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MICROWAVE ASSISTED SYNTHESIS OF BIS-PYRAZOLES USING GLUTARIMIDE

S.S.Rajput [1*], S.N.Patel [2], S.B.Chaudhari[3]

[1] Department of Chemistry, SVS's Dadasaheb Rawal College Dondaicha 425408, Maharashtra, India*
E-mail: rajputss65@gmail.com
[2] Department of Chemistry, S.P.D.M. College, Shirpur 425405, Maharashtra, India
[3] Departments of Chemistry, R.C.Patel ASC College, Shirpur 425405, Maharashtra, India

Abstract:
A series of bis-chalcones and their bis-pyrazolesderivatives were synthesizedBis-chalcones were prepared by condensing 1-(6-methylpyridin-2-yl) piperidine-2,6-dionewith substituted aldehydes using solid support neutral Al_2O_3 in microwave. The resultant bis-chalcone products underwent ring closer with hydrazine hydrate in presence of neutral Al_2O_3 under microwave irradiation offer bis-pyrazoles derivatives.

Keywords:6-methyl 2-amino pyridine, cyclic imides, Bis-chalcone, Bis-Pyrazole.

Introduction:

The aim of green chemistry is not only the use of raw components obtained from renewable sources, biodegradable catalyst, and solvents but also involved the improvement of such a protocols which reduce or abolish damaging environmental impacts or reduce generation of hazardous substances, reduce health risk with search for more competent methods to do chemistry for synthesis of prospective scaffolds[i]. Green chemistry has not only grown up in research of academics to become a dynamicstream for organic synthesis but also it grown up in chemical industries, while green chemistry has integrated human health as well as the environment[i]. This progress is marked by significant contributions from institutions with different goals by incorporating green methodologies by designing of chemical supports and paths that are environmentallymoderate for pollution prevention.

For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. Heterocyclic compounds have always been on the lead of attention because of their numerous uses in pharmaceutical applications [ii]. Pyrazole a five-membered, two-nitrogen-containing heterocycle ring is extensively found as the central structure in a large variety of compounds that possess important agrochemical and pharmaceutical activities[iii]. The development of simple synthetic routes for novel medicinally activecompounds from readily available reagents is one of the major tasks in organic synthesis. Pyrazoles and derivatives have attracted considerable attention because of

theextensive variety of biological activities they exhibit, including antiviral, antitumor, antibacterial, antipyretic, amoebicidal, anti-inflammatory, and analgesic activities. [iv-vii]

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.

Result and Discussion:

The Bis- chalcones (**2a-e)** were prepared as starting material to obtain the desired Bis-pyrazole (**3a-e)** derivatives. The sequence leading to the title compounds is outlined in Scheme II. The desired compounds were prepared by the reaction of bis-chalcones with Hydrazine hydrate in presence of neutral alumina under microwave irradiation the product obtained in short time with high percentage purity

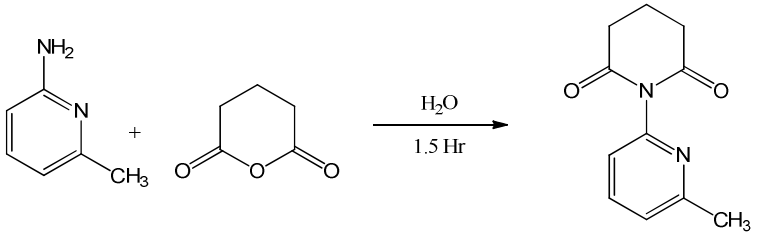
Experimental Section:

General Procedure of Synthesis:

***Preparation of1-(6-methylpyridin-2-yl)piperidine-2,6-dione: (1)**

0.01 mole of the appropriately 6-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^{o}Cabout 1.5 hr. the crude product was separated and recrystalised from isopropyl alcohol **(Scheme-1)**

ReactionScheme:

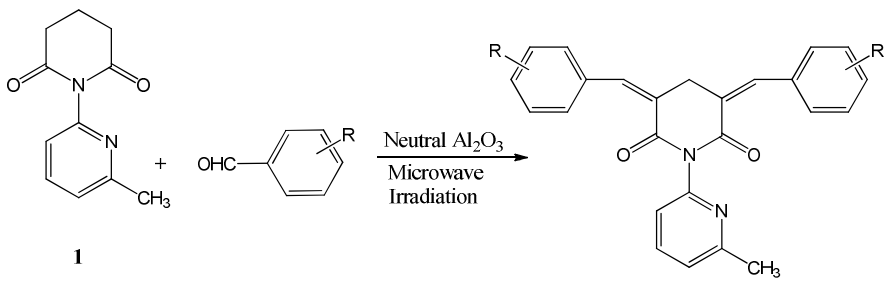


1

Scheme-1

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

The bis-chalcones (2a-e) derivatives were synthesized by the mixture of 0.01 moles N-6-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)**



