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Silica-bonded *N*-propyl sulfamic acid: A recyclable catalyst for microwave-assisted synthesis of spirooxindoles via three-component reaction

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Silica bonded *N*-propyl sulfamic acid (**SBNPSA**) is employed as a solid acid catalyst for the synthesis of spirooxindoles via three-component reaction in good yields and short reaction times in ethanol under irradiation micrwave conditions. Irradiation of the combination of isatin or acenaphthoquinone, an activated methylene reagent, and 1,3-dicarbonyl compounds in the presence of catalytic (**SBNPSA**) was found to be a suitable and efficient method for the synthesis of the biologically important spirooxindoles.

Keywords: Silica-bonded *N*-propyl sulfamic acid (**SBNPSA**); Spirooxindoles; isatin; three-component; Irradiation microwave

INTRODUCTION

Combinatorial chemistry is now routinely applied to find out novel biologically active compounds. In this context, multicomponent reactions (MCRs) are powerful tools in the modern drug discovery process in terms of lead finding and lead optimization [1,2]. However, the range of easily accessible and functionalized small heterocycles is rather limited. The development of new, rapid, and robust routes toward focused libraries of such heterocycles is therefore of great importance. Spirooxindole derivatives are important classes of heterocyclic compounds.The heterocyclic spirooxindole ring system is a widely distributed structural framework that is present in a number of pharmaceuticals and natural products [3], including cytostatic alkaloids like spirotryprostatins and strychnophylline [4]. The unique structural array and the highly pronounced pharmacological activity displayed by this class of spirooxindole compounds have made them attractive synthetic targets [5]. Oxa and azaspiro derivatives are well-known [6], but the preparation of corresponding quinazolinone analogues has not yet evolved. Polyfunctionalized heterocyclic compounds play important roles in the drug discovery process, and analysis of drugs in late development or on the market shows that 68% of them are heterocycles [7,8]. Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds has received significant attention.

The quinone moiety is involved in a wide variety of biochemical processes including electron transport and oxidative phosphorylation [3]. Various biological properties including enzyme inhibition, antibacterial, antifungal, and anticancer activities have been reported for quinones and quinone derivatives [9]. The antitumor activity of the quinone moiety has been studied thoroughly, and it is known that they act as topoisomerase inhibitors via DNA intercalation [10]. Quinone-annulated heterocycles are found in nature, and most of them exhibit interesting biological activities. The chemistry of quinone-annulated heterocycles is dependent largely on the substituent being either on the quinone or on adjacent rings [11]. These activities, combined with diverse chemical behavior make quinones attractive targets in organic synthesis. The indole framework is common in a wide variety of pharmacologically and biologically active compounds [12]. Furthermore, it has been reported that sharing of the indole 3-carbon atom during the formation of spiroindoline derivatives enhances the biological activity highly [13]. The spiro-oxindole system is the core structure of some pharmacological agents and natural alkaloids [14]. Similarly, xanthenes have been reported to possess diverse biological and therapeutic properties such as antibacterial, antiviral, and anti-inflammatory activities, as well

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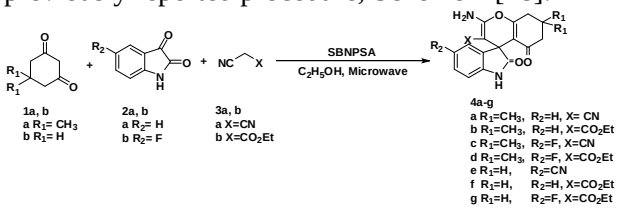
as being used in photodynamic therapy [14]. Other useful applications of these heterocycles are as dyes, fluorescent materials for visualization of biomolecules and in laser technologies [15]. Considering the above reports, and as part of our program aimed at developing new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds [16].

EXPERIMENTAL

All materials and solvents were purchased from Merck and Fluka. Melting points were determined in open capillary tubes in an Electrothermal IA 9700 melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker-300 MHz instrument using tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Irradiation was carried out in a domestic microwave oven (Electra, 2450 MHz, 700 W) for optimized time. silica bonded *N*-propyl sulfamic acid (**SBNPSA**) was prepared according to our previously reported procedure, Scheme **1** [18].



Scheme 1. Synthesis of spirooxindoles via three-component reaction with isatin (2) in the presence of silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) as catalyst under irradiation microwave conditions.

*General procedure for the synthesis of spirooxindoles (**4a–j**):*

Silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) (0.1 g) was added to a stirred mixture of isatin (1 mmol), malononitrile (1 mmol) and phthalhydrazide (1 mmol) in ethanol (5 mL), and was irradiated in a microwave oven at 700 W for the appropriate time (Table 1). After complete conversion as indicated by TLC, water was added and the product was extracted with ethyl acetate (2 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting product was recrystallized from ethanol to afford pure product (4a–j).

