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One-pot Three-component Synthesis of Spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline] Derivatives Catalyzed by Melamine Trisulfonic Acid

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Novel spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline] derivatives were prepared by the three-component reaction of isatins 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and Meldrum's acid in the presence of a catalytic amount of melamine trisulfonic acid. This protocol provides a simple one-step procedure with the advantages of easy work-up, mild reaction conditions and environmentally benign.

Keywords: Spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline]; Melamine trisulfonic acid; Catalysis; Green chemistry.

INTRODUCTION

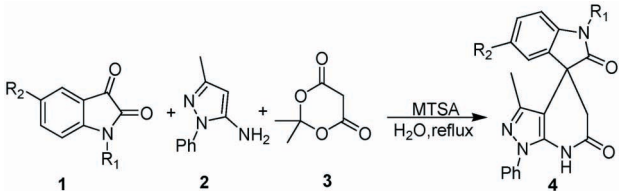
Multi-component reactions (MCRs), in which multiple reactions are combined into the synthetic operation have been used extensively to form carbon-carbon bonds in the synthetic chemistry.[1] Such reactions offer a wide range of possibilities for the efficient constrution of highly complex molecules in a single procedure, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. In the past decade, there has been tremendous development in three- and four-component reactions, and great efforts continue to be made to develop new MCRs.[2]

Indole moiety is probably the most well-known heterocycle and a common and important feature of a variety of natural products and medicinal agents.[3] Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity.[4] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[5] Pyrazolo[3,4-*b*]pyridines have been studied for over a century due to a variety of chemical and biological significance. They have been reported as antibacterial,[6] antimicrobial,[7] antiviral,[8] oncogenic Ras inhibiting[9] and cyclooxygenase inhibiting activities.[10]

Recently, melamine trisulfonic acid (MTSA) has emerged as a promising solid acid catalyst for acid-catalyzed reactions, such as acetylation of alcohols, phenols, and amines,[11] oxathioacetalyzation of aldehydes,[12] the nitrosation of secondary amines and oxidation of urazoles.[13] This catalyst is safe, easy to handle, and environmentally benign, and presents fewer disposal problems. MTSA as a solid acid catalyst is prepared from reaction of melamine with neat chlorosulfonic acid at room temperature.[13]

Herein, we describe a simple and efficient protocol for rapid preparation of spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline] derivatives using a catalytic amount of recyclable MTSA in water (Scheme I). To the best of our knowledge, it is probably the first example of synthesizing spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline] derivatives using MTSA as catalyst in aqueous media. This process provides an opportunity to use water and avoids environmentally harmful conventional organic solvents.

Scheme I



EXPERIMENTAL

^{1}H NMR spectra were determined on Bruker AV-400 spectrometer at room temperature using tetramethylsilane (TMS) as an internal standard (DMSO-d_6 solution), coupling constants (J) were measured in Hz; Elemental analysis were performed by a Vario-III elemental analyzer; Melting points were determined on a XT-4 binocular microscope and were uncorrected; Commercially available reagents were used throughout without further purification unless otherwise stated.

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Preparation of MTSA catalyst

A 250 mL suction flask charged with 5 mL chlorosulfonic acid (75.2 mmol) was equipped with a gas inlet tube for conducting HCl gas over an adsorbing solution. Melamine (3.16 g, 25.07 mmol) was added in small portions over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately. After completion of the addition of melamine, the mixture was shaken for 30 min; meanwhile, the residual HCl was removed by suction. Melamine trisulfonic acid (7.7 g, 85%) was obtained as a white solid.

General procedure for the preparation of 4

A mixture of isatins (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol), Meldrum's acid (1 mmol) and MTSA (0.05 mmol) in water (5 mL) was heated at reflux for an appropriate time (TLC). After completion of the reaction, the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with water and cooled ethanol to afford the products. The filtrate was evaporated under reduced pressure, after removal of the water, MTSA was recovered. The recovering washed with CH_2Cl_2, dried in an oven at 100 °C for 30 min prior to use.