1

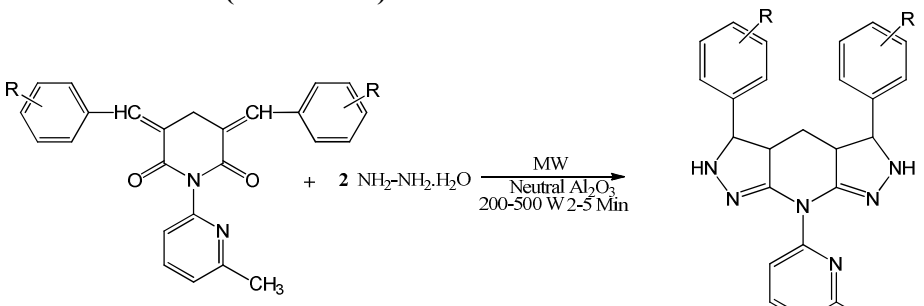
Scheme-II

2 a-e

R= a= 4-NO_2 b= 4-OH
c= 4-CN d= 4-Br
e= 2-Br

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



2a-e

R= a= 4-NO_2 b= 4-OH
c= 4- CN d= 4-Br
e= 2-Br

3a-e

Scheme-III

Physiochemical and Analytical data for Compounds:

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

Whitish Solid, Yield (60%) M.P. 152-154^{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 (64.50%); H (5.80%); N (13.64%). **IR (KBr):** 1704, 1591, 1375, 3202cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):** 2.1(S, 3H, CH_3-Pyridine),1.4(m, 2H, CH_2), 2.8(t, 2H, CH_2), 8.23-7.08 (m, 3H, pyridine).

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

Brown solid, Yield (70%) M.P. 130-132^{0}CM.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 (63.74%); H (3.70%); N (11.65%). **IR (KBr):** 1675, 1348, 1311, 3040, 2980, 2920, 1585, 2750 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.10-7.05 (m, 7H, Ar-H and =CH), 2.40 (S, 3H, -CH_3), 1.80 (S, 2H, -CH_2)

(3Z,5Z)-1-(6-methylpyridin-2-yl)-3,5-bis(4-Hydroxybenzylidene)piperidine-2,6-dione (2b): Brown solid, Yield (61%) M.P. 146-148^{0}CM.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 (72.50%); H (4.52%); N (6.50%). **IR (KBr):**1710, 1338, 1303, 3110, 2931, 1590, 1600, 2750 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.12-7.10 (m, 7H, Ar-H and =CH), 2.38 (S, 3H, -CH_3), 1.90 (S, 2H, -CH_2), 10.10 (S, 1H, OH)

(3Z,5Z)-1-(6-methylpyridin-2-yl)-3,5-bis(4-Cyanobenzylidene)piperidine-2,6-dione(2c): Yellow solid, Yield (76%) M.P. 131-133^{0}CM.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 (75.10%); H (4.10%); N (13.05%). **IR (KBr):**1720, 2465, 2232, 1311, 3035, 2900, 2971, 1510, 1590, 2710 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.00-6.37 (m, 7H, Ar-H and =CH), 2.38 (S, 3H, -CH_3), 1.88 (S, 2H, -CH_2)

(3Z,5Z)-1-(6-methylpyridin-2-yl)-3,5-bis(4-Bromobenzylidene)piperidine-2,6-dione (2d): Yellow solid, Yield (84%) M.P. 102-104^{0}CM.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 (55.60%); H (3.20%); N (5.12%). **IR (KBr):** 1680, 742, 855, 1328, 1305, 3050, 2947, 1560, 1605, 2740 cm^{-1}. **^{1}HNMR (500 MHz, DMSOd^6,δ ppm):**8.42-6.45 (m, 7H, Ar-H and =CH), 2.49 (S, 3H, -CH_3), 1.90 (S, 2H, -CH_2)

(3Z,5Z)-1-(6-methylpyridin-2-yl)-3,5-bis(2-Bromobenzylidene)piperidine-2,6-dione (2e): Dark Yellow solid, Yield (76%) M.P. 78-80^{0}CM.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 (55.72%); H (3.30%); N (5.20%). **IR (KBr):**1710, 735, 848, 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), 1.96 (S, 2H, -CH_2)