3-Amino-5'-nitro-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo (1,2-b)phthalazin]-(1'H)-2'-one-2-carboxylate (table 1, entry 1, 4a):

Yellow solid. m.p.: 280–282°C. IR (KBr) ν_{max}/cm^{-1}: 3377, 3256, 2207, 1710, 1693, 1669, 1609, 1552, 1470, 1437, 1375, 1285, 1255, 1166, 698. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.11 (d, 1H, J = 8.4 Hz), 7.95 (m, 3H), 8.21 (m, 2H), 8.46 (s, 2H, NH_2), 8.62 (d, 1H, J = 7.65 Hz), 11.67 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 64.1, 69.5, 111.0, 114.5, 121.7, 127.6, 128.0, 128.2, 129.5, 135.3, 135.6, 143.5, 148.6, 152.8, 153.0, 157.0, 173.7. MS (m/z): 402 (M^+). Anal. Calcd. for $C_{19}H_{10}N_6O_5$: C, 56.72; H, 2.50; N, 20.88%. Found: C, 56.80; H, 2.47; N, 20.82%.

Ethyl 3-amino-1'-allyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carboxylate (table 1, entry2, 4b):

Yellow solid. m.p.: 254–256°C. IR (KBr) ν_{max}/cm^{-1}: 3385, 3254, 1735, 1709, 1668, 1608, 1572, 1456, 1423, 1377, 1285, 1256, 1178, 692. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.80 (s, 3H), 3.78 (q, 2H, J = 6.9 Hz), 4.25 (2H, J = 17.55 Hz), 5.18 (d, 1H, J = 9.95 Hz), 5.46 (d, 1H, J = 17.55 Hz), 5.83 (m, 1H), 6.90 (t, 1H, J = 7.6 Hz), 6.95 (d, 1H, J = 7.65 Hz), 7.25 (t, 1H, J = 7.65 Hz), 7.36 (d, 1H, J = 6.85 Hz), 7.85 (s, 2H, NH_2), 7.95 (t, 2H, J = 7.65 Hz), 8.05 (d, 1H, J = 9.15 Hz), 8.26 (d, 1H, J = 7.9 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 14.4, 43.7, 59.5, 70.5, 79.7, 111.6, 117.8, 122.7, 124.1, 125.4, 127.1, 127.3, 127.9, 128.5, 130.1, 132.2, 134.7, 135.5, 152.6, 153.1, 157.1, 162.8, 171.8. MS (m/z): 444 (M^+). Anal. Calcd. for $C_{24}H_{20}N_4O_5$: C, 64.86; H, 4.54; N, 12.61%. Found: C, 64.75; H, 4.51; N, 12.55%.

3-Amino-1'-allyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carbonitrile (table 1, entry 3, 4c):

Yellow solid. m.p.: 276–277°C. IR (KBr) ν_{max}/cm^{-1}: 3384, 3260, 2200, 1715, 1692, 1665, 1613, 1560, 1469, 1438, 1377, 1285, 1255, 1170, 698. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.35 (2H, J = 13.0 Hz), 5.16 (d, 1H, J = 10.7 Hz), 5.30 (d, 1H, J = 16.8 Hz), 5.81 (m, 1H), 7.00 (d, 1H, J = 7.6 Hz), 7.05 (t, 1H, J = 7.65 Hz), 7.32 (t, 1H, J = 8.4 Hz), 7.54 (d, 1H, J = 7.65 Hz), 7.96 (m, 3H), 8.25 (d, 1H, J = 6.85 Hz), 8.35 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 42.5, 60.3, 70.0, 110.2, 114.7, 117.0, 123.9, 125.0, 125.3, 127.5, 128.1, 128.0, 129.1, 131.0, 131.7, 135.0, 135.6, 143.0, 152.4, 153.1, 156.8, 171.5. MS (m/z): 397 (M^+). Anal. Calcd. for $C_{22}H_{15}N_5O_3$: C, 66.49; H, 3.80; N, 17.62%. Found: C, 66.57; H, 3.75; N, 17.58%.

Ethyl 3-amino-1'-benzyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-

b)phthalazin]-(1'H)-2'-one-2-carboxylate (table 1, entry 4, 4d):

Yellow solid. m.p.: 290–291ºC. IR (KBr) ν_{max}/cm^{-1}: 3425, 3317, 1702, 1697, 1529, 1427, 1385, 1299, 1264, 1143, 700. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.63 (m, 3H), 3.41 (m, 2H), 4.86 (2H, J = 16.05 Hz), 6.80 (d, 1H, J = 7.65 Hz), 6.90 (t, 1H, J = 7.65 Hz), 7.18 (t, 1H, J = 7.65 Hz), 7.25 (t,1H, J = 6.85 Hz), 7.30 (t, 2H, J = 7.65 Hz), 7.38 (d,1H, J = 7.65 Hz), 7.50 (d, 2H, J = 7.65 Hz), 7.95 (m, 3H), 8.15 (s, 2H, NH_2), 8.29 (d, 1H, J = 9.15 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 14.1, 43.9, 56.5, 59.1, 70.3, 109.3, 123.1, 124.0, 127.5, 127.8, 127.9, 128.1, 128.9, 129.2, 130.0, 134.8, 135.6, 136.6, 144.5, 152.8, 157.0, 163.6, 172.3. MS (m/z): 494 (M^+). Anal. Calcd. for $C_{28}H_{22}N_4O_5$: C, 68.01; H, 4.48; N, 11.33%. Found: C, 67.95; H, 4.42; N, 11.28%.

