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A straightforward Microwave assisted green synthesis of Functionalized Spirooxindole-Pyrrolothiazole Derivatives *via* Three-Component 1,3-Dipolar Cycloaddition Reactions

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Abstract: A novel one pot microwave assisted Silica sulfuric acid mediated multicomponent domino reaction for fast, integrated and adaptable synthesis of highly functionalized Spirooxindole-Pyrrolothiazole **(4a-k)** has been established. The reaction proceed through the 1,3-dipolar cycloaddition of azomethine ylides generated in situ by the condensation of dicarbonyl compounds (isatin) and secondary amino acids (L-thioproline) with dipolarophiles 2,2,2-trifluoroethanol (TFE) medium. The products were obtained in good to excellent yield within short periods of 10–20 min at microwave. The potential of the methodology is proved by development of huge library of Spiro-thiazolidine (Spirooxindole- Pyrrolothiazole) with point diversity.

Keywords: Spirooxindole-Pyrrolothiazole derivatives, Silica sulfuric acid (SSA), 1,3-dipolar cycloaddition reaction and L-thioproline.

INTRODUCTION:

Sulfur-containing bioactive heterocyclic's are frequently found in naturally occurring compounds and usually show various biological activities [1]. Significant attention has been paid to Sulfur bearing heterocycles, as they are the integral part of many natural products and biologically and pharmaceutically active molecules.1,3-dipolar cycloaddition reactions have been extensively investigated as an important bond forming organic reaction. The 1,3-dipolar cycloadditions have involved a reasonable interest because it represents an important class of substances especially substituted thiazolidine, pyrrolidine, and pyrrolizidine rings with highly pronounced biological activities [2]. In this regard, spiropyrrolidine and their derivatives have fascinated scrupulous attention as they have provided as useful synthetic intermediates [3] and also execute as antitumoral, antiviral,

antibiotic agents, local aneasthetics, and inhibitors of human NK-1 receptor, etc. and also been originate in a fascinating array of bioactive natural products [4]. Moreover, functionalized pyrrolothiazoles [5] are the central skeletons for numerous alkaloids and pharmacologically important compounds. As significance, the incorporation of these scaffolds, spirooxindole and pyrrolothiazole, into a molecule may result in the discovery of new drug candidates **(Fig. 1)**.

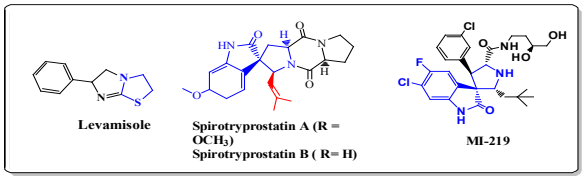
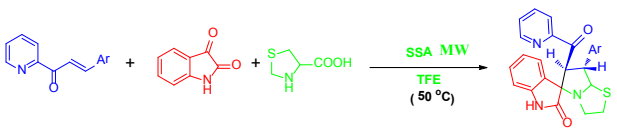


Figure 1. Biologically important molecules are containing a spiro core.

Currently challenges to build up innovative organic transformations that are not only efficient, selective and high yielding but also environmentally friendly make the choice of a suitable reaction medium necessary for a triumphant synthesis. Recently, microwave assisted organic synthesis (MAOS) has emerged as a new field in organic synthesis, which is recognized (renowned) as a ''green'' technology. It has been applied as a very resourceful way to accelerate the course of many organic reactions, produce higher yields, higher the regio- and stereoselectivity, lowering the quantities of side products in a short period of time with easy and simple workup [6]. The selection of an appropriate catalyst is crucial for enhancing the efficiency of most chemical processes. Solid acid catalysts are the finest alternative to existing homogeneous protic acids, being less toxic, easy to handle and most importantly having the additional possibility to be recycled numerous times. In last few decades, silica has been working as porous support to immobilize a series of acid species towards the design of novel solid acid catalysts. These materials have been employed in a number of organic reactions, including acylation, alkylation, protection reactions, oxidation,hydrolysis, condensation deprotection reactions, and multicomponent reactions [7-13] outstanding to its several advantages, such as exceptional stability (chemical and thermo), high surface areas, lower corrosivity, easier work-up, good accessibility, the good dispersion of active reagent sites associated with selectivity and the fact that the organic groups can be robustly anchored to the silica surface to provide catalytic centers [14]. Recently, we are concerned in finding efficient reactions catalyzed by silica functionalized silica sulfuric acid (SSA) as catalyst.

