Microwave-Assisted Catalyst Free Three Component Synthesis of Mono and Bis Spiro Pyrazolopyridines in Solvent Free Reaction

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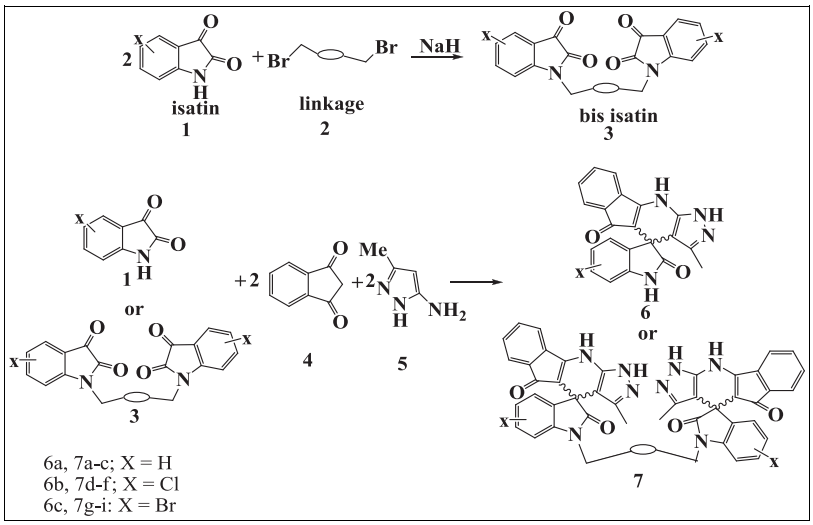

Multicomponent synthesis of mono and bis-spiro pyrazolopyridines from isatin derivatives, indanedione, and 3-methyl-5-aminopyrazole under microwave irradiation in the absence of any catalyst or solvent with high yield and short reaction time is reported.

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INTRODUCTION

The pyrazolopyridine ring system represents the core skeleton of a pharmaceutically important class of heterocyclic compounds possessing a broad range of biological activities, such as potent cyclin kinase 1(CDK1) inhibitor [1], HIV reverse transcriptase inhibitor [2], chemokine receptor 1 antagonists [3], protein kinase inhibitors [4], inhibitors of cyclic guanosine monophosphate degradation [5], inhibitors of xantine oxidases [6], antiviral [7], potent antimalarial agents [8] vasodilator,[9] antimicrobial [10], anti-inflammatory [11], anxiolytic [12], hypoglycemic [13], and antitumor agents [14].

Compounds with spiro skeleton not only constitute subunits in numerous alkaloids but also are templates for drug discovery and have been used as scaffolds for combinatorial libraries [15]. On the other hand, isatin is a privileged lead molecule for designing potential bioactive agents, and its derivatives have been shown to possess a broad range of bioactivity as many of which have been assessed as anti-HIV [16], antiviral [17], antifungal [18], antitumor [19], and anticonvulsant agents [20]. In order to enhance the activity of isatin, it is a hot topic to construct isatin containing pyrazolopyridine moiety in green, efficient, and simple condition.

Recently, the application of microwaves in organic synthesis is very popular, because they often proceed much faster and deliver products in higher yield and higher purity. It has been demonstrated that the use of microwave irradiation can allow precise control of reaction parameters. The energy of the microwave is directly transferred to the molecules of the reaction mixture via dielectric heating, which is relatively faster and more efficient than conventional heating procedure. Because this heating caused by dipolar polarization.

RESULT AND DISCUSSION

In our interest for the development of green synthetic strategies to obtain heterocyclic pharmaceutical compounds [21–25], we have concentrated on to report the first microwave- assisted catalyst free multicomponent synthesis of spiropyrazolopyridines via 5-aminopyrazole, isatin derivatives, and indane-1,3-dione. Furthermore, to improve the pharmaceutical properties of pyrazolopyridines, we were triggered to prepare novel *bis* spiropyrazolopyridines.