3-Amino-1'-benzyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carbonitrile (table 1, entry 5, 4e):

Yellow solid. m.p.: 266ºC. IR (KBr) ν_{max}/cm^{-1}: 3375, 3259, 2198, 1667, 1612, 1469, 1372, 1163, 699 . ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 4.95 (2H, J = 16.05 Hz), 6.88 (d, 1H, J = 8.4 Hz), 7.03 (t, 1H, J = 6.85 Hz), 7.25 (d, 2H, J = 6.9 Hz), 7.30 (t, 2H, J = 7.65 Hz), 7.41 (d, 2H, J = 7.6 Hz), 7.55 (d, 1H, J = 7.65 Hz), 7.96 (m, 2H), 8.05 (d, 1H, J = 6.85 Hz), 8.28 (d, 1H, J = 9.15 Hz), 8.40 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 44.0, 60.3, 70.0, 110.2, 115.1, 123.9, 125.1, 125.4, 127.5, 127.7, 128.0, 128.2, 129.1, 129.3, 131.0, 135.0, 135.6, 136.0, 143.1, 152.5, 153.2, 156.8, 171.8. MS (m/z): 447 (M^+). Anal. Calcd. for $C_{26}H_{17}N_5O_3$: C, 69.79; H, 3.83; N, 15.65%. Found: C, 69.72; H, 3.78; N, 15.60%.

Ethyl 3-amino-1'-butyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carboxylate (table 1, entry 6, 4f):

Pale yellow solid. m.p.: 258–260°C. IR (KBr) ν_{max}/cm^{-1}: 3428, 3320, 2934, 1730, 1704, 1675, 1610, 1528, 1469, 1429, 1377, 1298, 1264, 1142, 757, 699. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.79 (m, 3H), 0.88 (t, 3H, J = 6.85 Hz), 1.36 (m, 2H), 1.61 (m, 2H), 3.65 (t, 2H, J = 7.65 Hz), 3.80 (m, 2H), 6.91 (t, 1H, J = 7.6 Hz), 7.03 (d, 1H, J = 8.4 Hz), 7.25 (t, 1H, J = 7.65 Hz), 7.35 (d, 1H, J = 7.65 Hz), 7.94 (m, 3H), 7.60 (s, 2H, NH_2), 8.26 (d, 1H, J = 6.85 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 14.0, 14.3, 20.1, 29.7, 59.3, 70.0, 80.2, 108.8, 122.7, 124.0, 126.8, 127.6, 128.1, 128.5, 129.0, 130.2, 134.8, 135.5, 144.7, 151.4, 152.7, 157.2, 163.6, 171.8. MS (m/z): 460 (M^+). Anal. Calcd. for $C_{25}H_{24}N_4O_5$: C, 65.21; H, 5.25; N, 12.17%. Found: C, 65.27; H, 5.20; N, 12.12%.

3-Amino-1'-butyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carbonitrile (table 1, entry 7, 4g):

Yellow solid. m.p.: 222–223ºC. IR (KBr) ν_{max}/cm^{-1}: 3384, 3260, 2938, 2197, 1668, 1612, 1562, 1468, 1434, 1375, 1257, 1146. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.85 (t, 3H, J = 6·9 Hz), 1.34 (m, 2H), 1.58 (m, 2H), 3.70 (m, 2H), 7.04 (t, 1H, J =7.65 Hz), 7.14 (d, 1H, J = 7.65 Hz), 7.36 (t, 1H, J =7.6 Hz), 7.50 (d, 1H, J = 6.85 Hz), 7.96 (t, 2H, J = 7.6 Hz), 8.00 (d, 1H, J = 8.45 Hz), 8.27 (d, 1H, J = 7.6 Hz), 8.36 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 14.1, 19.8, 29.7, 60.5, 70.0, 109.8, 114.8, 123.5, 125.0, 125.3, 127.7, 128.1, 128.3, 129.2, 131.3, 134.9, 135.6, 143.6, 152.3, 153.1, 156.9, 171.4. MS (m/z): 413 (M^+). Anal. Calcd. for $C_{23}H_{19}N_5O_3$: C, 66.82; H, 4.63; N, 16.94%. Found: C, 66.93; H, 4.58; N, 16.88%.

2.2c 3-Amino-1'-methyl-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)-2'-one-2-carbonitrile (table 1, entry 8, 4h):

Yellow solid. m.p.: 282–284°C. IR (KBr) ν_{max}/cm^{-1}: 3455, 3328, 2197, 1727, 1665, 1610, 1472, 1370, 698 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.20 (s, 3H), 7.06 (t, 1H, J = 7.65 Hz), 7.10 (d, 1H, J = 7.65 Hz), 7.38 (t, 1H, J = 8.4 Hz), 7.50 (d, 1H, J = 6.9 Hz), 7.96 (m, 3H), 8.25 (d, 1H, J = 8.4 Hz), 8.37 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 27.3, 60.1, 69.8, 109.7, 114.9, 123.8, 124.9, 125.3, 127.5, 128.1, 128.3, 129.2, 131.2, 135.0, 135.6, 144.2, 152.4, 153.1, 156.8, 171.5. MS (m/z): 371 (M^+). Anal. Calcd. for $C_{20}H_{13}N_5O_3$: C, 64·69; H, 3·53; N, 18·86%. Found: C, 64·63; H, 3·48; N, 18·81%.