To the best of our knowledge, there is no report on microwave assisted silica sulfuric acid (SSA) catalyst 1,3-dipolar cycloaddition reaction of azomethine ylides with substituted prop-2-en-1-one as dipolarophlies representatives in 2,2,2-trifluoroethanol (TFE) medium. In continuation of our ongoing program for the development of sustainable processes[15] herein, we wish to report for the first time the role of silica sulfuric acid (SSA) for the facile and efficient synthesis of Spirooxindole-Pyrrolothiazole Derivatives derivatives (**4a-k**), in a highly regio- and stereoselective manner through microwave assisted 1,3-dipolar cycloaddition reaction of isatin (**1**), secondary amino acids (L-thioproline) (**2**) and substituted prop-2-en-1-one as dipolarophlies (**3**) in 2,2,2-trifluoroethanol (TFE) **(Scheme 1)**. Mild reaction conditions with tremendous conversion, higher yields in shorter reaction time and the effortless recyclability of Silica sulfuric acid (SSA) makes this protocol attractive, sustainable and environmentally benign.



Scheme 1

Materials and Methods

All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with a 200, 300, 400 MHz spectrometers for ^{1}H NMR and 50, 75 MHz for ^{13}C NMR in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, coupling constant *J* in Hz.). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad singlet (br, s). Melting points were determined in open capillary tubes on an electrically heated block and are uncorrected. Mass spectra and HRMS were taken in the ESI positive ion mode. The reaction progress was routinely monitored by thin layer chromatography (TLC) on pre-coated silica gel plates. Column chromatography was performed over silica gel (230-400 flash). All compounds were characterized by TLC, ^{1}H NMR and ^{13}C NMR, MS and HRMS.

General procedure for the synthesis of spiro[indoline-3,5'-pyrrolo[2,1-b]thiazol]-2-one derivatives (4a-k)

An equimolar mixture of appropriate isatin (**1**), secondary amino acids (L-thioproline) (**2**) substituted prop-2-en-1-one as dipolarophlies (**3a-k**) and trifluoroethanol (TFE) (2–3 mL) under microwaves with catalytic amount of Silica sulfuric acid (SSA). All these reactions were carried out by microwave irradiation for 10-30 min. at the power level 250 W and at the temperature of 50° C which was recorded by the temperature probe of the microwave. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3x10 mL). The combined ether extracts were concentrated in vacuum at 80 °C overnight. For further purification, the solid products were recrystallized from ethanol and the similar procedure was followed for the synthesis of all the products without any need for column chromatography. All the synthesized compounds were well characterized by ^{1}H NMR, ^{13}C NMR, and Mass analysis.

Spectral analysis:

(6'S,7'R)-7'-phenyl-6'-picolinoyl-3',6',7',7a'-tetrahydro-2'H-spiro[indoline-3,5'-pyrrolo[2,1-b]thiazol]-2-one (4a)

White solid; m.p. 200~202 °C; IR (KBr): v= 3310, 3108, 3032, 2896, 1698, 1627, 1522, 804, 751;1H NMR ($CDCl_3$, 400 MHz) δ: 3.41 (d, *J*=4.2 Hz, 2H, CH_2), 3.52 (d,*J*=9.8 Hz, 1H, CH_2), 3.96 (d, *J*=8.7 Hz, 1H, CH_2), 4.16 (t, *J*=10.0 Hz, 1H, CH), 4.47~4.54 (m, 1H, CH), 5.30 (d, *J*=11.6 Hz, 1H, CH), 6.97 (d, *J*=8.0 Hz, 1H, ArH), 6.91 (t, *J*=8.0 Hz, 1H, ArH), 7.11 (t, *J*=8.0 Hz, 1H, ArH), 7.35 (d, *J*=8.0 Hz, 1H, ArH), 7.40~7.44 (m, 4H, ArH), 7.77 (d, *J*=8.4 Hz, 1H, ArH), 7.98 (s, 1H, ArH), 8.16 (s, 1H, NH), 8.43 (d, *J*=4.4 Hz, 1H, ArH);13C NMR (DMSO-*d6*, 100 MHz) δ:37.45, 44.52, 51.49, 61.22,72.43, 74.92, 105.84, 112.21, 120.41, 120.88, 122.14, 124.45, 125.31, 125.75, 126.29, 127.16, 127.91, 129.61, 136.63, 144.78, 148.34, 157.61, 176.72, 193.88; HRMS calcd for $C_{25}H_{22}N_3O_2S$[M+H]+: 428.1427, found: 428.1429.

