, 1540, 1590, 2748 cm⁻¹. **¹HNMR (500 MHz, DMSO-d₆, δ ppm):** 8.10-6.37

(m, 7H, Ar-H and =CH), 2.40 (s, 3H, -CH₃), 1.88 (s, 2H, -CH₂).

(3Z,5Z)-1-(4-methylpyridin-2-yl)-3,5-bis(4-Bromobenzylidene)piperidine-2,6-dione (2d)

Yellow solid, Yield (90%) M.P. 110-112^oC M.F. C₂₅H₁₈Br₂N₂O₂, M.W= 538, **Elemental Analysis:** Calculated C (55.79%); H (3.37%); N (5.20%). Found C (55.78%); H (3.18%); N (5.28%). **IR (KBr):** 1708, 745, 852, 1320, 1305, 3050, 2967, 2935, 1560, 1610, 2740 cm⁻¹. **¹HNMR (500 MHz, DMSO-d₆, δ ppm):** 8.40-6.40 (m, 7H, Ar-H and =CH), 2.56 (s, 3H, -CH₃), 1.84 (s, 2H, -CH₂).

(3Z,5Z)-1-(4-methylpyridin-2-yl)-3,5-bis(2-Bromobenzylidene)piperidine-2,6-dione (2e)

Yellow solid, Yield (86%) M.P. 84-86^oC M.F. C₂₅H₁₈Br₂N₂O₂, M.W= 538, **Elemental Analysis:** Calculated C (55.79%); H (3.37%); N (5.24%). Found C (55.71%); H (3.26%); N (5.28%). **IR (KBr):** 1715, 735, 856, 2477, 1330, 3044, 2964, 2924, 1551, 1598 cm⁻¹. **¹HNMR (500 MHz, DMSO-d₆, δ ppm):** 8.50-6.70 (m, 7H, Ar-H and =CH), 2.58 (s, 3H, -CH₃), 1.86 (s, 2H, -CH₂).

8-(4-methylpyridin-2-yl)-3,5-bis (4-NitroPhenyl)-2,3,3a,4,4a,5,6,8-octahydro dipyrzolo [3,4-b:4',3'-e] pyridine (3a)

Dark Yellow solid, Yield (78%); M.P. 232-234^oC, M.F. C₂₅H₂₂N₈O₄, M.W. 498, **Elemental analysis calculated** C (60.24 %); H (4.45%); N (22.48%) **Found** C (60.22%); H (4.20%); N (22.30%) **IR (KBr cm⁻¹):** 735, 855, 1350, 1500-1600, 3010, 2960, 1550, 1970 cm⁻¹.

¹HNMR (500 MHz, DMSO-d₆, δ ppm): 8.58-7.50 (m, 5H, Ar-H); 3.61(d, 1H, -CH), 2.60-2.64(d, 1H, -CH), 2.10 (s, 3H, CH₃), 1.4 (d, 2H, -CH₂), 10.50(s, 1H, N-H).

8-(4-methylpyridin-2-yl)-3,5-bis (4-HydroxyPhenyl)-2,3,3a,4,4a,5,6,8-octahydro dipyrazolo [3,4-b:4',3'-e] pyridine (3b)

Orange solid, Yield (62%); M.P. 218-220 °C, M.F. C₂₅H₂₄N₆O₂, M.W. 440, Elemental analysis calculated C (68.17%); H (5.49%); N(19.08%) Found C (68.10%); H (5.33%); N (19.11%) IR (KBr cm⁻¹): 742, 858, 3270, 1500-1600, 3100, 2980, 1555, 1975 cm⁻¹.

¹HNMR (500 MHz, DMSO-d₆, δ ppm): 8.52-7.56 (m, 5H, Ar-H); 3.50(d, 1H, -CH), 2.65-2.63(d, 1H, -CH), 2.11 (S, 3H, CH₃), 1.3 (d, 2H, -CH₂), 10.55(S, 1H, N-H).