Ethyl 3-amino-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b) phthalazin]-(1'H)-2'-one-2-carboxylate (table 1, entry 9, 4i):

Yellow solid. m.p.: 284–286°C. IR (KBr) ν_{max}/cm^{-1}: 3439, 3327, 1742, 1700, 1665, 1528, 1294, 1140. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.85 (t, 3H, J = 7·65 Hz), 3.80 (m, 2H), 6.80 (d, 1H, J = 7.65 Hz), 6.85 (t, 1H, J = 6.85 Hz), 7.18 (t, 1H, J = 7.65 Hz), 7.28 (d, 1H, J = 7.65 Hz), 7.52 (s, 2H, NH_2), 7.93 (m, 3H), 8.25 (d, 1H, J = 9.15 Hz), 10.74 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 14.1, 59.6, 70.5, 81.3, 109.8, 122.1, 124.3, 127.3,

127.5, 128.0, 128.5, 129.1, 130.0, 134.7, 135.5, 143.9, 151.3, 152.6, 157.0, 163.7, 173.5. MS (m/z): 404 (M^+). Anal. Calcd. For $C_{21}H_{16}N_4O_5$: C, 62.37; H, 3.99; N, 13.85 %. Found: C, 62.28; H, 3.94; N, 13.78%.

3-Amino-5,10-dioxo spiro[(3'H)-indol-3',1-5,10-dihydro-1(H)-pyrazolo(1,2-b)phthalazin]-(1'H)- 2'-one-2-carbonitrile (table 1, entry 10, 4j):

Yellow solid. m.p.: 269–270ºC. IR (KBr) ν_{max}/cm^{-1}: 3440, 3350, 2207, 1755, 1679, 1654, 1467, 1364, 1258, 1163. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.95 (d, 1H, J = 7.65 Hz), 6.95 (t, 1H, J = 7.65 Hz), 7.26 (t, 1H, J = 7.6 Hz), 7.45 (d, 1H, J = 7.65 Hz), 7.96 (m, 3H), 8.23 (d, 1H, J= 7·65 Hz), 8.34 (s, 2H, NH_2), 10.90 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 60.5, 70.2, 110.9, 114.8, 123.2, 125.2, 125.9, 127.5, 128.1, 128.3, 129.2, 131.0, 134.9, 135.6, 142.7, 152.2, 153.1, 156.9, 173.0. MS (m/z): 357 (M^+)· Anal. Calcd. For $C_{19}H_{11}N_5O_3$: C, 63.87; H, 3.10; N, 19.60%. Found: C, 63.83; H, 3.06; N, 19.55 %.

Typical procedure for preparation of 2-amino-7,7-dimethyl-20,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,30-indoline]-3-carbonitrile (4a):

A mixture of isatin (0.15 g), malononitrile (0.05 g), 5,5-dimethyl-1,3-cyclohexanedione (0.15 g), and silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) (0.01 g) in ethanol (6 mL) was stirred and irradiated in a microwave oven at 700 W for the appropriate time (Table 2). Upon completion, monitored by TLC (*n*-hexane/ethyl acetate: 2/1), the reaction mixture was allowed to cool to room temperature. The solid was filtered off and washed with water and cool ethanol to give the desired products. The crude product was recrystallized from EtOH to the yields:

Ethyl-2-amino-50-fluoro-20,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,30-indoline]-3-carboxylate (table 2, entry1, 4a):

White solid. Mp 273–274 ºC, IR (KBr) ν_{max}/cm^{-1}: 3595, 3366, 3160, 1715, 1695, 1656, 1520, 1295. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.7 (t, 3H, J=7.1 Hz, CH_3), 1.86 (m, 2H, CH_2), 2.19 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 3.70 (q, 2H, J=6.5 Hz, CH_2), 6.64–6.86 (m, 3H, ArH), 7.90 (s, 2H, NH_2), 10.17 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.58, 20.05, 27.45, 37.5, 47.70, 59.36, 76.30,108.72, 111.7, 113.53,114.11, 138.30, 140.83, 156.60, 159.65, 165.06, 167.99, 180.34, 195.38. MS, m/z (%): 372 (M^+, 65), 299 (100), 271 (25), 42 (45).Anal. Calcd for $C_{19}H_{17}FN_2O_5$: C, 61.29; H, 4.60; N, 7.52%. Found: C, 61.12; H, 4.77; N, 7.69%.

Ethyl-2-amino-20,5-dioxo-5,6,7,8-tetrahydrospiro-[chromene-4,30-indoline]-3-carboxylate (table 2, entry 2, 4b) :

White solid. Mp 263–265 ºC, IR (KBr) ν_{max}/cm^{-1}: 3369, 3247, 3160, 1695, 1649, 1524, 1299. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.79 (t, 3H, J=7.1 Hz, CH_3), 1.85 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 3.73 (q, 2H, J=6.1 Hz, CH_2), 6.66–7.05 (m, 4H, ArH), 7.87 (s, 2H, NH_2), 10.15 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.57, 20.12, 27.39, 37.58, 47.15, 59.27, 76.80, 108.49,114.64, 120.98, 122.88, 127.59, 136.56, 144.48, 159.44, 164.69, 168.12, 180.35, 195.29. MS, m/z (%): 354 (M^+, 40), 281 (100), 253 (25), 55 (30), 39 (30). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91%. Found: C, 64.08; H, 5.44; N, 8.23%.

