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Montmorillonite Clay Catalyzed Three Component, One-Pot Synthesis of 5-Hydroxyindole Derivatives

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A highly efficient and environmentally benign protocol has been developed for the first time to produce a wide range of biologically active 5-hydroxyindole derivatives using montmorillonite KSF clay as a reusable solid acid catalyst. The use of recyclable clay makes this procedure quite simple, more convenient and cost-effective.

Key Words : 3CC reaction, Solid acid catalysis, Nenitzescu reaction, 5-Hydroxyindole

Introduction

Indole nucleus is frequently found in many pharmacophores and natural products.[1] Thus, indole derivatives are considered as 'privileged scaffolds' in medicinal chemistry. In particular, 5-hydroxyindole motifs are present in many drug molecules such as serotonin, a neurotransmitter; indomethacin, a non-steroidal anti-inflammatory agent; L-761,066, a selective; a potent COX-2 inhibitor and LY311727 which is a first selective inhibitor of secretory phospholipase *s*-PLA2 (Figure 1).[2] Recently, 5-hydroxyindoles have been used as novel 5-lipoxygenase (5-LO) inhibitors.[3,4] Consequently, several approaches have been developed for the synthesis of 5-hydroxyindoles.[5] In particular, annulation of quinones with enamines, derived in situ from 1,3-diketones and aryl amines, so called Nenitzescu reaction is one of the simplest and direct methods for the synthesis of 5-hydroxyindole derivatives.[6] A few catalysts such as zinc(II) iodide and ceric(IV) ammonium nitrate are reported to accomplish the Nenitzescu reaction. However, most of these procedures involve the use of strongly acidic and toxic reagents in stoichiometric amounts and the yields and selectivity reported are far from satisfactory. Therefore, the use of inexpensive and environmentally safe solid acids would extend the scope of this transformation. Recently, the use of solid acidic catalysts like clays, zeolites and ion-exchange resins has received much attention in different areas of organic synthesis because of their environmental compatibility, reusability, greater selectivity, non-corrosiveness, low cost and ease of handling.[7] Furthermore, clay contains both the Bronsted and Lewis acidic sites in their natural and ion-exchanged forms which enables them to function as efficient catalysts for various transformations.[8]

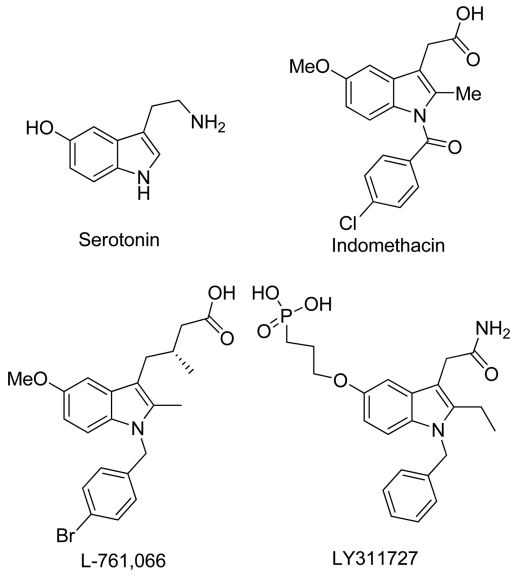


Figure 1. Biologically active 5-hydroxyindole derivatives.

Experimental

Commercial reagents were used without further purification, all solvents were purified by standard techniques and Infrared spectra were recorded on Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. NMR spectra were recorded in $CDCl_3$ on Varian Gemini 200, Brucker 300 and Varian Unity 400 NMR spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as an internal standard. Coupling constants (*J*) are quoted in hertz. Column chromatographic separations were carried out on silica gel (60-120 mesh) and flash chromatographic separations were carried out using 230-400 mesh, silica gel. Mass spectra were recorded on Micromass VG-7070H for EI and VG Autospec M for FABMS.

