Research Article

Synthesis and Characterisation of 8-(5-methylpyridin-2-yl)-3,5-bis (Substituted Phenyl)-2,3,3a,4,4a,5,6,8-octahydro dipyrazolo [3,4-b:4',3'-e] Pyridine

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Abstract

The development of new strategies for synthesis of bis- chalcones and bis-pyrazoles has been reported as a simple ecofriendly microwave supported solvent free synthesis of bis-chalcones was carried out by the reaction of 1-(5-methylpyridin-2-yl) piperidine-2,6-dione with different substituted benzaldehyde in presence of neutral alumina. In the similar way the novel bis-pyrazoles were developed from bis-chalcones and hydrazine hydrate with neutral alumina. The current methodology contribute a innovative and competent method for the synthesis of chalcones and pyrazoles with some advantages such as excellent yields, short reaction time, better recoverability.

Keywords: Glutaric anhydride, 5-methyl 2-amino pyridine, cyclic imides, Bis-chalcone

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Introduction

The development of a clean procedure for the preparation of heterocyclic compounds is a major task in modern heterocyclic chemistry in view of the environmental, practical and economic issues [1]. Microwave-assisted organic synthesis has opened up new openings for the synthetic chemists by providing new paths not applied by conventional methods. Microwave-assisted synthesis is an eco-friendly and efficient method of synthesis of organic compounds as compared to the conventional method of synthesis. In this method, reaction occurs more rapidly, safely and with greater chemical yields and therefore, this method becomes superior to the conventional method [2]. The conventional method, requiring a longer reaction time and larger quantities of solvents and reagents, causes environmental pollution and contributes to the health hazards.

Pyrazoles are heterocyclic five membered ring structure having three carbon atoms and two nitrogen atoms fixed at first and third position. Most of the pyrazole derivatives have been developed for different biological actions. Hence it has been synthesized the different substituted pyrazoles by using microwave assisted clean and efficient reactions in a recent way to get better yield by eco-friendly reaction[3].

Pyrazole is five membered heterocyclic rings which is useful principal compound for planning strong bioactive agent [3]. The interesting groups of this compound has diverse biological activities such as antibacterial [4], antifungal [4], anti-inflammatory [5], herbicidal, plant growth regulating, fungicidal, bactericidal, anti-pyretic [6]. Anti-neurotoxic effects, COX enzymatic activity, Anti-neurotoxic activity, Ulcerogenic activity, Acute toxicity [7], Antiplatelet Activity [8], Anti-Oxidant [9], Neuroprotective effects[10], Anti-neurotoxic activity [10].

Materials and Methods

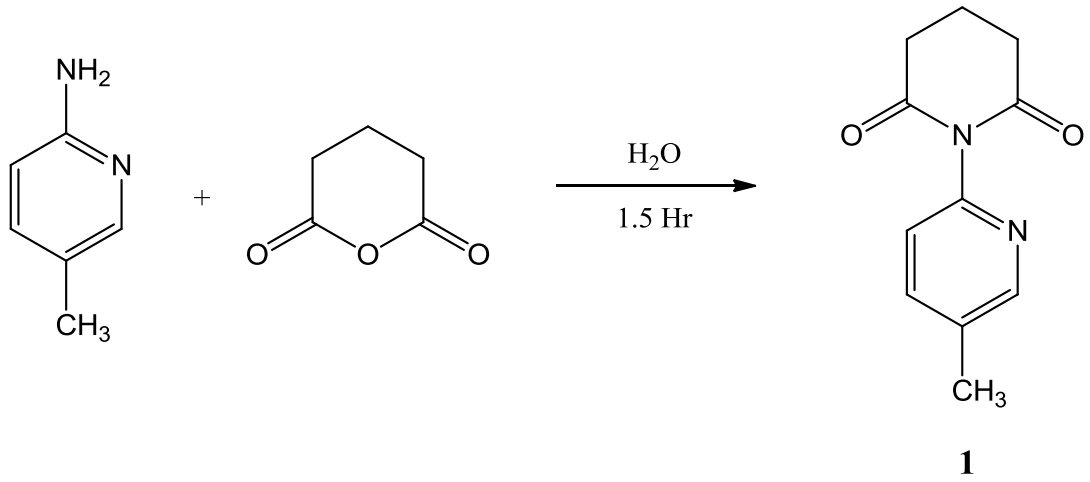
All research chemicals were purchased from Sigma-Aldrich and S.D. Fine Chemicals India Pvt. Ltd. and used as such for the reactions. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates. Melting points of the synthesized compounds were determined by open capillary 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) piperidine-2,6-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 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 recrystalised from isopropyl alcohol (**Scheme-1**).