2-Amino-20,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,30-indoline]-3-carbonitrile (table 2, entry 3, 4c):

White solid. Mp 251–252 ºC, IR (KBr) ν_{max}/cm^{-1}: 3365, 3283, 3160, 2195, 17223, 1655, 1347, 1214. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.91 (s, 2H, CH_2), 2.20 (s, 2H, CH_2), 2.65 (s, 2H, CH_2), 6.77–7.10 (m, 4H, ArH), 7.20 (s, 2H, NH_2), 10.38 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 20.25, 27.16, 36.80, 47.30, 57.95, 109.58, 112.30, 122.2, 123.65, 128.58, 134.98, 142.44, 159.06, 166.49, 178.57, 195.47. MS, m/z (%): 307 (M^+, 50), 251 (100), 209 (50), 140 (55), 39 (30). Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67%. Found: C, 66.31; H, 4.43; N, 13.84%.

Ethyl-2-amino-50-fluoro-7,7-dimethyl-20,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,30-indoline]-3-carboxylate (table 2, entry 4, 4d):

White solid. Mp 240–242 ºC, IR (KBr) ν_{max}/cm^{-1}: 3395, 3350, 2954, 1707, 1689, 1665, 1487, 1170. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.76 (t, 3H, J=6.5 Hz, CH_3), 0.97 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.05 (d, 1H, J=16.6 Hz), 2.15 (d, 1H, J=15.7 Hz), 2.56 (m, 2H, CH_2), 3.72 (q, 2H, J=6.5 Hz, CH_2), 6.66–6.84 (m, 3H, ArH), 7.90 (s, 2H, NH_2), 10.18 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.59, 27.38, 28.07, 31.99, 47.60, 51.08, 59.35, 76.28, 108.87, 110.66, 113.39, 116.67, 138.24, 140.86, 159.63, 163.21, 167.97, 180.23, 195.23. MS, m/z (%): 400 (M^+, 25), 327 (100), 299 (22), 83 (25), 41 (45). Anal. Calcd for $C_{21}H_{21}FN_2O_5$: C,

62.99; H, 5.29; N, 7.00%. Found: C, 62.74; H, 5.54; N, 7.25%.

2-Amino-50-fluoro-7,7-dimethyl-20,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,30-indoline]-3-carbonitrile (table 2, entry 5, 4e):

Pink solid. Mp 270–273 ºC, IR (KBr) ν_{max}/cm^{-1}: 3357, 3299, 3160, 2964, 2192, 1725, 1648, 1345, 1225. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz) *δ*: 1.00 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.05 (d, 1H, J=15.9 Hz), 2.17 (d, 1H, J=16.0 Hz), 2.53 (m, 2H, CH_2), 6.65–6.77 (m, 3H, ArH), 7.71 (s, 2H, NH_2), 10.25 (s, 1H, NH). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) *δ*: 27.36, 28.12, 33.13, 47.37, 51.23, 59.16, 110.17, 112.29, 117.80, 123.09, 124.45, 129.58, 133.80, 144.53, 160.02, 167.52, 179.45,196.27. MS, m/z (%): 353 (M^+, 30), 269 (100), 227 (55), 42 (75). Anal. Calcd for $C_{19}H_{16}FN_3O_3$: C, 64.58; H, 4.56; N, 11.89%. Found: C, 64.27; H, 4.87; N, 12.14%.

Ethyl-2-amino-7,7-dimethyl-20,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,30-indoline]-3-carboxylate (table 2, entry 6, 4f):

White solid. Mp 257–258 ºC, IR (KBr) ν_{max}/cm^{-1}: 3366, 3187, 2926, 1667, 1612, 1223. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz) *δ*: 0.79 (t, 3H, J=6.57 Hz, CH_3), 0.95 (s, 3H, CH_3),1.03 (s, 3H, CH_3), 2.00 (d, 1H, J=15.7 Hz), 2.16 (d, 1H, J=15.7 Hz), 2.57 (m, 2H, CH_2), 3.69 (q, 2H, J=5.2 Hz, CH_2), 6.68–7.04 (m, 4H, ArH), 7.87 (s, 2H, NH_2), 10.15 (s, 1H, NH). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) *δ*: 13.56, 27.12, 28.24, 32.0, 47.05, 51.08, 59.30, 76.75, 108.59, 113.53, 120.99, 122.68, 127.63, 136.45, 144.49, 159.56, 162.87, 168.10, 180.26, 195.13. MS, m/z (%): 382(M^+, 90), 309 (100), 281 (25), 83 (25), 41 (23). Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33%. Found: C, 65.72; H, 6.03; N, 7.57%.

2-amino-7,7-dimethyl-20,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,30-indoline]-3-carbonitrile (table 2, entry 7, 4g):

white solid. Mp 268–270 ºC, IR (KBr) ν_{max}/cm^{-1}: 3378, 3314, 2906, 2191, 1722, 1658, 1220. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 0.99 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.08 (d, 1H, J=16.1 Hz), 2.17 (d, 1H, J=15.9 Hz,), 2.52 (m, 2H, CH_2), 6.76–7.15 (m, 4H, ArH), 7.22 (s, 2H, NH_2), 10.40 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 27.46, 28.06, 32.40, 47.25, 50.44, 57.89, 109.69, 111.22, 117.81, 122.14, 123.47, 128.63, 134.87, 142.49, 159.22, 164.61, 178.50, 195.37. MS, m/z (%): 335 (M^+, 50), 251 (100), 210 (25), 83 (23), 66 (23), 39 (35). Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53%. Found: C, 67.94; H, 5.23; N, 12.64%.