Representative Procedure for the Synthesis of 5-Hydroxyindole Derivatives. A mixture of aniline (1 mmol), dimedone (1 mmol) and montmorillonite KSF clay (0.5 g) in 1,2-dichloroethane (5 mL) was kept under reflux for 15 min. To this mixture, 1,4-benzoquinone (1 mmol) was added and the resulting mixture was allowed to stir under reflux for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the mixture was filtered and washed with dichloromethane (10 mL). The combined organic layers were concentrated in vacuo and the resulting residue

Table 1. Montmorillonite KSF clay catalyzed Nenitzescu reaction

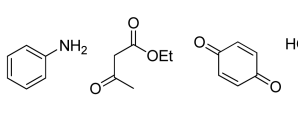
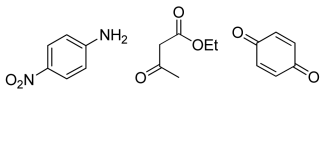
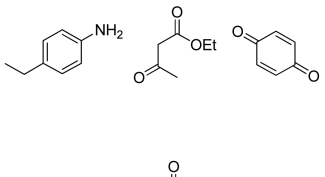
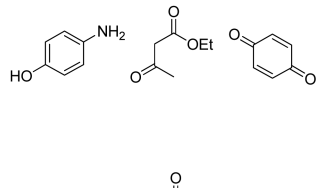
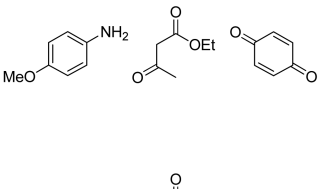
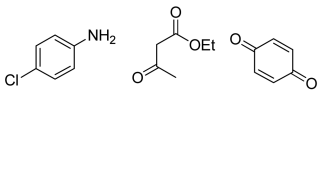
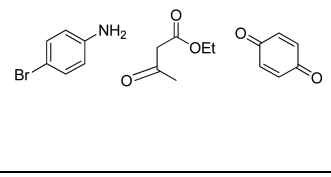
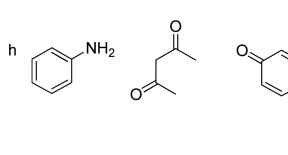
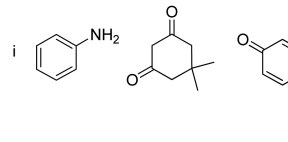
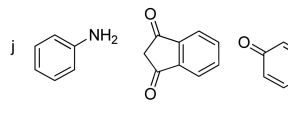
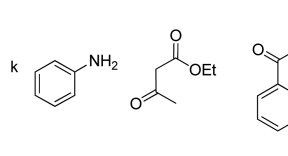
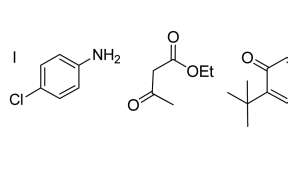
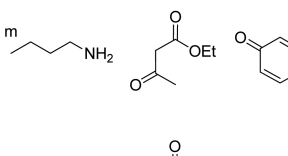
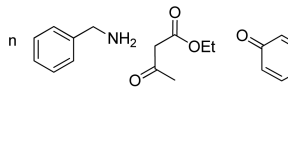
Entry	Amine (**1**)	1,3-Diketone (**2**)	Quinone (**3**)	Product (**4**)[a]	Time (h)	Yield (%)[b]
a					1.0	95
b					1.2	89
c					1.0	92
d					1.0	91
e					1.4	92
f					2.1	89
g					2.1	85

Table 1. Continued

Entry	Amine (**1**)	1,3-Diketone (**2**)	Quinone (**3**)	Product (**4**)[a]	Time (h)	Yield (%)[b]
h					1.0	94
i					1.8	78
j					2.0	73
k					2.1	89
l					1.3	84
m					0.3	92
n					1.0	82

[a]All products were characterized by NMR, IR and mass spectroscopy. [b]Yield refers to pure products after chromatography.

was purified by column chromatography on silica gel (Merck, 60-120 mesh, ethyl acetate-hexane, 1:9) to afford the pure 5-hydroxyindole derivative.

Spectral Data for the 5-Hydroxyindole Derivatives.

Ethyl 5-Hydroxy-2-methyl-1-phenyl-1*H*-indole-3-carboxylate (4a): White solid, mp 139-140 °C; (271.4 mg, yield: 96%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.46 (t, J = 6.7 Hz, 3H), 2.25 (s, 3H), 4.40 (q, J = 6.7 Hz, 2H), 6.63 (s, 1H), 6.75-6.83 (m, 2H), 7.23-7.37 (m, 2H), 7.48-7.60 (m, 3H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.5, 14.1, 58.6, 103.7, 105.4, 110.2, 111.5, 126.8, 127.4, 128.1, 129.1, 131.5, 135.9, 144.5, 152.4, 165.3; IR (KBr): ν 3259, 2920, 2851, 1659, 1466, 1382, 1188, 1081, 865, 696 cm^{-1}; HRMS (ESI): *m*/*z* [M+H] calcd for $C_{18}H_{18}NO_3$: 296.1286; found: 296.1280.