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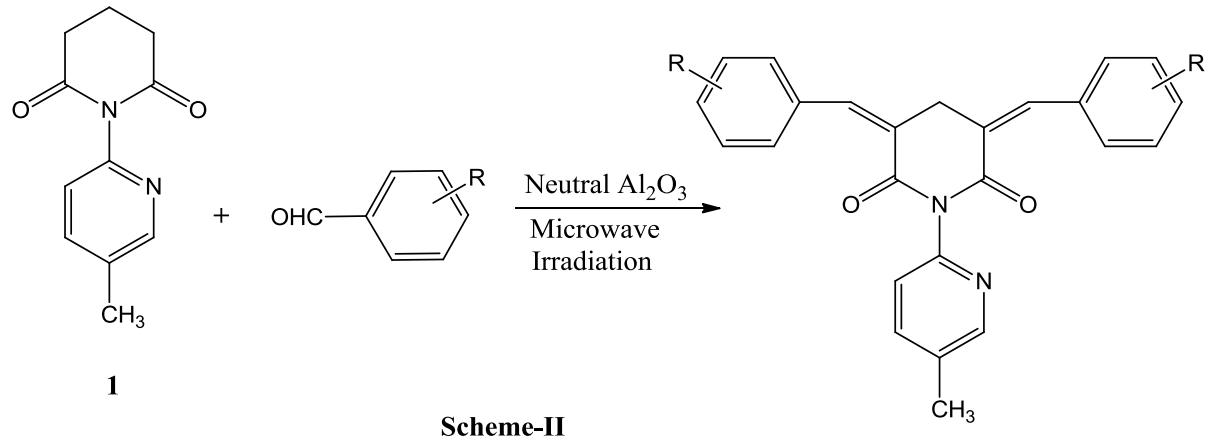
Scheme 1

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

The bis-chalcones (14 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**).



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Scheme-II

2 a-e

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

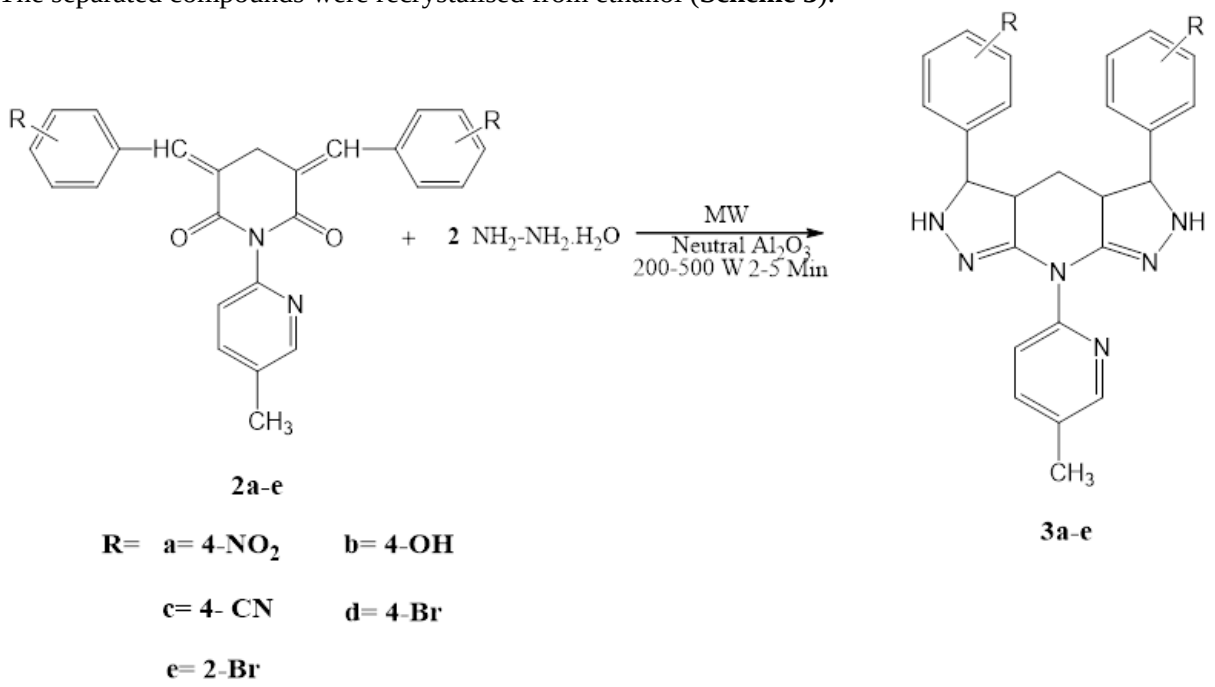
c= 4-CN d= 4-Br

e= 2-Br

Scheme 2

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

The bis-pyrazole (3 a-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 Al_2O_3 under microwave supported solvent less condition on 800 W power for 5-8 min. The separated compounds were recrystalised from ethanol (**Scheme 3**).