Initially, the reaction of isatin **(1a)**, indan-1,3-dione **(4)**, and 5-aminopyrazole **(5)** was studied (i) at reflux condition and (ii) under microwave condition. As expected, the

reaction at 140°C under microwave irradiation proceeded in higher yield and shorter reaction time without any undesirable by-product. Further optimization of the reaction was performed by checking the solvent such as EtOH, CH_3CN, DMF, and H_2O. On the contrary, the reaction worked well under solvent free conditions (Table 1).

To investigate the scope of this synthesis, different synthesized *bis* isatin and *mono* isatins were reacted with indane1,3-dione and aminopyrazole under microwave reactor condition, and the results were listed in Table 2. All of synthesized compounds were prepared in racemic mixture.

All of synthesized compound are new and were characterized by ir, nmr, and elemental analysis.

CONCLUSION

Finally, we develop an efficient and convenient procedure for the synthesis of *mono* and bis spiro pyrazolopyridines through three component synthesis of bis isatin derivatives, indan-1,3-dione, and aminopyrazole in the absence of catalyst under microwave condition (Scheme 1). This procedure offers advantages such as reduced reaction time, mild reaction condition, productivity and higher yield, and ease of execution. This simple process makes this procedure economic, benign, and a waste-free chemical process for the synthesis of pyrazolopyridines.

Table 1

Optimization of reaction and solvent on the model reaction.

Entry	Reaction condition	Solvent	Time (min)	Yield (%)
1	Reflux	EtOH	120	75
2	Microwave	EtOH	7	78
3	Microwave	CH_3CN	7	74
4	Microwave	DMF	9	80
5	Microwave	H_2O	5	85
6	Microwave	Solvent free	2	97

EtOH, ethanol; DMF, dimethylformamide.

Table 2

Synthesis of fused mono, bis spiro pyrazolopyridine derivatives.

Entry	Product	Time (min)	Yield (%)
1	**6a**	2	97
2	**6b**	3	95
3	**6c**	4	93
4	**7a**	3	94
5	**7b**	2	97
6	**7c**	4	92
7	**7d**	3	98
8	**7e**	3	95
9	**7f**	4	93
10	**7g**	2	96
11	**7h**	3	94
12	**7i**	2	97

[a]Yield after crystallization from EtOH.

EXPERIMENTAL

Infrared spectra were determined on a Shimadzo IR-470 spectrometer (Japan). ^{1}H nmr and ^{13}C nmr spectra were recorded on a 500 MHz Bruker DRX-500 (Germany) in $CDCl_3$ as solvent and tetramethylslane as internal standard. Chemicals were purchased from Merck and Fluka. Elemental analyses were performed on a Carlo-Erba EA1110CNNO-S analyzer (China) and agreed with the calculated values. All microwave-assisted reactions were performed using a Discover single mode cavity microwave synthesizer (CEM Corp., India). All solvents used were dried and distilled according to standard procedures.

General procedure for the synthesis of mono and bis spiropyrazolopyridines. A mixture of isatin derivatives (1 mmol), indandione (2 mmol), and 3-methyl-5-aminopyrazole (1 mmol) was irradiated with microwave (300 W) for required reaction time (2–4 min) at 140°C. After completion of the reaction, the mixture was washed with water and filtered to separate the product as pure crystalline products from EtOH in 92–98% yields.