Ethyl-20-amino-2,50-dioxo-50,60,70,80-tetrahydro-2Hspiro[acenaphthylene-1,40-chromene]-30-carboxylate (table 2, entry 8, 6a):

Yellow solid. Mp 225–227 ºC, IR (KBr) ν_{max}/cm^{-1}: 3400, 3295, 2989, 1726, 1677, 1520, 1354. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz) *δ*: 0.04 (t, 3H, J=7.1 Hz, CH_3), 1.47 (m, 2H, CH_2), 2.65 (t, 2H, J=6.2 Hz, CH_2), 3.45 (q, 2H, J=7.1 Hz, CH_2), 4.52 (t, 2H, J=7.1 Hz, CH_2), 6.58 (s, 2H, NH_2), 7.22–8.48 (m, 6H, ArH). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) *δ*: 12.25, 27.43, 36.82, 59.43, 63.40, 75.09, 119.40, 119.90, 122.78, 124.21, 127.80, 127.99, 128.72, 128.83, 129.50, 129.61, 129.71, 132.21, 136.02, 141.23, 164.17, 168.32, 195.60. MS, m/z (%): 389 (M^+, 20), 316 (100), 176 (80), 149 (40), 55 (25). Anal. Calcd for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60%. Found: C, 70.75; H, 5.12; N, 3.78%.

20-Amino-2,50-dioxo-50,60,70,80-tetrahydro-2Hspiro[acenaphthylene-1,40-chromene]-30-carbonitrile (table 2, entry 9, 6b):

Yellow solid. Mp 245–247 ºC, IR (KBr) ν_{max}/cm^{-1}: 3372, 3189, 2192, 1718, 1672, 1595, 1344, 1205. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz) *δ*: 1.92 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 2.71 (m, 2H, CH_2), 7.32–8.66 (m, 6H, ArH), 7.92 (s, 2H, NH_2). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) *δ*: 20.27, 27.17, 36.50, 51.46, 58.50, 113.55, 117.99, 120.47, 121.81, 124.95, 128.90, 129.33, 130.19, 131.86, 132.67, 140.87, 143.82, 159.10, 166.93, 195.87, 204.06. MS, m/z (%): 342 (M^+, 23), 230 (70), 202 (50), 175 (40), 84 (30), 42 (100). Anal. Calcd for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.12; N, 8.18%. Found: C, 73.54; H, 4.28; N, 8.34%.

Ethyl-20-amino-70,70-dimethyl-2,50-dioxo-50,60,70,80-tetrahydro-2H-spiro[acenaphthylene-1,40-chromene]-30-carboxylate (table 2, entry 10 , 6c):

White solid. Mp 261–263 ºC, IR (KBr) ν_{max}/cm^{-1}: 3380, 3269, 2953, 1718, 1687, 1519, 1222. ^{1}H NMR (DMSO-*d*$_6$, 300 MHz) *δ*: 0.53 (t, 3H, J=7.0 Hz, CH_3), 0.93 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.92 (d, 1H, J=15.9 Hz), 2.07 (d, 1H, J=16.0 Hz), 2.62 (m, 2H, CH_2), 7.22–8.12 (m, 6H, ArH), 7.94 (s, 2H, NH). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) *δ*: 12.66, 27.17, 28.23, 32.15, 50.48, 51.16, 58.86, 77.67, 115.32, 119.46, 119.58, 124.23, 128.17, 128.68, 129.71, 129.89, 136.45, 141.09, 145.76, 159.85, 163.41, 167.91, 195.73, 205.65. MS, m/z

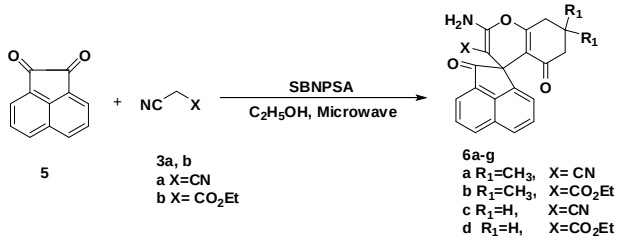
(%): 418 (M^++1, 25), 344 (100), 271 (30), 83 (25). Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36%. Found: C, 71.78; H, 5.70; N, 3.95%.

20-Amino-70,70-dimethyl-2,50-dioxo-50,60,70,80-tetrahydro-2H-spiro[acenaphthylene-1,40-chromene]-30-carbonitrile (table 2, entry 11, 6d):

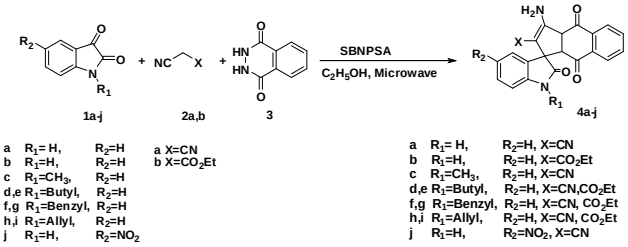
Yellow solid. Mp 260–262 ºC, IR (KBr) ν_{max}/cm^{-1}: 3369, 3187, 2953, 2192, 1718, 1666, 1597, 1215. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.02 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.06 (d, 1H, J=16.6 Hz), 2.12 (d, 1H, J=16.5 Hz), 2.63 (m, 2H, CH_2), 7.35 (s, 2H, NH2), 7.38–8.26 (m, 6H, ArH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 27.65, 27.93, 32.50, 50.17, 51.44, 58.48, 112.48, 117.99, 120.28, 121.88, 124.99, 128.94, 129.36, 130.25, 131.90, 132.65, 140.99, 143.66,159.24, 165.03, 195.77, 204.05. MS, m/z (%): 370 (M^+, 75), 286 (100), 259 (45), 83 (25), 39 (30). Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56%. Found: C, 74.45; H, 5.15; N, 7.31%.