(3R,6'S,7'R,7a'S)-7'-(naphthalen-2-yl)-6'-picolinoyl-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (4b)

White solid; m.p. 168~170 °C; IR (KBr): v= 3204, 3084, 3028, 2937, 2895, 1717, 1703, 1618, 1506, 1472, 781, 756;1H NMR (CDCl3, 400 MHz) δ: 3.07 (d, *J*=4.0 Hz, 2H, CH2), 3.58 (d,*J*=10.0 Hz, 1H, CH2), 3.93 (d, *J*=10.0 Hz, 1H, CH2), 4.13 (t, *J*=10.0 Hz, 1H, CH), 4.49~4.54 (m, 1H, CH), 5.32 (d, *J*=11.6 Hz, 1H, CH), 6.51 (d, *J*=8.0 Hz, 1H, ArH), 6.91 (t, *J*=8.0 Hz, 1H, ArH), 7.03 (t, *J*=8.0 Hz, 1H, ArH), 7.22 (t, *J*=6.0 Hz, 1H, ArH), 7.37 (d, *J*=8.0 Hz, 1H,

ArH), 7.41~7.46 (m, 4H, ArH), 7.75 (d, *J*=8.4 Hz, 1H, ArH), 7.79 (d, *J*=7.6 Hz, 1H, ArH), 7.84 (d, *J*=8.8 Hz, 2H, ArH), 8.04 (s, 1H, ArH), 8.11 (s, 1H, NH), 8.50 (d, *J*=4.4 Hz, 1H, ArH);13C NMR (DMSO-*d6*, 100 MHz) δ:35.63, 42.54, 51.37, 60.05,71.32, 73.85, 108.53, 110.36, 120.45, 120.83, 121.12, 123.45, 125.39, 125.86, 126.48, 127.16, 127.59 127.89, 128.26, 129.57, 136.63, 142.65, 147.34, 151.56, 157.64, 178.75, 198.43; HRMS calcd for $C_{29}H_{24}N_3O_2S$[M+H]+: 478.1589, found: 478.1608.

(3R,6'S,7'R,7a'S)-7'-(2-chlorophenyl)-6'-picolinoyl-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (4c)

White solid; m.p. 208~210 **°C**; IR (KBr): v= 3211, 3087, 3030,2978, 1745, 1712, 1627, 1533, 1469, 752; 1H NMR (DMSO-*d6*,400 MHz) δ: 2.91 (dd,*J*1=11.2 Hz, *J*2=4.4 Hz, 1H, CH2), 3.02 (dd, *J*1=10.8 Hz, *J*2=6.0 Hz, 1H, CH2), 3.33 (d, *J*=9.6 Hz, 1H, CH2), 3.68 (d, *J*=9.6 Hz, 1H, CH2), 4.04~4.09 (m, 1H, CH), 4.46 (t, *J*=5.6 Hz,1H, CH), 5.16 (d, *J*=10.4 Hz, 1H, CH), 6.42 (d, *J*=7.6 Hz, 1H, ArH), 6.78 (t, *J*=7.6 Hz, 1H, ArH), 6.97 (t, *J*=7.6 Hz, 1H, ArH), 7.06 (d, *J*=7.2 Hz, 1H, ArH), 7.23~7.29 (m, 2H, ArH), 7.36~7.43 (m, 3H, ArH), 7.65 (t, *J*=7.6 Hz, 1H, ArH), 7.75 (d, *J*= 7.6Hz, 1H, ArH), 8.43 (d, *J*=4.4 Hz, 1H, ArH), 10.34 (s, 1H, NH);13C NMR (DMSO-*d6*, 100 MHz) δ:35.25, 42.76, 51.38, 60.07, 71.42, 73.45, 108.93, 110.87, 120.45, 120.77, 120.91, 123.63, 126.68, 127.25, 127.54, 127.88, 128.10, 129.24, 136.65, 142.56, 147.37, 151.39, 157.28, 178.61, 197.86;HRMS calcd for $C_{25}H_{19}ClN_3O_2S$[M-H]+: 460.0887, found: 460.0892.

(3R,6'S,7'R,7a'S)-7'-(2,4-dichlorophenyl)-6'-picolinoyl-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (4d)