8-(4-methylpyridin-2-yl)-3,5-bis(4-CyanoPhenyl)-2,3,3a,4,4a,5,6,8-octahydro dipyrazolo [3,4-b:4',3'-e] pyridine (3c)

Yellow solid, Yield (86%); M.P. 170-172 °C, M.F. C₂₇H₂₂N₈, M.W. 459, Elemental analysis calculated C (70.73 %); H(4.84%); N(24.44%) Found C (70.35%); H (4.70%); N (24.34%) IR (KBr cm⁻¹): 760, 858, 2262, 1500-1600, 3030, 2960, 1566, 1974 cm⁻¹.

¹HNMR (500 MHz, DMSO-d₆, δ ppm): 8.61-7.60 (m, 5H, Ar-H); 3.52 (d, 1H, -CH), 2.61-2.65(d, 1H, -CH), 2.20 (S, 3H, CH₃), 1.41 (d, 2H, -CH₂), 10.60 (S, 1H, N-H).

8-(4-methylpyridin-2-yl)-3,5-bis(4-BromoPhenyl)-2,3,3a,4,4a,5,6,8-octahydro dipyrazolo [3,4-b:4',3'-e] pyridine (3d)

Brown solid, Yield (88%); M.P. 220-222°C, M.F. C₂₅H₂₂Br₂N₆, M.W. 566, Elemental analysis calculated C (53.02%); H (3.92%); N (14.84%) Found C (53.12%); H (3.60%); N (14.30%) IR (KBr cm⁻¹): 750, 860, 1500-1600, 3240, 2910, 1560, 1964 cm⁻¹.

¹HNMR (500 MHz, DMSO-d₆, δ ppm): 8.62-7.59 (m, 5H, Ar-H); 3.66(d, 1H, -CH), 2.71-2.68 (d, 1H, -CH), 2.18 (S, 3H, CH₃), 1.46 (d, 2H, -CH₂), 10.68 (S, 1H, N-H).

8-(4-methylpyridin-2-yl)-3,5-bis(2-BromoPhenyl)-2,3,3a,4,4a,5,6,8-octahydro dipyrazolo [3,4-b:4',3'-e] pyridine (3e)

Brown solid, Yield (74%); M.P. 184-186°C, M.F. C₂₅H₂₂Br₂N₆, M.W. 566, Elemental analysis calculated C (53.02%); H (3.92%); N (14.84%) Found C (53.10%); H (3.80%); N (14.80%) IR (KBr cm⁻¹): 745, 858, 1500-1600, 3275, 2970, 1562, 1960 cm⁻¹.

¹HNMR (500 MHz, DMSO-d₆, δ ppm): 8.52-7.50 (m, 5H, Ar-H); 3.60 (d, 1H, -CH), 2.65-2.60 (d, 1H, -CH), 2.14 (S, 3H, CH₃), 10.56 (S, 1H, N-H).

Physical Data of the Synthesized compounds.

Compound code	Molecular Formula	Molecular Weight	% Yield	M.P (°C)	Colour
1	C ₁₁ H ₁₂ O ₂ N ₂	204	80	150-154	White solid
2a	C ₂₅ H ₁₈ N ₄ O ₆	470	88	136-138	Brown solid
2b	C ₂₅ H ₂₀ N ₂ O ₄	412	61	135-138	Orange solid
2c	C ₂₇ H ₁₈ N ₄ O ₂	430	84	165-168	LightYellow solid
2d	C ₂₅ H ₁₈ Br ₂ N ₂ O ₂	538	90	110-112	Yellow solid
2e	C ₂₅ H ₁₈ Br ₂ N ₂ O ₂	538	86	84-86	Yellow solid
3a	C ₂₅ H ₂₂ N ₈ O ₄	498	78	232-234	Dark Yellow solid
3b	C ₂₅ H ₂₄ N ₆ O ₂	440	62	218-220	Orange solid
3c	C ₂₇ H ₂₂ N ₈	459	86	170-172	Yellow solid
3d	C ₂₅ H ₂₂ Br ₂ N ₆	566	88	220-222	Brown solid
3e	C ₂₅ H ₂₂ Br ₂ N ₆	566	74	184-186	Brown solid

RESULT AND DISCUSSION

The study concluded that all synthesized compounds (2a-e & 3a-e). in microwave assisted solvent free synthesis using neutral Al₂O₃ as a solid support exhibited good yield. The Method is green and competent 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 probable to show good microbial activity.

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