8-(6-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 (72%); M.P. 252-254 ^{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 (60.04%); H (4.30%); N (22.20%)**IR (KBr cm^{-1}): 732, 852, 1350, 1500-1600, 3010, 2960, 1548, 1960 cm^{-1}**
^{1}HNMR (500 MHz, DMSOd^6,δ ppm): 8.50-7.50 (m, 5H, Ar-H); 3.60(d, 1H, -CH), 2.65-2.70(d, 1H, -CH), 2.15 (S, 3H, CH_3), 1.40 (d, 2H, -CH2), 10.48(S, 1H, N-H)

8-(6-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 (61%); M.P. 208-210^{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 (68.10%); H (5.30%); N (19.05%)**IR (KBr cm^{-1}): 752, 854, 3250, 1500-1600, 3126, 2970, 1556, 1951 cm^{-1}**
^{1}HNMR (500 MHz, DMSOd^6,δ ppm):8.52-7.56 (m, 5H, Ar-H); 3.56(d, 1H, -CH), 2.55-2.62(d, 1H, -CH), 2.16 (S, 3H, CH_3), 1.29 (d, 2H, -CH2), 10.60(S, 1H, N-H)

8-(6-methylpyridin-2-yl)-3,5-bis(4-CyanoPhenyl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (3c):
Yellow solid, Yield (74%); M.P. 160-163^{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 (70.65%); H (4.78%); N (24.41%)**IR (KBr cm^{-1}): 762, 852, 2210, 1500-1600, 3060, 2960, 1552, 1963 cm^{-1}**
^{1}HNMR (500 MHz, DMSOd^6,δ ppm):8.51-7.50 (m, 5H, Ar-H); 3.52 (d, 1H, -CH), 2.51-2.58(d, 1H, -CH), 2.20 (S, 3H, CH_3), 1.40 (d, 2H, -CH2), 10.58(S, 1H, N-H)

8-(6-methylpyridin-2-yl)-3,5-bis(4-BromoPhenyl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (3d):
Brown solid, Yield (70%); M.P. 230-232^{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 (53.08%); H (3.80%); N (14.60%)**IR (KBr cm^{-1}): 754, 862, 1500-1600, 3130, 2910, 1564, 1954 cm^{-1}**
^{1}HNMR (500 MHz, DMSOd^6,δ ppm):8.60-7.60 (m, 5H, Ar-H); 3.62(d, 1H, -CH), 2.72-2.66 (d, 1H, -CH), 2.15 (S, 3H, CH_3), 1.41 (d, 2H, -CH2), 10.58(S, 1H, N-H)

8-(6-methylpyridin-2-yl)-3,5-bis(2-BromoPhenyl)-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo[3,4-b:4',3'-e]pyridine (3e):
Yellow solid, Yield (70%); M.P. 164-166^{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 (3.85%); N (14.70%)**IR (KBr cm^{-1}): 755, 850, 1500-1600, 3075, 2970, 1562, 1960 cm^{-1}**
^{1}HNMR (500 MHz, DMSOd^6,δ ppm):8.55-7.55 (m, 5H, Ar-H); 3.63(d, 1H, -CH), 2.61-2.65(d, 1H, -CH), 2.11 (S, 3H, CH_3), 10.50(S, 1H, N-H)

Table 1:Physical Data of the synthesized compounds:

Compound code	Molecular Formula	Molecular Weight	% Yield	M.P (^{0}C)	Colour
1	$C_{11}H_{12}O_2N_2$	204	60	152-154	White solid
2a	$C_{25}H_{18}N_4O_6$	470	70	130-132	Brown solid
2b	$C_{25}H_{20}N_2O_4$	412	61	146-148	Brown solid
2c	$C_{27}H_{18}N_4O_2$	430	76	131-133	Yellow solid
2d	$C_{25}H_{18}Br_2N_2O_2$	538	84	102-104	Yellow solid
2e	$C_{25}H_{18}Br_2N_2O_2$	538	76	78-80	Dark Yellow solid
3a	$C_{25}H_{22}N_8O_4$	498	72	252-254	Dark Yellow solid
3b	$C_{25}H_{24}N_6O_2$	440	61	208-210	Orange solid
3c	$C_{27}H_{22}N_8$	459	74	160-163	Yellow solid
3d	$C_{25}H_{22}Br_2N_6$	566	70	230-232	Brown solid

3e	$C_{25}H_{22}Br_2N_6$	566	70	164-166	Yellow solid

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