White solid; m.p. 222~226 **°C**; IR (KBr): v= 3209, 3084, 3028, 2980, 1749, 1717, 1618, 1518, 1472, 756; 1H NMR (DMSO-*d6*, 400 MHz) δ: 2.91 (dd, *J*1=11.2 Hz, *J*2=4.8 Hz, 1H, CH2), 3.04 (dd, *J*1=10.8 Hz, *J*2=6.0 Hz, 1H, CH2), 3.35 (d, *J*=10.4 Hz, 1H, CH2), 3.69 (d, *J*=9.2 Hz, 1H, CH2), 4.05~4.10 (m, 1H, CH), 4.37 (t, *J*=5.2 Hz, 1H, CH), 5.18 (d, *J*=10.0 Hz, 1H, CH), 6.41 (d, *J*=7.6 Hz, 1H, ArH), 6.96 (t, *J*=8.0 Hz, 1H, ArH), 7.05 (d, *J*=7.6 Hz, 1H, ArH), 7.23~7.31 (m, 2H, ArH), 7.39~7.49 (m, 3H, ArH), 7.65 (t, *J*=9.2 Hz, 1H, ArH), 7.76 (d, *J*= 7.6Hz, 1H, ArH), 8.43 (d, *J*=4.4 Hz, 1H, ArH), 10.35 (s, 1H, NH); 13C NMR (DMSO-*d6*, 100 MHz) δ:35.32, 42.57, 50.88, 59.96, 70.92, 73.34, 108.78, 110.29, 120.24, 120.85, 121.11, 123.36, 126.79, 127.03, 127.46, 127.91, 128.25, 129.37, 136.35, 142.48, 147.53, 151.59, 157.46, 178.57, 197.73; HRMS calcd for $C_{25}H_{18}C_{l2}N_3O_2S$[M-H]+: 494.0498, found: 494.0526.23

(3R,6'S,7'R,7a'S)-7'-(3-nitrophenyl)-6'-picolinoyl-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (4e)

White solid; m.p. 245~247 **°C**; IR (KBr): v= 3209, 3084, 3028, 2930, 2826, 1734, 1699, 1618, 1545, 1506, 1472, 1337, 760;1H NMR (CDCl3, 400 MHz) δ: 2.98 (dd, *J*1=11.6 Hz, *J*2=8.4 Hz, 1H, CH2), 3.08 (dd, *J*1=11.6 Hz, *J*2=5.6 Hz, 1H, CH2), 3.55 (d, *J*=9.6 Hz, 1H, CH2), 3.90 (d, *J*=9.6 Hz, 1H, CH2), 4.09 (t, *J*=9.6 Hz, 1H,CH), 4.39~4.44 (m, 1H, CH), 5.18 (d, *J*=11.2 Hz, 1H, CH), 6.51 (d, *J*=8.0 Hz, 1H, ArH), 6.89 (t, *J*=7.6 Hz, 1H, ArH), 7.02 (t, *J*=7.6 Hz, 1H, ArH), 7.23~7.25 (m, 1H, ArH), 7.32 (d, *J*=7.6 Hz, 1H, ArH), 7.39 (t, *J*=7.6 Hz, 1H, ArH), 7.48~7.52 (m, 1H, ArH), 7.54 (d, *J*=7.6 Hz, 1H, ArH), 7.97 (d, *J*=8.0 Hz, 1H, ArH), 8.12 (d, *J*=8.4 Hz, 1H, ArH), 8.12 (s, 1H, NH), 8.48 (s, 1H, ArH), 8.50 (d, *J*=4.4 Hz, 1H, ArH);13C NMR (DMSO-*d6*, 100 MHz) δ:35.58, 43.69, 50.21, 60.46, 71.31, 74.25, 108.83, 109.65, 119.96, 120.48, 121.51, 123.47,

126.62, 127.35, 127.58, 128.02, 128.43, 129.55, 136.41, 142.78, 147.69, 151.84, 157.72, 178.71, 198.13; HRMS calcd for $C_{25}H_{21}N_4O_4S$[M+H]+: 473.1283, found: 473.1307.

(3R,6'S,7'R,7a'S)-7'-(2-bromophenyl)-6'-picolinoyl-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (4f)

White solid; m.p. 226~228 °C; IR (KBr): v= 3202, 3084, 3020, 2916, 1738, 1713, 1618, 1510, 1475, 779, 752;1H NMR (CDCl3, 400 MHz) δ: 3.07 (dd, *J*1=11.6 Hz, *J*2=5.6 Hz, 1H, CH2), 3.26 (dd, *J*1=11.2 Hz, *J*2=9.2 Hz, 1H, CH2), 3.54 (d, *J*=10.4 Hz, 1H, CH2), 3.91 (d, *J*=10.0 Hz, 1H, CH2), 4.26~4.30 (m, 1H, CH), 4.74 (t, *J*=9.2 Hz, 1H, CH), 5.27 (d, *J*=11.2 Hz, 1H, CH), 6.54 (d, *J*=7.6 Hz, 1H, ArH), 6.90 (t, *J*=7.2 Hz, 1H, ArH), 7.02 (t, *J*=7.2 Hz, 1H, ArH), 7.09 (d, *J*=7.9 Hz, 1H, ArH), 7.22 (t, *J*=6.0 Hz, 1H, ArH), 7.32 (t, *J*=7.2 Hz, 1H, ArH), 7.42 (t, *J*=8.4 Hz, 2H, ArH), 7.48 (t,*J*=7.6 Hz, 1H, ArH), 7.63 (d, *J*=8.0 Hz, 1H, ArH), 7.75 (d, *J*=7.6 Hz, 1H, ArH), 8.51 (d, *J*=4.0 Hz, 1H, ArH), 8.74 (s, 1H, NH);13C NMR (DMSO-*d6*, 100 MHz) δ:35.31, 42.82, 50.05, 60.34, 71.26, 74.37, 108.43, 109.75, 120.06, 120.49, 121.65, 123.78, 126.54, 127.45, 127.89, 128.22, 128.63, 129.72, 136.36, 142.58, 147.73, 151.44, 157.38, 178.83, 197.88; HRMS calcd for $C_{25}H_{19}N_3O_2S$[M+H]+: 504.0381, found:504.0363.24