2a-e

3a-e

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

c= 4- CN d= 4-Br

e= 2-Br

Scheme 3

Physiochemical and Analytical data for Compounds

1-(5-methylpyridin-2-yl) piperidine-2,6-dione : (1)

Whitish Solid, Yield (84%) M.P. 140-144^{0}C M.F. $C_{11}H_{12}O_2N_2$ M.W= 204, Elemental Analysis: Calculated C (64.69%); H (5.92%); N (13.72%). Found C (64.10%); H (5.82%); N (13.60%). IR (KBr): 1726, 1599, 1379, 3205 cm^{-1}. ^{1}HNMR (500 MHz, DMSOd^6, δ ppm): 2.3 (S, 3H, CH_3-Pyridine), 1.8 (m, 2H, CH_2), 2.6 (t, 2H, CH_2), 8.25 -7.20 (m, 3H, pyridine).

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

Brown solid, Yield (90%) M.P. 156-158^{0}C M.F. $C_{25}H_{18}N_4O_6$ M.W= 470, Elemental Analysis: Calculated C (63.83%); H (3.86%); N (11.91%). Found C (63.75%); H (3.75%); N (11.75%). IR (KBr): 1709, 1348, 1311, 3040, 2980, 2920, 1585, 2750 cm^{-1}. ^{1}HNMR (500 MHz, DMSOd^6, δ ppm): 8.15-7.05 (m, 7H, Ar-H and =CH), 2.42 (S, 3H, -CH_3), 1.84 (S, 2H, -CH_2)

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

Orange solid, Yield (65%) M.P. 120-124^{0}C M.F. $C_{25}H_{20}N_2O_4$ M.W= 412, Elemental Analysis: Calculated C (72.80%); H (4.89%); N (6.79%). Found C (72.70%); H (4.72%); N (6.70%). IR (KBr): 1710, 1338, 1303, 3140, 2931, 1590, 1600, 2750 cm^{-1}. ^{1}HNMR (500 MHz, DMSOd^6, δ ppm): 8.10-7.08 (m, 7H, Ar-H and =CH), 2.45 (S, 3H, -CH_3), 1.90 (S, 2H, -CH_2), 10.04 (S, 1H, OH)

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

LightYellow solid, Yield (82%) M.P. 170-174 ^{0}C M.F. $C_{27}H_{18}N_4O_2$ M.W= 430, Elemental Analysis: Calculated C (75.34%); H (4.21%); N (13.02%). Found C (75.20%); H (4.14%); N (13.25%). IR (KBr): 1720, 2465, 2232, 1311, 3035, 2900, 2971, 1540, 1580, 2710 cm^{-1}. ^{1}HNMR (500 MHz, DMSOd^6, δ ppm): 8.09-6.37 (m, 7H, Ar-H and =CH), 2.42 (S, 3H, -CH_3), 1.84 (S, 2H, -CH_2)

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

Yellow solid, Yield (91%) M.P. 108-110 ^{0}C M.F. $C_{25}H_{18}Br_2N_2O_2$, M.W= 538, Elemental Analysis: Calculated C (55.79%); H (3.37%); N (5.20%). Found C (55.70%); H (3.28%); N (5.18%). IR (KBr): 1712, 742, 852, 1328, 1305, 3050, 2967, 1560, 1605, 2740 cm^{-1}. ^{1}HNMR (500 MHz, DMSOd^6, δ ppm): 8.52-6.40 (m, 7H, Ar-H and =CH), 2.59 (S, 3H, -CH_3), 1.92 (S, 2H, -CH_2)

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

Yellow solid, Yield (80%) M.P. 90-92 ^{0}C M.F. $C_{25}H_{18}Br_2N_2O_2$, M.W= 538, Elemental Analysis: Calculated C (55.79%); H (3.37%); N (5.24%). Found C (55.78%); H (3.36%); N (5.23%). IR (KBr): 1720, 735, 855, 2477, 1330, 3044, 2964, 1551, 1598 cm^{-1}. ^{1}HNMR (500 MHz, DMSOd^6, δ ppm): 8.45-6.70 (m, 7H, Ar-H and =CH), 2.50 (S, 3H, -CH_3), 1.90 (S, 2H, -CH_2)

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

Dark Yellow solid, Yield (76%); M.P. 218-220 ^{0}C, M.F. $C_{25}H_{22}N_8O_4$, M.W. 498, Elemental analysis calculated C (60.24 %); H (4.45%); N (22.48%) Found C (60.14%); H (4.40%); N (22.20%) IR (KBr cm^{-1}): 732, 852, 1354, 1500-1600, 3010, 2960, 1548, 1960 cm^{-1}

