July - Sep © 2015 Transactions; 2(7): 358-364

International Journal of Research and Applications

ISSN (online): 2349-0020 ISSN (print): 2394-4544 http://www.ijraonline.com/

Research Article

An efficient green synthesis of substituted indolin-2-one derivatives using Piperidine catalyzed Henry reaction of isatins

[1] Suresh Budde, [2] Jagadeesh Kumar Ega, [1] Brahmeshwari Gavaji * and [2] Ravinder Vadde *

Corresponding Author:
Jkjagadeeshkumare@gmail.com

DOI:
http://dx.doi.org/
10.17812/IJRA.2.7(61)2015

Manuscript:
Received: 26th July, 2015
Accepted: 1st Aug, 2015
Published: 30th Sep, 2015

Publisher:
Global Science Publishing Group, USA
http://www.globalsciencepg.org/

ABSTRACT

An efficient method has been developed for the synthesis of 3-hydroxy-3-(nitro methyl) indolin-2-one by performing the reaction between isatin and nitro methane or nitroetane in the presence of piperidine as a catalyst. The reaction is rapid; yields are soaring and shun the use of solvents for reaction. The protocol is applicable for substituted isatins as well as substituted nitroalkanes.

Keywords: Indoline, isatin , nitroalkanes , Piperidine , Henry reaction .

[1 1* 2 2*] Department of Chemistry, Kakatiya University, Warangal, Telangana - 506009.

IJRA - Year of 2015 Transactions:
Month: July - September
Volume – 2, Issue – 7, Page No's:358-364
Subject Stream: Chemistry

Paper Communication: Author Direct

Paper Reference Id: IJRA-2015: 2(7)358-364

DOI: 10.17812/IJRA.2.7(61)2015

International Journal of Research and Applications
July-Sep © 2015 Transactions 2(7):358-364

eISSN : 2349 - 0020
pISSN : 2394 - 4544

CHEMISTRY RESEARCH ARTICLE

An efficient green synthesis of substituted indolin-2-one derivatives using piperidine catalyzed Henry reaction of isatins

[1] Suresh Budde , [2] Jagadeesh Kumar Ega, [1] Brahmeshwari Gavaji * and [2] Ravinder Vadde *
Department of Chemistry, Kakatiya University, Warangal, Telangana - 506009.

ABSTRACT

An efficient method has been developed for the synthesis of 3-hydroxy-3-(nitro methyl) indolin-2-one by performing the reaction between isatin and nitro methane and nitroetane in the presence of piperidine as a catalyst. The reaction is rapid; yields are soaring and shun the use of solvents for reaction. The protocol is applicable for substituted isatins as well as substituted nitroalkanes.

Keywords: Indoline, isatin , nitroalkanes , Piperidine , Henry reaction .

1. INTRODUCTION

Hydroxy indolines are also useful in the synthesis of chiral ligands which are used to obtain high enantio selectivities in numerous catalytic reactions. Due to their distinct biological and chemical properties, their construction has stimulated by the synthetic chemist Because of the important medicinal value of 3-hydroxy indolines, an efficient and general protocol for the synthesis of these molecule is desirable. Other reported methods accomplished the synthesis of 3-hydroxy-3-(nitro methyl) indolin-2-ones by using base with organic solvents. In view of this, there is still need to develop a general and efficient method for the synthesis of more functionalized 3-hydroxy-3-(nitro methyl) indolin-2-one derivatives (Scheme 1.1 and 1.2). The use of nonmetallic reagents is an area of growing interest because of environmental regulations. Synthesis, electrochemical behavior, neuro protective agents and antiplasmodial activities of substitued-indol-3-ones have been reported. Indole fragment is featured widely in a wide variety of pharmacologically and biologically active compounds. Oxindole derivatives are known to possess a variety of biological activity. The biological and pharmacological properties of isatin derivatives have led to extensive use of these compounds as key intermediates in organic synthesis.