(3R,6'S,7'R,7a'S)-6'-picolinoyl-7'-(p-tolyl)-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (4g)

White solid; m.p. 228~230 °C; IR (KBr): v= 3190, 3097, 3028, 2945, 2868, 1738, 1713, 1618, 1510, 1472, 777, 752; 1H NMR (DMSO-*d6*, 400 MHz) δ: 2.24 (s, 3H, CH3), 2.87 (dd, *J*1=10.8 Hz, *J*2=4.8 Hz, 1H, CH2), 2.96 (dd, *J*1=10.8 Hz, *J*2=6.0 Hz, 1H, CH2), 3.34 (d, *J*=7.6 Hz, 1H, CH2), 3.63 (d, *J*=8.8 Hz, 1H, CH2), 4.11~4.16 (m, 1H, CH), 4.55 (t, *J*=9.2 Hz, 1H, CH), 5.11 (d, *J*=10.4 Hz, 1H, CH), 6.40 (d, *J*=7.6 Hz, 1H, ArH), 6.77 (t, *J*=7.2 Hz, 1H, ArH), 6.96 (t, *J*=7.6 Hz, 1H, ArH), 7.06 (d, *J*=7.2 Hz, 1H, ArH), 7.15 (d, *J*=8.0 Hz, 2H, ArH), 7.28 (d, *J*=7.6 Hz, 1H, ArH), 7.35 (d, *J*=8.0 Hz, 2H, ArH), 7.41~7.45 (m, 1H, ArH), 7.66 (t, *J*=7.6 Hz, 1H, ArH), 8.43 (d, *J*=4.4 Hz, 1H, ArH), 10.30 (s, 1H, NH);13C NMR (DMSO-*d6*, 100 MHz) δ:21.25, 35.82, 48.32, 51.13, 61.83, 71.05, 73.43, 109.28, 113.96, 120.02, 120.75, 124.17, 126.35, 127.47, 128.56, 129.46, 131.65, 137.36, 142.48, 148.36, 151.54, 158.19, 178.68, 197.75;HRMS calcd for $C_{26}H_{22}N_3O_2S$[M-H]+: 440.1433, found: 440.1454.

(3R,6'S,7'R,7a'S)-7'-(4-methoxyphenyl)-6'-picolinoyl-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (4h)

White solid; m.p. 153~155 °C; IR (KBr): v= 3204, 3097, 3036, 2937,2839, 1738, 1709, 1614, 1510, 1472, 1248, 773, 756; 1H NMR (DMSO-*d6*, 400 MHz) δ: 2.87 (dd, *J*1=10.8 Hz, *J*2=4.4 Hz, 1H, CH2), 2.97 (dd, *J*1=10.8 Hz, *J*2=6.0 Hz, 1H, CH2), 3.35 (d, *J*=8.8 Hz, 1H, CH2), 3.64 (d, *J*=8.8 Hz, 1H, CH2), 3.71 (s, 3H, OCH3), 3.81 (t, *J*=10.0 Hz, 1H, CH), 4.11~4.12 (m, 1H, CH), 5.08 (d, *J*=10.8 Hz, 1H, CH), 6.41 (d, *J*=7.6 Hz, 1H, ArH), 6.78 (t, *J*=7.6 Hz, 1H, ArH), 6.92 (d, *J*=9.2 Hz, 2H, ArH), 6.97 (t, *J*=7.6 Hz, 1H, ArH), 7.07 (d, *J*=7.6 Hz, 1H, ArH), 7.28 (d, *J*=8.0 Hz, 1H, ArH), 7.39 (d, *J*=8.8 Hz, 2H, ArH), 7.43~7.46 (m, 1H, ArH), 7.67 (t, *J*=7.6 Hz, 1H, ArH), 8.44 (d, *J*=4.4 Hz, 1H, ArH), 10.31 (s, 1H, NH); 13C NMR (DMSO-*d6*, 100 MHz) δ:18.56, 34.71, 48.45, 51.07, 55.01, 56.01, 62.81, 71.09, 73.94, 109.11, 114.13, 120.72, 120.84, 124.26, 126.43, 127.52, 128.96, 129.39, 131.95, 137.09, 142.61, 148.16, 151.84, 158.23, 178.75, 197.56;HRMS calcd for $C_{26}H_{22}N_3O_3S$[M-H]+: 456.1382, found: 456.1365.25