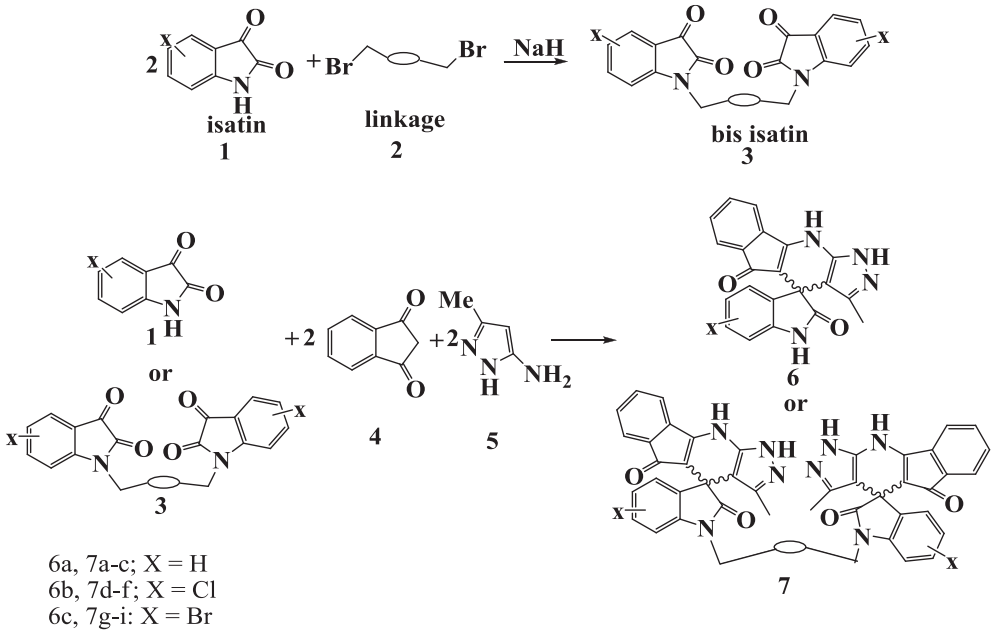
3-Methyl-1H-spiro[indeno[2,1-e]pyrazolo[3,4-b]pyridine-4,3′-indoline]-2′,5(10H)-dione, (6a). mp. 267°C dec; as a red solid; ir (KBr): 3430, 2925, 1685, 1540, 1367; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.56 (s, 3H), 7.25–7.29 (m, 4H), 7.47 (m, 2H), 7.53 (m, 2H), 11.58 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 27.83, 30.32, 105.13, 118.94, 133.17, 135.48, 135.97, 136.76, 140.03, 140.63, 141.06, 143.51, 143.87, 144.87, 146.57, 147.00, 147.94, 149.20, 149.23, 175.65, 189.24; Anal. Calcd. for $C_{21}H_{14}N_4O_2$: C, 71.18; H, 3.98; N, 15.81. Found: C, 71.27; H, 3.88; N, 15.79.

5′-Chloro-3-methyl-1H-spiro[indeno[2,1-e]pyrazolo[3,4-b]pyridine-4,3′-indoline]-2′,5(10H)-dione, (6b). mp. 253°C dec; as a red solid; ir (KBr): 3450, 2965, 1687, 1611 1560, 1379; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.53 (s, 3H), 7.20–7.26 (m, 4H), 7.77 (m, 2H), 8.53 (m, 1H), 11.58 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 28.00, 32.78, 107.90, 117.43, 123.45, 123.78, 132.11, 133.87, 135.79, 136.96, 140.57, 141.65, 142.08, 142.63, 143.44, 142.85, 145.15, 157.91, 159.98, 175.01, 188.51; Anal. Calcd. for $C_{21}H_{13}ClN_4O_2$: C, 64.87; H, 3.37; N, 14.41. Found: C, 64.76; H, 3.28; N, 14.49.

5′-Bromo-3-methyl-1H-spiro[indeno[2,1-e]pyrazolo[3,4-b]pyridine-4,3′-indoline]-2′,5(10H)-dione, (6c). mp. 289°C dec; as a red solid; ir (KBr): 3445, 2975, 1685, 1617, 1550, 1375; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.52 (m, 3H), 7.29–7.35 (m, 4H), 7.43 (m, 2H), 7.47 (m, 1H), 11.58 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 27.65, 29.08, 103.67, 105.17, 107.96, 111.20, 111.75, 113.00, 115.23, 115.65, 117.19, 121.09, 121.78, 123.76, 145.14, 145.46, 145.98, 149.00, 150.11, 153.20, 175.45, 189.33; Anal. Calcd. for $C_{21}H_{13}BrN_4O_2$; C, 58.22; H, 3.02; N, 12.93. Found: C, 58.23; H, 3.14; N, 12.89.