3-Hydroxy-3-(nitro methyl) indolin-2-one derivatives formation by using piperidine as catalyst

Scheme 1.1 and 1.2

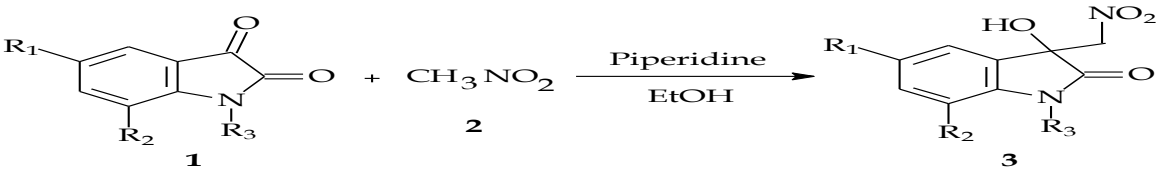
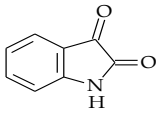
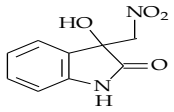
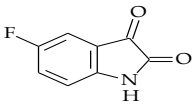
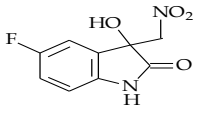
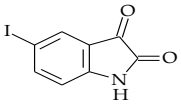
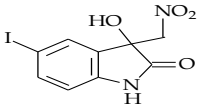
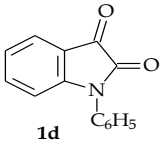
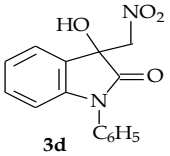
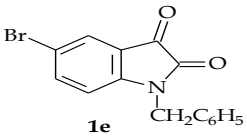
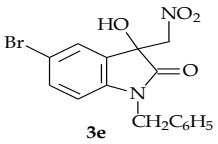
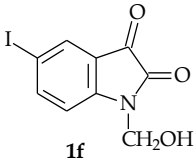
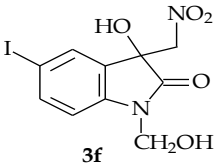


Table 1: Reaction time and yields of 3-hydroxy-2-oxindole derivatives

Entry	Isatin (1)	Product (3)	Reaction time (min)	Yield (%)
1	 1a	 3a	72	93
2	 1b	 3b	75	91
3	 1c	 3c	90	90
4	 1d	 3d	85	91
5	 1e	 3e	72	93
6	 1f	 3f	90	89

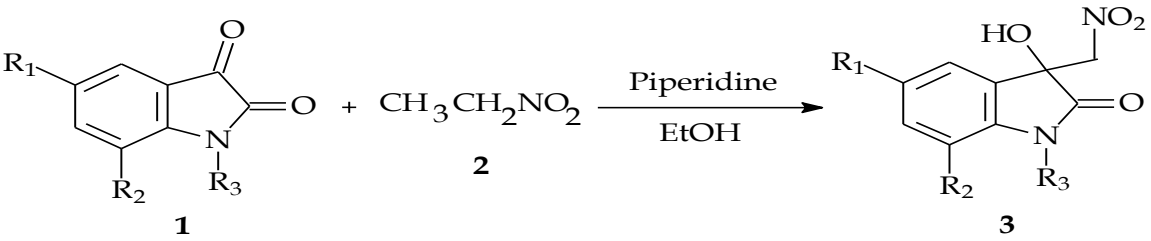
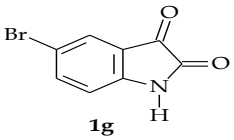
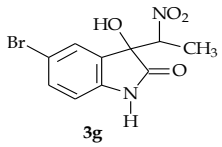
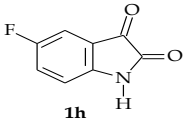
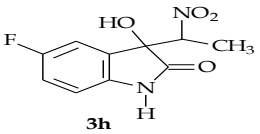
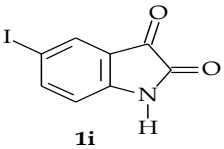
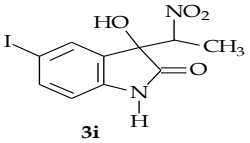
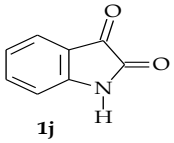
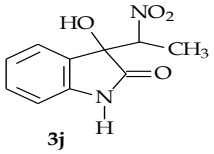
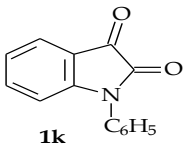
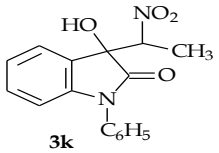
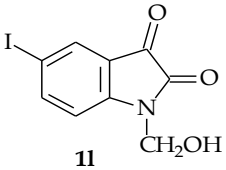
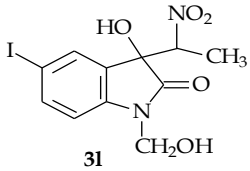