RESULTS AND DISCUSSION

We wish to report an efficient and green protocol for the three-component synthesis of some chromene derivatives at ambient temperature in excellent yields (Schemes 2 and 3). As part of our endeavour to discover new spirooxindoles of biocidal interest, and guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably, we investigated a three-component reaction of isatin with malononitrile and phthalhydrazide, in order to synthesize a new class of spirooxindoles with fused phthalazines. To the best of our knowledge, there have been no reports on the synthesis of pyrazolophthalazinyl spiro-3′-oxindoles. We wish to report here a simple and efficient method for the synthesis of pyrazolophthalazinyl spiro-3′-oxindoles, through the three-component

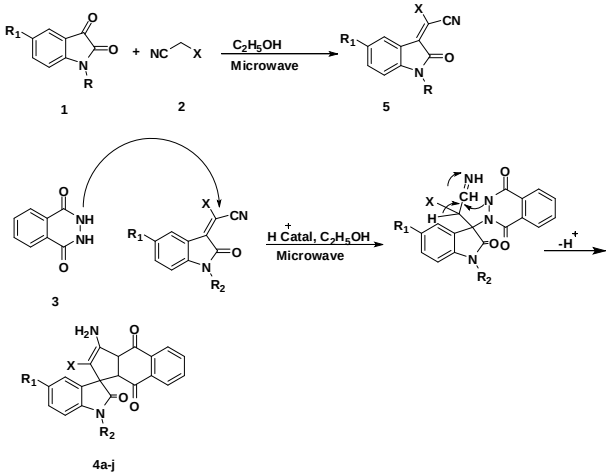


Scheme 2. Synthesis of spirooxindoles via three-component reaction with acenaphthoquinone (5) in the presence of silica-bonded N-propyl sulfamic acid (SBNPSA) as catalyst under irradiation microwave conditions.



Scheme 3. Synthesis of pyrazolophthalazinyl spiro-3′-oxindoles 4a–j in the presence of silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) as catalyst under irradiation microwave conditions.

condensation of isatin, malononitrile and phthalhydrazide using silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) as a catalyst (Scheme 4).



Scheme 4. The mechanism for the synthesis of pyrazolophthalazinyl spiro-3′-oxindoles of 4a–j.

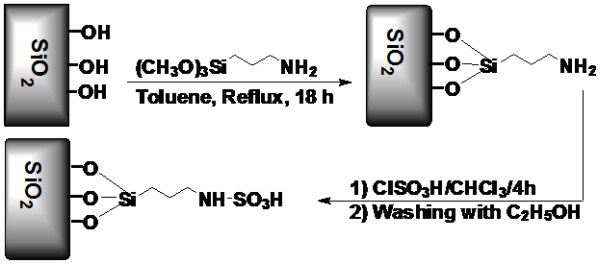
The structures of compounds 4a–j were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The ^{1}H NMR spectrum of 4a exhibited a broad singlet at δ 8.34 due to –NH_2, a singlet at δ 10.90 due to –NH isatin and aromatic protons in the range δ 6.95–8.223. Table 1 summarizes our results on the one-pot reaction of various isatin derivatives and malononitrile/ethyl cyanoacetate with phthalhydrazide (scheme 4). All the completed reactions afforded the corresponding pyrazolophthalazinyl spiro-3′-oxindoles in good yields.

A possible mechanism for the formation of 4a–j is proposed in Scheme 5. The process represents a typical cascade reaction in which the isatin 1 first condenses with malononitrile/ethyl cyanoacetate 2 to afford isatylidene malononitrile derivative 5. This step can be regarded as a fast Knoevenagel addition. Then, its cyclization affords the corresponding product 4a–j.

Table 1. Synthesis of pyrazolophthalazinyl spiro-3′-oxindoles 4a–j. The reactions were run at microwave conditions and in the presence of silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) as catalyst.

Entry	Product	Time (min)	[a]Yield (%)	Mp(°C)
1	4a	35	93(92, 91, 91)[b]	281-283
2	4b	40	89(89, 87, 87)[b]	255-257
3	4c	34	90(89, 88, 88)[b]	276-278
4	4d	34	94(94, 93, 91)[b]	291-292
5	4e	31	97(97, 96, 95.5)[b]	266-267
6	4f	41	91.5(91, 89, 89)[b]	259-261
7	4g	35	94.5(93, 93, 92)[b]	223-224
8	4h	30	95(95, 94, 93)[b]	283-285
9	4i	32	90.5(90, 88, 88)[b]	284-286
10	4j	30	94(93, 93, 92)[b]	268-270

[a,b] Isolated yield. The reactions were run at microwave conditions and in the presence of silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) catalyst. [b]Yield of catalyst recycled three times.