^{1}HNMR (500 MHz, DMSOd^6, δ ppm): 8.50-7.50 (m, 5H, Ar-H); 3.63(d, 1H, -CH), 2.62-2.66(d, 1H, -CH), 2.12 (S, 3H, CH_3), 1.42 (d, 2H, -CH2), 10.48(S, 1H, N-H)

8-(5-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 (65%); M.P. 190-192 ^{0}C, M.F. $C_{25}H_{24}N_6O_2$, M.W. 440, Elemental analysis calculated C (68.17%); H (5.49%); N(19.08%) Found C (68.12%); H (5.38%); N (19.01%) IR (KBr cm^{-1}): 744, 851, 3240, 1500-1600, 3100, 2960, 1552, 1955 cm^{-1}

^{1}HNMR (500 MHz, DMSOd^6, δ ppm): 8.62-7.56 (m, 5H, Ar-H); 3.50(d, 1H, -CH), 2.65-2.63(d, 1H, -CH), 2.11 (S, 3H, CH_3), 1.3 (d, 2H, -CH2), 10.55(S, 1H, N-H)

8-(5-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 (84%); M.P. 162-164 ^{0}C, M.F. $C_{27}H_{22}N_8$, M.W. 459, Elemental analysis calculated C (70.73 %); H(4.84%); N(24.44%) Found C (70.55%); H (4.72%); N (24.30%) IR (KBr cm^{-1}): 760, 858, 2262, 1500-1600, 3030, 2960, 1566, 1974 cm^{-1}

^{1}HNMR (500 MHz, DMSOd^6, δ ppm): 8.61-7.60 (m, 5H, Ar-H); 3.52 (d, 1H, -CH), 2.61-2.65(d, 1H, -CH), 2.22 (S, 3H, CH_3), 1.44 (d, 2H, -CH2), 10.60 (S, 1H, N-H)

Table 1 It shows Physical Data of the synthesized compounds 1, (2a-2e) and (3a-3e)

Compound code	Molecular Formula	Molecular Weight	% Yield	M.P (^{0}C)	Colour
1	$C_{11}H_{12}O_2N_2$	204	84	140-144	White solid
2a	$C_{25}H_{18}N_4O_6$	470	90	156-158	Brown solid
2b	$C_{25}H_{20}N_2O_4$	412	65	120-124	Orange solid
2c	$C_{27}H_{18}N_4O_2$	430	82	170-174	LightYellow solid
2d	$C_{25}H_{18}Br_2N_2O_2$	538	91	108-110	Yellow solid
2e	$C_{25}H_{18}Br_2N_2O_2$	538	80	90-92	Yellow solid
3a	$C_{25}H_{22}N_8O_4$	498	76	218-220	Dark Yellow solid
3b	$C_{25}H_{24}N_6O_2$	440	65	190-192	Orange solid
3c	$C_{27}H_{22}N_8$	459	84	162-164	Yellow solid
3d	$C_{25}H_{22}Br_2N_6$	566	86	232-234	Brown solid
3e	$C_{25}H_{22}Br_2N_6$	566	74	176-178	Brown solid

8-(5-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 (86%); M.P. 232-234^{0}C, M.F. $C_{25}H_{22}Br_2N_6$, M.W. 566, Elemental analysis calculated C (53.02%); H (3.92%); N (14.84%) Found C (53.05%); H (3.60%); N (14.20%) IR (KBr cm^{-1}): 750, 860, 1500-1600, 3240, 2910, 1560, 1964 cm^{-1}

^{1}HNMR (500 MHz, DMSOd^6, 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, CH_3), 1.46 (d, 2H, -CH2), 10.68 (S, 1H, N-H)

8-(5-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. 176-178^{0}C, M.F. $C_{25}H_{22}Br_2N_6$, 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}

^{1}HNMR (500 MHz, DMSOd^6, 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, CH_3), 10.56 (S, 1H, N-H)

Result and Discussion

The study concluded that all synthesized compounds (2a-e & 3a-e). in microwave assisted solvent free synthesis using neutral Al_2O_3 as a solid support exhibited good yield. In this protocol, we have developed a novel and efficient way for the synthesis of chalcones and pyrazoles. In this method, reaction occurs more rapidly, safely and with greater chemical yields and therefore, this method becomes superior to the conventional method. The resulting compounds are bis-chalcones and bis-pyrazoles are expected to show good microbial activity.

Conclusion

All the Synthesized compounds were prepared by microwave irradiation technique. The method was green and efficient time saving. The product obtained in very short time with high percentage yield and purity also better than Conventional method. The resulting compounds are bis-chalcones and bis-pyrazoles are expected to show good microbial activity

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