Table 1: Reaction time and yields of 3-hydroxy-2-oxindole derivatives

Entry	Isatin (1)	Product (3)	Reaction time (min)	Yield (%)
7	 1g	 3g	86	94
8	 1h	 3h	90	89
9	 1i	 3i	86	90
10	 1j	 3j	72	92
11	 1k	 3k	90	89
12	 1l	 3l	90	88

2. MATERIALS AND METHOD

General procedure for the synthesis of substituted indolin-2-one derivatives 3a-l

To a solution of nitromethane (2, 2mmol) in ethanol (5 mL) catalytic amount of piperidine was added and stirred for 30min below room temperature. To this reaction mixture, isatin (1a-l 1.0 mmol) were added drop wise and stirred at room temperature for 1.5-2.0 h. The reaction mixture was stirred at room temperature for stipulated time (Table 1). After the complete consumption of isatins as indicated by TLC, then the reaction mixture was poured on 10 mL ice cold water to obtain the crude 3a-l as solids. The Crude solid of 3a-l was further purified by silica gel column chromatography using ethyl acetate: hexane (1:3) as eluent to give the pure compounds 3a-l.All novel compounds are characterized by M.P, NMR, ^{13}C NMR, Mass and IR spectral data.

Physical, analytical and spectral data of indolin-2-one derivatives 3a-l

3-Hydroxy-3-(nitromethyl)-1, 3-ihydro-2*H*-indolin-2-one

(3a, Table 1, Entry 1): White solid M.p. 139−141 °C; Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.99; H, 3.88; N, 13.49%; IR (KBr, cm^{-1}): 3264, 3157, 2922, 1726, 1734, 1621, 1550, 1468, 1377, 1186, 755; ^{1}H NMR (300 MHz, DMSO-d_6) : δ 10.36(br s, 1H), 7.34(d, 1H, *J* = 7.36 Hz), 7.22(t, 1H, *J* = 7.74, Hz), 6.96 (t, 1H *J* = 7.36 Hz), 6.87 (d, 1H, *J* = 7.74 Hz) 6.58 (br s, 1H), 4.89 (d, 1H, *J* = 12.46 Hz), 4.82 (d, 1H, *J* = 12.46 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.5, 142.7, 130.6, 127.7, 124.7, 122.4, 110.8, 78.7, 73.4 ppm; MS(ESI): *m*/*z* = 231 $[M+Na]^+$.

5-Fluoro-3-(nitromethyl)-1, 3-dihydro-2*H*-indolin-2-one

(3b, Table 1, Entry 2): Yellow solid. M.p. 161−163 °C; Anal. Calcd for $C_9H_7FN_2O_4$: C, 47.80; H, 3.12; N, 12.39. Found: C, 47.92; H, 3.14; N, 12.43%; IR (KBr, cm^{-1}): 3328, 2929, 1704, 1614, 1555, 1495, 1468, 1384, 1142, 723; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.39(br s, 1H), 7.14(d, 1H, *J* = 7.74 Hz), 6.94(dt, 1H, *J* = 9.06, 2.26 Hz), 6.84-6.80(m, 1H), 6.69(br s, 1H), 4.90-4.82(m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 179.9.

3-Hydroxy-5-Iodo-3-(nitromethyl)-1,3-dihydro-2*H*-indolin-2-one

(3c, Table 1, Entry 3): White solid. M.p. 273−275 °C; Anal. Calcd for $C_9H_7IN_2O_4$: C, 32.36; H, 2.11; N, 8.39. Found: C, 32.49; H, 2.12; N, 8.43%; IR (KBr, cm^{-1}): 3392, 3247, 3008, 1730, 1611, 1539, 1476, 1373, 1182, 824; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.55 (brs, 1H), 7.64 (d, 1H, *J* = 1.51 Hz), 7.53(dd, 1H, *J* = 8.30, 1.70 Hz), 6.70(d, 1H, *J* = 8.30 Hz), 6.66(br s, 1H), 4.91-4.81 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.2, 142.4, 138.6, 133.1, 130.5, 112.6, 84.2, 78.1, 72.6 ppm; MS(ESI): *m*/*z* = 334 $(M)^+$.