3-Methyl-1-phenyl-1,5-dihydro-spiro[pyrazolo[3,4-*b*]-pyridine-4,3′-indoline]-2′,6(7*H*)-dione (4a)

Yellow power, m.p. 236-237 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.71 (s, 1H, NH), 10.63 (s, 1H, NH), 7.50-7.46 (m, 4H, Ar-H), 7.37-7.22 (m, 3H, Ar-H), 7.02-6.92 (m, 2H, Ar-H), 2.99 (d, 1H, J = 15.6 Hz, CH_2), 2.65 (d, 1H, J = 15.6 Hz, CH_2), 1.50 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.7, 169.5, 144.6, 142.0, 140.8, 138.2, 131.7, 129.7, 129.3, 127.5, 124.3, 123.4, 122.6, 110.4, 100.8, 46.2, 30.7, 12.2; Anal. calcd for $C_{20}H_{16}N_4O_2$: C 69.76 H 4.68, N 16.27; found: C 69.60, H 4.72, N 16.20.

5′-Chloro-3-methyl-1-phenyl-1,5-dihydro-spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline]-2′,6(7*H*)-dione (4b)

Orange red power, m.p. 181-183 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.77 (s, 1H, NH), 10.71 (s, 1H, NH), 7.60-7.47 (m, 4H, Ar-H), 7.38-7.31 (m, 3H, Ar-H), 6.95-6.86 (m, 1H, Ar-H), 3.08 (d, 1H, J = 16 Hz, CH_2), 2.68 (d, 1H, J = 15.6 Hz, CH_2), 1.53 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.4, 169.3, 144.4, 141.0, 140.9, 138.1, 133.8, 129.7, 129.2, 127.6, 126.6, 124.5, 123.4, 111.9, 100.2, 46.5, 30.9, 12.3; Anal. calcd for $C_{20}H_{15}ClN_4O_2$: C 63.41, H 3.99, N 14.79; found: C 63.36, H 4.05, N 14.85.

3,5′-Dimethyl-1-phenyl-1,5-dihydro-spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline]-2′,6(7*H*)-dione (4c)

Orange power, m.p. 234-235 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.70 (s, 1H, NH), 10.54 (s, 1H, NH), 7.55-7.45 (m, 4H, Ar-H), 7.37-7.36 (m, 1H, Ar-H), 7.07-7.02 (m, 2H, Ar-H), 6.86-6.81 (m, 1H, Ar-H), 2.90 (d, 1H, J = 15.6 Hz, CH_2), 2.65 (d, 1H, J = 15.6 Hz, CH_2), 2.23 (s, 3H, CH_3), 1.53 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.7, 169.5, 144.6, 140.7, 139.4, 138.2, 131.9, 131.5, 129.7, 129.5, 127.5, 124.7, 123.4, 110.2, 101.0, 46.2, 30.9, 21.1, 12.3; Anal. calcd for $C_{21}H_{18}N_4O_2$: C 70.38, H 5.06, N 15.63; found: C 70.33, H 4.99, N 15.56.

5′-Fluoro-3-methyl-1-phenyl-1,5-dihydro-spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline]-2′,6(7*H*)-dione (4d)

Orange power, m.p. 144-145 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.71 (s, 1H, NH), 10.64 (s, 1H, NH), 7.50-7.38 (m, 4H, Ar-H), 7.37-7.35 (m, 1H, Ar-H), 7.21-7.19 (m, 1H, Ar-H), 7.13-6.93. (m, 1H, Ar-H), 6.92-6.91 (m, 1H, Ar-H), 3.11 (d, 1H, J = 16 Hz, CH_2), 2.63 (d, 1H, J = 15.6 Hz, CH_2), 1.52 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.7, 169.3, 157.5, 144.5, 140.8, 138.4, 133.4, 133.3, 129.7, 127.6, 123.4, 115.8, 112.3, 111.3, 100.3, 46.7, 30.9, 12.3; Anal. calcd for $C_{20}H_{15}FN_4O_2$: C 66.29, H 4.17, N 15.46; found: C 66.32, H 4.09, N 15.52.