1,1′-(Hexane-1,6-diyl(bis(3-methyl-1H-spiro[indeno[1,2-b]pyrazolo[3,4-e]pyridine-4,3′-indoline]-2,5(10H)-dione, (7a). mp. 267°C dec; as a brown solid; ir (KBr): 3446, 2925, 1685, 1558, 1614, 1375; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.48 (m, 14H), 3.75 (m, 4H), 6.95 (s, 4H), 7.09–7.16 (m, 4H), 7.25 (m, 2H), 7.32 (m, 2H), 7.43 (m, 2H), 7.53 (d, 2H, J = 6.8 Hz), 11.58 (s, 2H), 12.30 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz):

Scheme 1. Synthesis of mono and bis spiropyrazolopyridines.



δ_C 20.94, 25.43, 27.12, 30.11, 45.51, 101.13, 118.10, 118.94, 130.07, 135.09, 135.87, 135.97, 136.01, 136.43, 136.72, 140.03, 140.63, 140.96, 143.51, 143.87, 144.23, 145.64, 151.43, 158.43, 175.45, 189.33; Anal. Calcd. for $C_{48}H_{38}N_8O_4$: C, 72.90; H, 4.84; N, 14.17. Found: C, 72.87; H, 4.74; N, 14.23.

1,1′-(Pentane-1,5-diyl(bis(3-methyl-1H-spiro[indeno[1,2-b] pyrazolo[3,4-e] pyridine-4,3′-indoline]-2,5 (10H)-dione, (7b).mp. 295°C dec; as a brown solid; ir (KBr): 3045, 2927, 1679, 1571, 1608, 1352; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.53 (s, 6H), 1.78 (s, 6H), 3.76 (s, 4H), 6.92–6.99 (m, 4H), 7.11–7.14 (m, 2H), 7.19 (d, 2H, J = 6.8 Hz), 7.21–7.26 (m, 2H), 7.36 (t, 2H, J = 7.4 Hz), 7.46 (t, 2H, J = 7.4 Hz), 7.71–7.77 (d, 2H, J = 6.4 Hz),11.59 (s, 2H),12.31 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 18.83, 23.42, 26.94, 29.31, 48.42, 103.18, 103.54, 107.83, 109.11, 113.17, 113.89, 117.01, 123.45, 123.85, 127.24, 129.83, 131.52, 131.83, 140.05, 143.85, 145.36, 147.15, 153.64, 177.43, 190.23; Anal. Calcd. for $C_{47}H_{36}N_8O_4$: C, 72.67; H, 4.67; N, 14.42. Found: C, 72.66; H, 4.63; N, 14.38.

1,1′-(Butane-1,4-diyl(bis(3-methyl-1H-spiro[indeno[1,2-b] pyrazolo[3,4-e] pyridine-4,3′-indoline]-2,5 (10H)-dione, (7c). mp. 297°C dec; as a brown solid; ir (KBr): 3062, 2931, 1685, 1558, 1608, 1363; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.51 (m, 4H), 1.85 (s, 6H), 3.83 (s, 4H), 6.90–6.95 (m, 4H), 7.14–7.23 (m, 6H), 7.32 (t, 2H, J = 6.8 Hz), 7.36 (t, 2H, J = 7.2 Hz), 7.71 (d, 2H, J = 6.8 Hz) 11.58 (s, 2H), 12.29 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 15.53, 25.43, 27.94, 50.12, 105.17, 105.71, 107.98, 108.03, 110.11, 115.00, 117.19, 117.83, 123.51, 123.83, 130.07, 130.51, 130.83, 137.41, 141.01, 145.23, 147.20, 147.45, 176.43, 190.11; Anal. Calcd. for $C_{46}H_{34}N_8O_4$: C, 72.43; H, 4.49; N, 14.69. Found: C, 72.55; H, 4.58; N, 14.61.