(3R,6'S,7'R,7a'S)-7'-(2-methoxyphenyl)-6'-picolinoyl-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (4i)

White solid; m.p. 241~243 ºC;IR (KBr): v= 3203, 3025, 2928, 1742,1704, 1618, 1525, 1472, 787, 748;1H NMR (DMSO-*d6*, 400 MHz) δ: 2.91 (dd, *J*1=10.8 Hz, *J*2=6.0 Hz, 1H, CH2), 2.99 (dd, *J*1=10.8 Hz, *J*2=4.8 Hz, 1H, CH2), 3.31 (d, *J*=9.2 Hz, 1H, CH2), 3.64 (d, *J*=9.2 Hz, 1H, CH2), 3.81 (s, 3H, OCH3), 4.09~4.14 (m, 1H, CH), 4.31 (t, *J*=8.8 Hz, 1H, CH), 5.32 (d, *J*=10.8 Hz, 1H, CH), 6.40 (d, *J*=7.6 Hz, 1H, ArH), 6.77 (t, *J*=7.6 Hz, 1H, ArH), 6.93~6.99 (m, 3H, ArH), 7.07 (d, *J*=7.6 Hz, 1H, ArH), 7.21 (t, *J*=8.0 Hz, 1H, ArH), 7.27 (d, *J*=8.0 Hz, 1H, ArH), 7.43 (t, *J*=6.8 Hz, 1H, ArH), 7.49 (d, *J*=7.6 Hz, 1H, ArH), 7.65 (t, *J*=8.0 Hz, 1H, ArH), 8.46 (d, *J*=4.4 Hz, 1H, ArH), 10.26 (s, 1H, NH); 13C NMR (DMSO-*d6*, 100 MHz) δ:35.13, 42.65, 51.49, 55.38, 59.95, 71.36, 73.28, 108.81, 111.17, 120.35, 120.47, 120.61, 123.85, 126.43, 127.17, 127.69, 127.79, 127.98, 129.14, 136.78, 142.45, 147.88, 151.76, 157.19, 178.59, 197.49;HRMS calcd for $C_{26}H_{22}N_3O_3S$[M-H]+: 456.1382, found: 456.1373.

(3R,6'S,7'R,7a'S)-7'-(2,3-dimethoxyphenyl)-6'-picolinoyl-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (4j)

White solid; m.p. 144~146 ºC; IR (KBr): v= 3213, 3031, 2909, 1745,1709, 1622, 1537, 1471, 758;1H NMR (DMSO-*d6*, 400 MHz) δ: 2.90 (dd, *J*1=10.8 Hz, *J*2=6.0 Hz, 1H, CH2), 2.96 (dd, *J*1=10.8 Hz, *J*2=4.8 Hz, 1H, CH2), 3.40~3.46 (m, 1H, CH2), 3.64 (d, *J*=9.2 Hz, 1H, CH2), 3.79 (s, 3H, OCH3), 3.87 (s, 3H, OCH3), 3.99~4.04 (m, 1H, CH), 4.37 (t, *J*=10.8 Hz, 1H, CH), 5.25 (d, *J*=10.8 Hz, 1H, CH), 6.41 (d, *J*=8.0 Hz, 1H, ArH), 6.79 (t, *J*=7.6 Hz, 1H, ArH), 6.92 (d, *J*=8.0 Hz, 1H, ArH), 6.97 (t, *J*=7.6 Hz, 1H, ArH), 7.06 (t, *J*=7.6 Hz, 2H, ArH), 7.13 (d, *J*=6.8 Hz, 1H, ArH), 7.27 (d, *J*=8.0 Hz, 1H, ArH), 7.44 (t, *J*=6.4 Hz, 1H, ArH), 7.66 (t, *J*=7.6 Hz, 1H, ArH), 8.45 (d, *J*=4.0 Hz, 1H, ArH), 10.29 (s, 1H, NH); 13C NMR (DMSO-*d6*, 100 MHz) δ:18.27, 34.59, 41.57, 51.24, 55.29, 60.04, 71.19, 74.19, 108.81, 110.93, 118.95, 120.41, 120.57, 120.61, 123.79, 124.01, 126.24, 127.17, 129.12, 133.24, 136.76, 142.41, 147.87, 151.66, 152.27, 178.52, 197.43;HRMS calcd for $C_{27}H_{24}N_3O_4S$[M-H]+: 486.1488, found: 486.1563.26