5′-Bromo-3-methyl-1-phenyl-1,5-dihydro-spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline]-2′,6(7*H*)-dione (4e)

Orange power, m.p. 198-200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.78 (s, 1H, NH), 10.71 (s, 1H, NH), 7.50-7.44 (m, 6H, Ar-H), 7.39-7.36 (m, 1H, Ar-H), 6.91-6.89 (m, 1H, Ar-H), 3.07 (d, 1H, J = 15.6 Hz, CH_2), 2.69 (d, 1H, J = 15.6 Hz, CH_2), 1.53 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.3, 169.3, 144.4, 141.4, 140.8, 138.1, 134.2, 132.0, 129.7, 127.6, 127.1, 123.7, 123.4, 114.2, 112.4, 100.3, 46.4, 30.9, 12.3; Anal. calcd for $C_{20}H_{15}BrN_4O_2$: C 56.75, H 3.57, N 13.24; found: C 56.71, H 3.49, N 13.32.

1′,3-Dimethyl-1-phenyl-1,5-dihydro-spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline]-2′,6(7*H*)-dione (4f)

Blackish green power, m.p. 110-112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.75 (s, 1H, NH), 7.50-7.46 (m, 4H, Ar-H), 7.39-7.28 (m, 3H, Ar-H), 7.13-7.07 (m, 2H, Ar-H), 3.18 (s, 3H, CH_3), 3.04 (d, 1H, J = 16 Hz, CH_2), 2.67 (d, 1H, J = 16 Hz, CH_2), 1.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 176.8, 169.4, 144.5, 143.6, 140.8, 138.2, 130.9, 129.7, 129.4, 127.5, 123.9, 123.4, 123.2, 109.5, 100.6, 45.8, 30.9, 26.7, 12.2; Anal. calcd for $C_{21}H_{18}N_4O_2$: C 70.38, H 5.06, N 15.63; found: C 70.40, H

5.02, N 15.50.

RESULTS AND DISCUSSION

The choice of an appropriate reaction media is of crucial importance for successful synthesis. Initially, the three-component reaction of isatin (**1a**), 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2**) and Meldrum's acid (**3**) as a simple model substrate was investigated to establish the feasibility of the strategy and optimize the reaction conditions (Table 1). Different solvents and catalysts were screened in the model reaction. As could be seen in Table 1, the best result was obtained with a 5 mol% of MTSA as the catalyst in refluxing water and the desired product, 3-methyl-1-phenyl-1,5-dihydro-spiro[pyrazolo[3,4-*b*]pyridine-4,3′-indoline]-2′,6(7*H*)-dione **4a**, is obtained in good yield (entry 5). Using lower amount of catalyst resulted in lower yields, while higher amount of catalyst did not affect reaction times and yields (Table 1). When this reaction was carried out without any catalyst, TLC and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products, the yield of the expected product was very poor (Table 1, entry 1).

After optimizing the reaction conditions, a variety of isatins were employed under similar circumstances to evaluate the substrate scope of this reaction. The results are shown in Table 2. As anticipated from our original results, these reactions proceeded very cleanly at refluxing water and no undesirable side reactions were observed. The ^{1}H NMR spectrum of **4a** exhibited two singlet at δ 10.71 and 10.63 (D_2O exchangeable) due to –NH, two double at δ 2.99 and 2.65 due to $–CH_2$ and aromatic protons in the range δ 6.92–7.50. Resonances at δ 46.2 (spiro carbon), δ 169.5 (–C=O group) and δ 178.7 (isatin –C=O group) were observed in the ^{13}C NMR spectrum.