1,1′-(Hexane-1,6-diyl(bis(5′-chloro-3-methyl-1H-spiro[indeno [1,2-b]pyrazolo[3,4-e]pyridine-4,3′-indoline]-2,5 (10H)-dione, (7d). mp. 308°C dec; as a brown solid; ir (KBr): 3068, 2933, 1710 (C═O), 1577, 1602, 1346; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.10 (m, 4H), 1.18 (m, 4H), 1.35 (s, 6H), 3.34 (m, 4H), 6.83 (d,2H, J = 8.4 Hz), 7.12 (d,2H, J = 8.0 Hz), 7.34 (m, 4H), 7.47 (m, 4H), 7.92 (m, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 19.88, 23.42, 27.55, 30.33, 47.37, 103.15, 105.71, 107.19, 117.45, 117.82, 119.53, 123.02, 127.46, 127.48, 135.14, 137.92, 141.36, 145.43, 147.26, 147.38, 149.25, 151.43, 155.98, 173.82, 190.14; Anal. Calcd. for $C_{48}H_{36}Cl_2N_8O_4$: C, 67.06; H, 4.22; N, 13.03. Found: C, 67.14; H, 4.26; N, 13.05.

1,1′-(Pentane-1,5-diyl(bis(5′-chloro-3-methyl-1H-spiro[indeno [1,2-b]pyrazolo[3,4-e]pyridine-4,3′-indoline]-2,5 (10H)-dione, (7e). mp. 308°C dec; as a red solid; ir (KBr): 3074, 2925, 1712 (C═O), 1606, 1568, 1342; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.54 (s, 6H), 1.73 (s, 6H), 3.74 (s, 4H), 7.04 (s, 2H),7.15–7.21 (m, 4H), 7.28 (t, 2H, J = 7.2 Hz), 7.38 (t, 3H, J = 7.0 Hz), 7.47 (t, 2H, J = 6.8 Hz), 7.75 (d, 2H, J = 6.8 Hz), 11.65 (s, 2H), 12.37 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 23.82, 27.02, 27.08, 29.32, 46.72, 102.03, 120.08, 120.42, 124.52, 127.05, 128.40, 131.08, 131.86, 135.02, 135.89, 136.06, 136.58, 136.64, 136.92, 141.80, 147.74, 158.40, 176.96, 188.94; Anal. Calcd. for $C_{47}H_{34}Cl_2N_8O_4$: C, 66.75; H, 4.05; N, 13.25. Found: C, 66.74; H, 4.09; N, 13.21.

1,1′-(Butane-1,4-diyl(bis(5′-chloro-3-methyl-1H-spiro[indeno [1,2-b]pyrazolo[3,4-e]pyridine-4,3′-indoline]-2,5 (10H)-dione, (7f). mp. 305°C dec; as a light brown solid; ir (KBr): 3070, 2927, 1683, 1577, 1606, 1342; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.51 (m, 4H), 1.85 (s, 6H), 3.83 (s, 4H), 6.90–6.95 (m, 4H), 7.14–7.23 (m, 6H), 7.32 (t, 2H, J = 6.8 Hz), 7.36 (t, 2H, J = 7.2 Hz), 7.71 (d, 2H, J = 6.8 Hz) 11.58 (s, 2H), 12.29 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 15.46, 23.12, 25.66, 47.31, 107.17, 108.00, 111.23, 115.47, 115.87, 117.05, 123.43, 125.41, 125.93, 127.07, 135.44, 135.82, 135.93, 143.01, 145.11, 147.33, 147.36, 147.48, 151.20, 175.14, 189.00; Anal. Calcd. for $C_{46}H_{32}Cl_2N_8O_4$: C, 66.43; H, 3.88; N, 13.47. Found: C, 66.37; H, 3.84; N, 13.42.