(3R,6'S,7'S,7a'S)-6'-picolinoyl-7'-(thiophen-2-yl)-1',6',7',7a'-tetrahydro-3'H-spiro[indoline-3,5'-pyrrolo[1,2-c]thiazol]-2-one (4k)

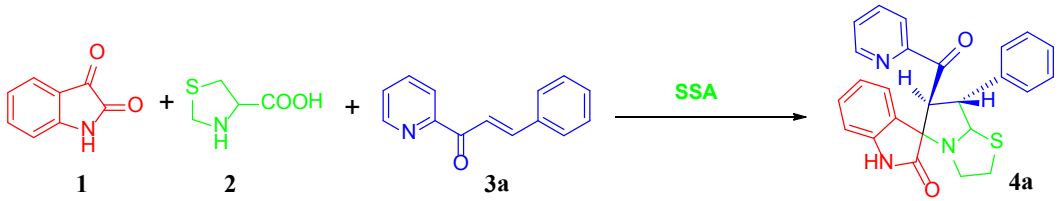
Colorless; m.p. 244~246 ºC;IR (KBr): v= 3188, 3119, 3015, 2930, 2860, 1747, 1705, 1618, 1514, 1475, 781, 756; 1H NMR (DMSO-*d6*, 400 MHz) δ: 2.99 (dd, *J*1=10.4 Hz, *J*2=3.2 Hz, 1H, CH2), 3.09 (dd, *J*1=10.8 Hz, *J*2=5.2 Hz, 1H, CH2), 3.35 (d, *J*=10.0 Hz, 1H, CH2), 3.63 (d, *J*=8.8 Hz, 1H, CH2), 4.12 (d, *J*=9.6 Hz, 1H, CH), 4.16~4.20 (m, 1H, CH), 5.04 (d, *J*=10.4 Hz, 1H, CH), 6.40 (d, *J*=8.0 Hz, 1H, ArH), 6.78 (t, *J*=7.6 Hz, 1H, ArH), 6.98 (t, *J*=8.8 Hz, 2H, ArH), 7.06 (d, *J*=8.0 Hz, 1H, ArH), 7.10 (d, *J*=2.4 Hz, 1H, ArH), 7.32 (d, *J*=8.0 Hz, 1H, ArH), 7.39 (d, *J*=5.2 Hz,1H, ArH), 7.46 (t, *J*=5.6 Hz, 1H, ArH), 7.69 (t, *J*=7.6 Hz, 1H, ArH), 8.46 (d, *J*=4.4 Hz, 1H, ArH), 10.29 (s, 1H, NH); 13C NMR (DMSO-*d6*, 100 MHz) δ:35.33, 42.67, 51.28, 60.12, 71.38, 73.65, 108.74, 110.23, 120.55, 120.90, 123.45, 126.57, 127.14, 127.53, 127.92, 128.23, 129.26, 136.54, 142.43, 147.24, 151.49, 157.35, 178.57, 197.79; HRMS calcd for $C_{26}H_{22}N_3O_2S$[M-H]+: 432.0841, found: 432.0871.

RESULTS AND DISCUSSION

To examine the feasibility of the microwave assisted for the 1,3-dipolar cycloaddition reaction, a sequence of trials was carried

out using isatin (**1**), secondary amino acids (L-thioproline) (**2**) and substituted prop-2-en-1-one as dipolarophlies (**3a**) as a model reaction under various solvents in the presence of Silica sulfuric acid (SSA) as catalyst . SSA catalyst could be prepared by simply treatment of the commercial silica gel (300-400 mesh) containing water with sulfuryl chloride (equivalent amount with water) under violently stirring [16]. Thus prepared catalyst was dried under vacuum at room temperature for 2 h before use. In order to develop a possible approach, the model reaction was examined using diverse solvents under microwave irradiation and the overall findings are given in **Table 1**. The mw assisted TFE mediated reaction takes place in the absence of any external basic and acidic catalysts. The results obtained from the thermal conditions showed that the product was obtained in a lower field (30–40%) after prolonged heating (60-90 min). Under microwave irradiation the temperature increase was fast to reach 50 °C and the reaction was achieved in 10 min. The influence of irradiation promoted a dramatic fall in the reaction time (10 min.), in comparison to 60 min. by conventional orbital shaking. The reaction has been performed under different solvents like acetonitrile, THF, benzene, toluene, methanol, ethanol, aqueous methanol and trifluoroethanol (TFE). But the product is formed in comparatively lower yield and purity. Under microwaves, 2,2,2-trifluoroethanol was found to be better than the other solvents. It is clear that TFE is the most adaptable solvent for absorbing microwave efficiently for synthesizing **4a** since a comparatively higher yield was achieved in a shorter time. Other compounds (**4b–k**) listed in **Table 3** are synthesized using TFE in mw.