Table 1. Optimization of reaction conditions for synthesis of **4a**[a]

Entry	Conditions	Catalyst	Time/h	Yield/%[b]
1	H_2O (reflux)	-	12	trace
2	H_2O (reflux)	MTSA (2 mol%)	5	69
3	H_2O (reflux)	MTSA (3 mol%)	5	78
4	H_2O (reflux)	MTSA (4 mol%)	4	86
5	H_2O (reflux)	MTSA (5 mol%)	4	94
6	H_2O (reflux)	MTSA (6 mol%)	4	93
7	H_2O (reflux)	MTSA (7 mol%)	4	93
8	H_2O (reflux)	H_2SO_4 (5 mol%)	8	35
9	H_2O (reflux)	*p*-TsOH (5 mol%)	7	68
10	H_2O (reflux)	NH_2SO_3H (5 mol%)	8	72
11	H_2O (reflux)	$FeCl_3$ (5 mol%)	9	42
12	EtOH (reflux)	MTSA (5 mol%)	5	63
13	CH_3CN (reflux)	MTSA (5 mol%)	6	70

[a] Reaction conditions: isatin (1 mmol); 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol); Meldrum's acid (1 mmol).
[b] Isolated yield.

Table 2. Preparation of spiro[pyrazolo[3,4-*b*]pyridine-4,3'-indolines][a]

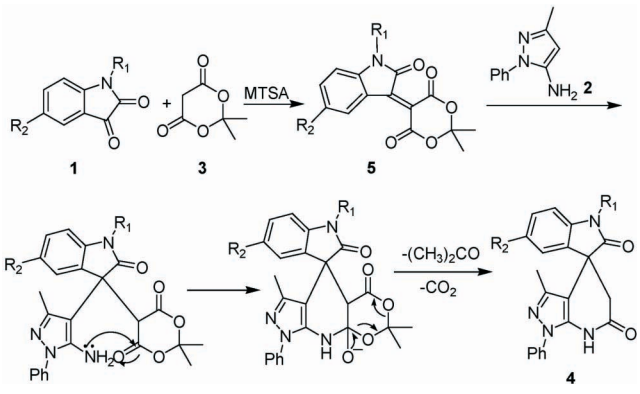
Entry	R^1	R^2	Time/h	Product	Yield/%[b]
1	H	H	4	**4a**	94 (90, 89, 85)[c]
2	H	Cl	3	**4b**	91
3	H	Me	5	**4c**	88
4	H	F	3	**4d**	92
5	H	Br	2.5	**4e**	93
6	Me	H	3.5	**4f**	87

[a] Reaction conditions: isatins (1 mmol); 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol); Meldrum's acid (1 mmol); MTSA (0.05 mmol); H_2O (5 mL); reflux.
[b] Isolated yield.
[c] The catalyst was reused for four runs.

The reusability of the catalyst was tested in the synthesis of **4a**. The catalyst was recovered after each run, washed with CH_2Cl_2, dried in an oven at 100 °C for 30 min prior to use, and tested for its activity in the subsequent run with no fresh catalyst added. The catalyst was tested for four runs. It was seen that the catalyst displayed very good reusability (Table 2, entry 1).

The formation of products **4a–4f** can be rationalized by initial formation of heterodiene **5** by standard Knoevenagel condensation of Meldrum's acid **3** and isatins **1** in the presence of a catalytic amount of MTSA. Subsequent Michael-type addition of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2** to the heterodienes **5** followed by cyclization, removing CO_2 and acetone afford the corresponding products **4a–4f** (Scheme II).

Scheme II



CONCLUSIONS

In conclusion, we have demonstrated a simple and environmental friendly protocol for the synthesis of spiro-[pyrazolo[3,4-*b*]pyridine-4,3′-indoline] derivatives using MTSA as a catalyst in aqueous media. The method employs inexpensive, non-toxic, and an easily available catalyst and eliminates the use of hazardous organic solvents. Further studies to delineate the scope and limitations of the present methodology are underway.

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