1,1′-(Pentane-1,4-diyl(bis(5′-bromo-3-methyl-1H-spiro[indeno [1,2-b]pyrazolo[3,4-e]pyridine-4,3′-indoline]-2,5 (10H)-dione, (7g). mp. 305°C dec; as a brown solid; ir (KBr): 3749, 2929,

1733 (C═O), 1564, 1608, 1344; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.57–1.90 (m, 12H), 3.85 (m, 4H), 7.15–7.87 (m, 14H), 11.67 (s, 2H), 12.39 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 21.83, 26.53, 27.17, 30.11, 49.51, 101.51, 103.11, 103.55, 105.23, 107.07, 113.15, 113.89, 117.23, 123.47, 127.01, 129.32, 131.11,131.51,131.66, 137.15, 141.81, 143.75, 147.81, 169.17, 188.42; Anal. Calcd. for $C_{47}H_{34}Br_2N_8O_4$: C, 60.40; H, 3.67; N, 11.99. Found: C, 60.48; H, 3.54; N, 11.67.

1,1′-(Butane-1,4-diyl(bis(5′-bromo-3-methyl-1H-spiro[indeno [1,2-b]pyrazolo[3,4-e]pyridine-4,3′-indoline]-2,5 (10H)-dione, (7h). mp. 311°C dec; as a orange solid; ir (KBr): 3080, 2929, 1716 (C═O), 1577, 1606, 1342; ^{1}H -MR (DMSO-d_6, 400 MHz): δ_H 1.54 (s, 4H), 1.79 (s, 6H), 3.82 (s, 4H), 7.13–7.15 (m, 6H),7.28–7.46 (m, 6H), 7.74 (s, 2H), 11.68 (s, 2H), 12.38 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 14.51, 17.83, 27.01, 27.36, 45.94, 111.36, 113.07, 113.83, 115.87, 117.23, 123.44, 127.07, 127.35, 127.91, 129.53, 131.13, 131.37, 134.43, 137.82, 139.51, 147.81, 149.24, 171.46, 187.36; Anal. Calcd. for $C_{46}H_{32}Br_2N_8O_4$: C, 60.01; H, 3.50; N, 12.17. Found: C, 60.11; H, 3.65; N, 12.14.

1,1′-(1,4-Phenylenebis (methylene) di (3-methyl-1H-spiro [indeno[1,2-b]pyrazolo 3,4-e]pyridine-4,3′-indoline]-2,5 (10H)-dione, (7i). mp. 288°C dec; as a brown solid; ir (KBr): 3068, 2925, 1730 (C═O), 1558,1610, 1348; ^{1}H nmr (DMSO-d_6, 400 MHz): δ_H 1.53 (s, 6H), 5.12 (s, 4H), 6.91–6.98 (m, 4H), 7.09–7.23 (m, 4H), 7.37 (d, 2H, J = 7.8 Hz), 7.46 (m, 2H), 7.55–7.58 (m, 2H),7.74 (m, 2H), 11.62 (s, 2H), 12.43 (s, 2H); ^{13}C nmr (DMSO-d_6, 100 MHz): δ_C 27.13, 29.21, 45.18, 103.75, 105.51, 107.36, 109.21, 111.13, 111.17, 113.51, 113.91, 115.07, 115.72, 117.23, 119.14, 123.25, 123.64, 125.27, 130.17, 130.84, 135.36, 137.41, 147.32, 177.23, 192.45; Anal. Calcd. for $C_{50}H_{34}N_8O_4$: C, 74.26; H, 4.53; N, 13.82. Found: C, 74.32; H, 4.57; N, 13.79.

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