Ethyl 5-Hydroxy-2-methyl-1-(4-nitrophenyl)-1*H*-indole-3-carboxylate (4b): Pale Brown Solid, mp 142-143 °C; (302.6 mg, yield: 89%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.43 (t, J = 6.9 Hz, 3H), 2.77 (s, 3H), 4.36 (q, J = 6.9 Hz, 2H), 6.72 (dd, J = 2.4, 6.4 Hz, 1H), 6.94 (d, J = 9.0 Hz, 2H), 7.14 (t, J = 8.6 Hz, 1 H), 7.27-7.41 (m, 1H), 7.79 (s, 1H), 8.02 (d, J = 9.2 Hz, 2H), 9.45 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.3, 14.2. 60.0, 106.1, 111.2, 112.9, 113.7, 119.3, 126.4, 126.2, 136.3, 137.6, 147.0, 149.7, 151.5, 154.1, 163.8; IR (KBr): ν 3379, 3329, 2986, 2923, 1671, 1469, 1383, 1295, 1218, 1171, 1030, 783 cm^{-1} HRMS (ESI): *m*/*z* [M+H] calcd for $C_{18}H_{17}N_2O_5$: 341.1137; found: 341.1151.

Ethyl 1-(4-Ethylphenyl)-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (4c): White solid, mp 144-145 °C; (297.1 mg, yield: 92%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.33 (t, J = 7.5 Hz, 3H), 1.45 (t, J = 7.1 Hz, 3H), 2.52 (s, 3H), 2.78 (q, J = 7.5 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 6.60 (dd, J = 2.2, 6.4

Hz, 1H), 6.77 (d, J = 8.6 Hz, 1H), 7.17-7.23 (m, 2H), 7.31-7.39 (m, 2H), 7.49 (d, J = 2.0 Hz, 1H), 8.95 (s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 12.8, 14.5, 15.3, 27.8, 58.9, 105.4, 110.8, 111.9, 115.6, 120.5, 127.7, 128.3, 129.1, 144.4, 144.9, 153.0, 165.1; IR (KBr): ν 3311, 2961, 2925, 1650, 1514, 1470, 1287, 1174, 1080, 823, 658 cm^{-1} HRMS (ESI): *m*/*z* [M+H] calcd for $C_{20}H_{22}NO_3$: 324.1599; found: 324.1608.

Ethyl 5-Hydroxy-1-(4-hydroxyphenyl)-2-methyl-1*H*-indole-3-carboxylate (4d): White solid, mp 180-181 ºC; (283.0 mg, yield: 91%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (t, J = 7.4 Hz, 3H), 2.49 (s, 3H), 4.43 (d, J = 7.4 Hz, 2H), 6.53 (s, 1H), 6.62-6.69 (m, 2H), 6.70-6.80 (m, 2H), 6.92 (d, J = 8.5 Hz, 1H), 7.07 (d, J = 9.5 Hz, 1H), 9.15 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.3, 14.4, 58.4, 104.3, 112.9, 114.9, 119.4, 128.3, 129.4, 134.5, 139.3, 145.1, 152.2, 158.9, 161.0, 170.9; IR (KBr): ν 3355, 2925, 2855, 1658, 1512, 1462, 1186, 1083, 829 cm^{-1}; HRMS (ESI): *m*/*z* [M+H] calcd for $C_{18}H_{18}NO_4$: 312.1235; found: 312.1221.

Ethyl 5-Hydroxy-1-(4-methoxyphenyl)-2-methyl-1*H*-indole-3-carboxylate (4e): White solid, mp 160-162 ºC; (299.0 mg, yield: 92%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (t, J = 6.9 Hz, 3H), 2.51 (s, 3H), 3.89 (s, 3H), 4.30 (q, J = 6.9 Hz, 2H), 6.70-6.82 (m, 3H), 6.98-7.10 (m, 2H), 7.24 (d, J = 8.8 Hz, 2H), 7.74 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.3, 14.0, 54.9, 58.4, 103.3, 113.9, 114.3, 118.4, 128.2, 128.4, 130.5, 139.3, 144.1, 156.2, 158.9, 165.0, 1170.5; IR (KBr): ν 3393, 2924, 1687, 1513, 1471, 1240, 171, 835 cm^{-1} HRMS (ESI): *m*/*z* [M+H] calcd for $C_{19}H_{20}NO_4$: 326.1392; found: 326.1404.