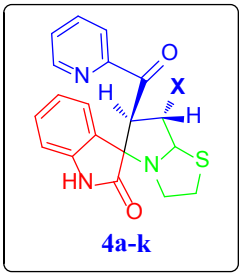
Table 1: Optimization of reaction conditions for the synthesis[a] of spiro[indoline-3,5'-pyrrolo[2,1-b]thiazol]-2-one **4a** under microwave and conventional process



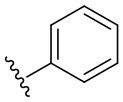
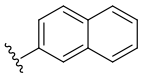
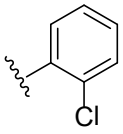
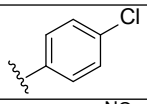
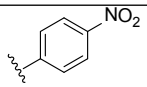
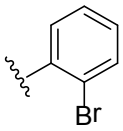
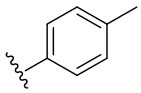
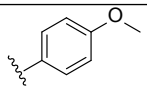
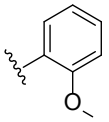
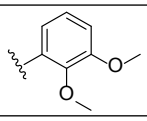
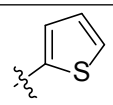
Entry	Solvent	Microwave				Conventional		
		Temp (°C)	Power (Watt)	Time (min)	Yield[b](%)	Temp (°C)	Time (min)	Yield[b] (%)
1	Acetonitrile	50	250	70	48	150	220	50
2	THF	50	250	70	42	150	310	32
3	Benzene	50	250	190	45	150	690	30
4	Toluene	50	250	200	50	150	500	35
5	Methanol	50	250	45	70	150	100	70
6	Ethanol	50	250	40	80	150	120	60
7	Aq. MeOH	50	250	40	72	150	90	70
8	***TFE***	***50***	***250***	***10***	***92***	150	60	73

[a]Reaction of isatin **1** (1 mmol), L-thioproline **2** (1 mmol) and **3a** (1 mmol).
[b]Isolated yield

Table 2: Synthetic results of spiro[indoline-3,5'-pyrrolo[2,1-b]thiazol]-2-one derivatives (**4a-k**)



4a-k

Entry	Product	X	Time (min)	Yield (%)[a]	Mp (°C)
1	**4a**		10	92	200-202
2	**4b**		12	81	168-170
3	**4c**		18	91	208-212
4	**4d**		10	92	222-226
5	**4e**		30	90	245-250
6	**4f**		15	89	226-228
7	**4g**		15	91	228-232
8	**4h**		20	88	155-157
9	**4i**		24	86	240-242
10	**4j**		10	88	144-146
11	**4k**		14	67	242-244

[a] Isolated yield

[b] Product was confirmed by 1H NMR, 13C NMR, and mass spectral analyses.

[c] Isolated yield after filtration through short pad of silica column.

The model reaction was furthermore studied by varying microwave power (150, 180, 250 and 300 W) and it was concluded that 250 W power output at 150 °C was required to accomplish maximum conversion to product **4a**. The reaction was repeated in microwave source to prove reproducibility, and no significant deviation was found.

Encouraged by this success, the optimized reaction condition was extended to isatin (**1**), secondary amino acids (L-thioproline) (**2**) and substituted prop-2-en-1-one as dipolarophlies (**3a-3k**) **to** explore its scope and generality. It can be seen from **Table 2** that all the substrates reacted in 2,2,2-trifluoroethanol under microwave irradiation smoothly and efficiently affording **4a–k** in good to excellent yields. A single product was isolated in all cases and no trace of the other isomer was formed even after prolonged reaction time.

In conclusion, we have demonstrated a simple one-pot microwave assisted Silica sulfuric acid (SSA) mediated three component reaction involving isatin, dipolarophlies, and secondary amino acids for the synthesis of a series of spiro-thiazol derivatives in TFE. Predominantly key features of this method include the higher yields of the products, mild reaction, broader substrate scope, conditions, and the straightforwardness of the procedure, which make it a valuable and attractive method for the synthesis of these important compounds.

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