Scheme 5. Preparation of silica bonded *N*-propyl sulfamic acid (**SBNPSA**).

The catalyst could be recycled and reused several times without any loss of efficiency. The possibility of recycling the catalyst was examined in the synthesis of pyrazolophthalazinyl spiro-3′-oxindoles (4a–j). When the reaction was completed, the mixture was filtered and the remaining was washed with warm ethanol, and the catalyst reused in the next reaction. The recycled catalyst could be reused three times without any additional treatment. No observation of any appreciable loss in the catalytic activity of **SBNPSA** was observed (Table 1 and Fig 1.). As shown Table 1, the results obtained from the reactions of the malononitrile/ethyl cyanoacetate with isatin indicate that the application of the microwave irradiation can considerably increase the efficiency of these reactions to produce (4a-j) in satisfactory yields (89-97%) and reduce the reaction times when compared with the conventional thermal conditions (Table 1).

We have developed for the synthesis of spirooxindoles. In the present exploration, the reaction of 1,3-dicarbonyl compounds (1a,b), isatin (2a,b), and activated methylene reagents (3a,b) in a molar ratio of 1:1:1 in the presence of catalytic silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) and ethanol for the appropriate time (Schemes 2,3) furnished spirooxindoles in moderate yields (Table 2).

Table 2. Synthesis of compounds 4a-g, 6a-d in EtOH by the reaction of 1,3-diketones (1), isatins (2) or acenaphthenequinone (5), and activated methylene compounds in the presence of silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) as catalyst.

Entry	Product	Time (min)	[a]Yield (%)	Mp(°C)
1	4a	10	90	274-275
2	4b	9	89	262-264
3	4c	6	90	250-253
4	4d	6	97	240-242
5	4e	5	85.5	271-273
6	4f	9	91.5	259-260
7	4g	5	94	268-270
8	6a	5	91	226-228
9	6b	10	79.5	244-246
10	6c	9	88	262-264
11	6d	5	95	261-263

[a] Isolated yield. The reactions were run at microwave conditions and in the presence of silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) as catalyst.

As shown in Table 2, Two types of substituted isatins and 1,3-cyclohexanediones were used in this reaction (Scheme 2). We examined one-pot reactions involving acenaphthoquinone (5), instead of isatin. Under these conditions, a variety of desired spirochromenes were also produced in excellent yields (Scheme 3, Table 2).

The possibility of recycling the catalyst was examined. For this reason, the reaction of isatin with malononitrile/ethyl cyanoacetate was studied in EtOH in the presence of **SBNPSA**. When the reaction was complete, the mixture was filtered, the residue was washed with warm ethanol and recycled catalyst was reused in the next reaction. No appreciable loss of catalytic activity was observed after twelve cycles (Fig. 1).

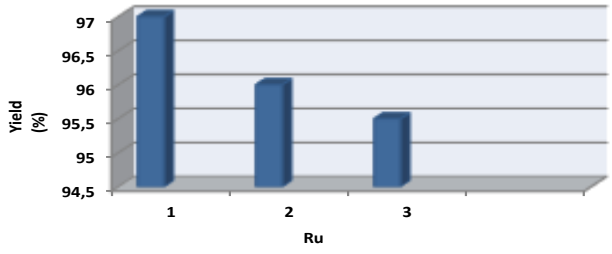


Figure 1. Recyclability of **SBNPSA** catalyst for the synthesis of compound (Table 1, 4e).

CONCLUSION

In conclusion, we have developed a simple and clean procedure for the synthesis of a series of spirochromene and spirooxindole derivatives catalyzed by silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) in water starting from commercially available starting materials. The use of inexpensive and available silica-bonded *N*-propyl sulfamic acid (**SBNPSA**) has made this procedure simple, convenient and practical. The utility of the described methodology in MCRs is highly promising as it allows for the combination of the synthetic virtues of the conventional MCR strategy with the ecological benefits and convenience of the procedure. The microwave irradiation reduced the reaction times in this synthesis. The catalyst was recovered and reused without any noticeable loss of reactivity. The mild reaction conditions and simplicity of the procedure offers improvements over many existing methods.

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N-ПРОПИЛ-СУЛФАМИНОВА КИСЕЛИНА, СВЪРЗАНА СЪС СИЛИЦИЕВ ДИОКСИД: РЕЦИКЛИРУЕМ КАТАЛИЗАТОР ЗА СИНТЕЗА НА СПИРО-ОКСИНДОЛИ ЧРЕЗ ТРИ-КОМПОНЕНТНА РЕАКЦИЯ, СТИМУЛИРАНА ОТ МИКРОВЪЛНИ

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(Резюме)

N-пропил-сулфаминовата киселина (**SBNPSA**), свързана със силициев диоксид е използвана като твърд киселинен катализатор за синтезата на спиро-оксиндоли чрез три-компонентна реакция с високи добиви и кратки времена за реакция в среда от етанол. Реакцията е стимулирана от микровълново електромагнитно поле. Най-подходящо е облъчването в комбинация с изатин и аценафтохинон (активиран метиленов реагент) и 1,3-ди-карбонилни съединения в присъствие на катализатор (**SBNPSA**). Методът е подходящ за синтезиране на биологично значими спиро-оксиндоли.