Ethyl 1-(4-Chlorophenyl)-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (4f): White solid, mp 124-125 ºC; (292.8 mg, yield: 89%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (t, J = 6.9 Hz, 3H), 2.52 (s, 3H), 4.30 (q, J = 6.9 Hz, 2H), 6.93-7.05 (m, 2H), 7.21 (d, J = 8.8 Hz, 2H), 751-7.60 (m,1H), 768-7.74 (m, 1H), 7.84 (s, 1H), 9.25 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.4,13.6, 58.4, 103.6, 104.2, 113.9, 114.3, 122.0, 122.4, 129.2, 135.1, 140.2, 141.1, 149.8, 154.2, 165.8; IR (KBr): ν 3310, 2923, 1664, 1587, 1472, 1266, 1180, 1081, 821 cm^{-1}; HRMS (ESI): *m*/*z* [M+H] calcd for $C_{18}H_{17}NClO_3$: 330.6486; found: 330.6491.

Ethyl 1-(4-Bromophenyl)-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (4g): Brown solid, mp 128-129 ºC; (317.0 mg, yield: 85%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (t, J = 6.9 Hz, 3H), 2.09 (s, 3H), 4.31 (q, J = 6.9 Hz, 2H), 6.93-6.99 (m, 2H), 7.32 (d, J = 8.6 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 781-7.88 (m, 2H), 8.25 (s, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 12.8, 13.7, 59.4, 103.8, 104.8, 113.1, 115.3, 122.1, 123.4, 129.7, 137.1, 141.2, 141.9, 149.8, 153.2, 162.8; IR (KBr): ν 3307, 2924, 1664, 1582, 1472, 1266, 1181, 1081, 818 cm^{-1}; HRMS (ESI): *m*/*z* [M+H] calcd for $C_{18}H_{17}NBrO_3$: 375.1145; found: 375.1151.

1-(5-Hydroxy-2-methyl-1-phenyl-1*H*-indol-3-yl)ethanone (4h): White solid, mp 136-137 ºC; (249.1 mg, yield: 94%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.55 (s, 3 H), 2.75 (s, 3H), 6.74 (t, J = 7.3 Hz, 1H), 6.99-7.06 (m, 2H), 7.08 (d, J = 2.2 Hz, 1H), 7.12-7.19 (m, 2H), 7.30 (d, J = 8.6 Hz, 1H), 7.69 (d, J = 2.2 Hz, 1H), 9.05 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.6, 15.0, 95.4, 109.9, 110.4, 115.4, 115.9, 116.9, 118.6, 126.3, 128.5, 139.5, 144.3, 147.9, 162.1; IR (KBr): ν 3312, 2923, 2853, 1641, 1460, 1392, 1299, 1185, 1065, 964, 746 cm^{-1} HRMS (ESI): *m*/*z* [M+H] calcd for $C_{17}H_{16}NO_2$: 266.1181; found: 266.1178.

6-Hydroxy-2,2-dimethyl-9-phenyl-2,3-dihydro-1*H*-carbazol-4(9*H*)-one (4i): Pale yellow solid, mp 150-152 ºC; (237.9 mg,yield: 78%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13 (s, 3H), 1.27 (brs, 3H), 2.38 (s, 2H), 2.70 (s, 2H), 6.94 (d, J = 8.5 Hz, 1H), 7.41-7.47 (m, 2H), 7.51-7.56 (m, 1H), 7.58-7.65 (m, 2H), 8.30 (s, 2H), 8.87 (brs 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 28.0, 28.9, 31.1, 34.7, 51.5, 95.4, 105.2, 110.4, 115.2, 124.8, 126.5, 128.0, 129.4, 135.6, 149.4, 149.8, 153.5, 191.8. IR (KBr): ν 3224, 2924, 2855, 1619, 1491, 1459, 1413, 1241, 696 cm^{-1}; HRMS (ESI): *m*/*z* [M+H] calcd for $C_{20}H_{20}NO_2$: 306.3704; found: 306.3714.

8-Hydroxy-5-phenylindeno[1,2-b]indol-10(5*H*)-one (4j): Brown solid, mp 139-140 ºC; (227.0 mg, yield: 73%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.03 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 7.3 Hz, 1H), 7.10-7.25 (m, 2H), 7.39-7.53 (m, 4H), 7.78-7.82 (m, 1H), 7.84-7.89 (m, 2H), 7.91-7.96 (m, 1H), 8.92 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 105.4, 121.6, 121.8, 122.0, 122.5, 123.1.123.4, 125.6, 127.9, 128.7, 129.4, 130.8, 132.1, 135.6, 138.0, 141.1, 152.4, 162.3, 191.8; IR (KBr): ν 3355, 2963, 2833, 1741, 1465, 1299, 1195, 1075, 984, 756 cm^{-1}; HRMS (ESI): *m*/*z* [M+H] calcd for $C_{21}H_{14}NO_2$: 312.3343; found: 312.3351.

Ethyl 5-Hydroxy-2-methyl-1-phenyl-1*H*-benzo[*g*]indole-3-carboxylate (4k): Brown solid, mp 243-244 ºC; (307.0 mg, yield: 89%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48 (t, J = 7.0 Hz, 3H), 2.46 (s, 3H), 4.38 (q, J = 7.0 Hz, 2H), 6.80 (d, J = 8.5 Hz, 1H), 7.03 (dd, J = 8.8, 7.0 Hz, 1H), 7.32 (dd, J = 8.0, 7.2 Hz, 1H), 7.51-7.56 (m, 2H), 7.71-7.75 (m, 4H), 8.24 (d, J = 6.3 Hz, 1H), 9.77 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.5, 14.4, 58.9, 101.2, 104.6, 125.0, 121.8, 122.5, 122.9, 123.1, 123.7, 124.3, 125.4, 128.6, 129.6, 130.2, 138.8, 142.9, 148.4, 165.0; IR (KBr): ν 3420, 2931, 1648, 1596, 1448, 1411, 1337, 1246, 1196, 1177, 1071, 743 cm^{-1}; HRMS (ESI): *m*/*z* [M+H] calcd for $C_{22}H_{20}NO_3$: 346.4325; found: 346.4331.

Ethyl 6-*Tert*-butyl-1-(4-chlorophenyl)-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (4l): White solid, mp 160-162 ºC; (323.4 mg, yield: 84%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39-1.52 (m, 12H), 2.74 (s, 3H), 4.35 (q, J = 7.0 Hz, 2H), 6.61 (d, J = 2.3 Hz, 1H), 6.84-7.03 (m, 1H), 7.12-7.15 (m, 1H), 7.47-7.58 (m, 2H), 8.68 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.1,14.2, 29.4, 33.6, 59.5, 95.3, 103.6, 107.9, 109.9, 112.3, 126.8, 134.1, 145.2, 153.7, 162.2, 163.4; IR (KBr): ν 3355, 2959, 2871, 1680, 1427, 1388, 1219, 665 cm^{-1}; HRMS (ESI): *m*/*z* [M+H] calcd for $C_{22}H_{25}NClO_3$: 386.8835;found: 386.8851.

Ethyl 1-Butyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (4m): White solid, mp 144-145 ºC; (253.0 mg, yield: 92%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.95 (t, J = 7.1 Hz, 3H), 1.31-1.45 (m, 5H), 1.69 (qt, 2H), 2.69 (s, 3H), 4.07 (t, J = 7.0 Hz, 2H), 4.29 (q, J = 7.0 Hz, 2H), 6.64 (dd, J = 2.4, 6.2 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1 H), 8.58 (s, 1H); ^{13}C NMR

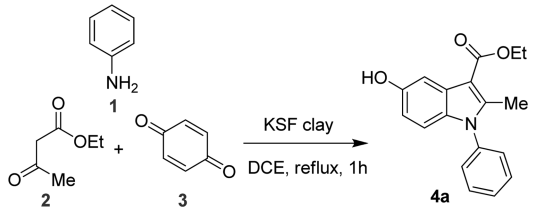
(75 MHz, DMSO-d_6) δ 11.5, 13.5, 14.4, 19.4, 31.3, 42.3, 58.5, 101.9, 105.3, 110.4, 111.2, 127.0, 129.8, 144.5, 152.4, 165.0; IR (KBr): ν 3262, 2965, 2866, 1652, 1472, 1376, 1183, 1036, 701 cm^{-1}; HRMS (ESI): *m/z* [M+H] calcd for $C_{16}H_{22}NO_3$: 276.1599; found: 276.1596.

Ethyl 1-Benzyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (4n): White solid, mp 142-144 °C; (253.3 mg, yield: 82%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.45 (t, *J* = 7.1 Hz, 3H), 2.23 (s, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 5.28 (s, 2H), 6.76 (dd, *J* = 4.7, 8.4 Hz, 1H), 7.12 (dd, *J* = 4.4, 8.2 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.32-7.35 (m, 3H), 7.36-7.39 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 12.7, 15.2, 47.3, 60.4, 104.8, 107.3, 111.2, 111.9, 126.8, 128.4, 128.6, 129.6, 132.2, 137.1, 146.5, 152.2, 168.3; IR (KBr): ν 3260, 2921, 2852, 1660, 1469, 1385, 1175, 1089, 872, 699 cm^{-1}; HRMS (ESI): *m/z* [M+H] calcd for $C_{19}H_{19}NO_3$: 309.1365; found: 309.1392.

Results and Discussion

Following our interest on catalytic use of solid acids,[9] we herein report an efficient and metal-free approach for the synthesis of 5-hydroxyindole derivatives *via* the Nenitzescu reaction using montmorillonite KSF clay as a heterogeneous solid acid. Accordingly, we first attempted the coupling of aniline (**1**), ethyl acetoacetate (**2**) and *p*-benzoquinone (**3**) in 1,2-dichloroethane in the presence of KSF clay. The reaction proceeded well in refluxing dichloroethane and the corresponding 5-hydroxyindole **4a** was obtained in 95% yield (Scheme 1).

Inspired by the above result, we next investigated the scope of the Nenitzescu reaction with several aryl amines, 1,3-dicarbonyl compounds and *p*-quinones. Interestingly, various 1,3-dicarbonyl compounds such as ethyl acetoacetate and acetyl acetone (entries a-h, k-m, Table 1) participated well in Nenitzescu reaction to give the corresponding 5-hydroxyindole derivatives. Cyclic 1,3-diketones such as dimedone and 1,3-indanedione also participated effectively in this reaction to give the respective annulated 5-hydroxyindoles (entries i and j, Table 1). Like *p*-quinone, 1,4-naphthaquinone and 2-*tert*-butyl-*p*-benzoquinone were also converted into their corresponding 5-hydroxyindoles (entries k and l, Table 1). The reaction was also proved its compatibility with all types of anilines, irrespective of the functional groups present on aromatic ring (entries a-l, Table 1). Aliphatic amine was also tested for the Nenitzescu reaction to produce the corresponding alkyl substituted 5-hydroxyindole (entry m, Table 1). The scope and generality of



Scheme 1. Three component coupling reaction for the synthesis of 5-hydroxyindole **4a**.

Table 2. Effect of various catalysts in the synthesis of **4a**

S.No.	Reaction conditions	Yield (%)
1.	Cellulose-SO_3H, reflux, 3 h	65
2.	*p*-TSA/CH_3CN, reflux, 2 h	70
3.	Carbon acid/EtOH, 3 h	52
4.	**Montmorillonite/DCE, 1 h**	**95**
5.	PMA/SiO_2, neat, 3 h	35

montmorillonite KSF clay catalyzed Nenitzescu reaction is illustrated with respect to various amines, 1,3-dicarbonyl compounds and *p*-quinones and the results are presented in Table 1.[10] The Nenitzescu reaction was studied in the formation of **4a** with various catalysts. Of these, montmorillonite KSF clay gave the best results in terms of yield and reaction time (Table 2).

Finally, the catalyst was separated by simple filtration. Thus recovered catalyst was reused in further cycles without significant loss of activity. For instance, treatment of aniline (**1**, 1 mmol), ethyl acetoacetate (**2**, 1 mmol) and *p*-benzoquinone (**3**, 1 mmol) in the presence of KSF clay (0.5 g) in refluxing 1,2-dichloroethane gave the 5-hydroxyindole in 95, 93, 90% yields respectively over three cycles. Thus this method is superior to homogeneous catalysis.

Conclusion

In summary, we have developed an efficient and metal-free approach for the synthesis of a variety of 5-hydroxyindole derivatives *via* the Nenitzescu reaction using KSF clay as a recyclable solid acid catalyst. The salient features of this procedure are high conversions, easy recovery and reuse of the catalyst and low-cost of the catalyst which makes it useful and attractive strategy for the preparation of 5-hydroxy indoles. This method works well with both acyclic and cyclic 1,3-diketones and also with aryl and alkyl amines.

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