3-Hydroxy-3-(nitromethyl)-1-phenyl-1,3-dihydro-2*H*-indolin-2-one

(3d, Table 1, Entry 4): White solid. M.p. 99−101 °C; IR (KBr, cm^{-1}): 3328, 2933, 1709, 1617, 1559, 1467, 1389, 1090, 761; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.55-7.40(m, 6H), 7.29(t, 1H, *J* = 7.5 Hz), 7.08(t, 1H, *J* = 7.4 Hz), 6.91(br s, 1H), 6.75(d, 1H, *J* = 7.7 Hz), 5.11-4.92(m, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.1, 143.7, 133.8, 129.7, 128.4, 128.1, 126.4, 125.4, 122.3, 109.1, 78.4, 72.7 ppm; MS(ESI): *m*/*z* = 307 $[M+Na]^+$; Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.50; H, 4.27; N, 9.89%.

1-Benzyl-5-bromo-3-hydroxy-3-(nitromethyl)-1,3-dihydro-2*H*-indolin-2-one

(3e, Table 1, Entry 5): Pale yellow solid. M.p. 121−123 °C; IR (KBr, cm^{-1}): 3334, 2921, 1711, 1621, 1561, 1457, 1391, 1097, 757; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.62(s, 1H), 7.41-7.19(m, 6H), 6.95(br s, 1H), 6.66(d, 1H, *J* = 8.3 Hz), 5.05(s, 2H), 4.95(d, 1H, *J* = 15.8 Hz), 4.85(d, 1H, *J* = 15.8 Hz) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): δ 179.2, 147.6, 140.4, 138.1, 135, 134.7, 132.7, 132.4, 120, 116.6, 101.0, 83.0, 77.7, 48.7 ppm; MS(ESI): *m*/*z* = 399 $[M+Na]^+$; Anal. Calcd for $C_{16}H_{13}BrN_2O_4$: C, 50.95; H, 3.47; N, 7.43. Found: C, 51.11; H, 3.48; N, 7.49%.

3-Hydroxy-1-(hydroxymethyl)-5-iodo-3-(nitromethyl)-1,3-dihydro-2*H*-indolin-2-one

(3f, Table 1, Entry 6): White solid. M.p. 267−269 °C; IR (KBr, cm^{-1}): 3249, 2945, 1711, 1608, 1549, 1476, 1370, 1033, 820. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.72(s, 1H), 7.65 (d, 1H, *J* = 8.3 Hz), 6.97(d, 1H, *J* = 8.3 Hz), 6.81(br s, 1H), 6.20(br s, 1H), 5.19-5.02(m, 2H), 4.91(s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.1, 142.3, 138.4, 132.8, 129.5, 112.3, 82.1, 77.9, 72.2, 62.8 ppm; MS(ESI): *m*/*z* = 387 $[M+Na]^+$; Anal. Calcd for $C_{10}H_9IN_2O_5$: C, 32.99; H, 2.49; N, 7.69. Found: C, 33.12; H, 2.50; N, 7.72%.

5-Bromo-3-hydroxy-3-(1-nitroethyl)-1,3-dihydro-2*H*-indolin-2-one

(3g, Table 1, Entry 7): Pale yellow solid. M.p. 167−169 °C; IR (KBr, cm^{-1}): 3356, 1729, 1628, 1572, 1558, 1487, 1371, 1161, 1091, 847; ^{1}H NMR (300 MHz, DMSO-d_6) (diastereomeric ratio, *threo:erythro*, 77:29* denotes minor diastereomer peaks): δ 10.54(br s, 1H), 10.48*(br s, 1H), 7.51(d, 1H, *J* = 1.7 Hz), 7.37(d, 1H, *J* = 8.1Hz), 6.8-6.7(m, 1H), 6.74(br s, 1H), 6.72*(br s, 1H), 6.7-6.6*(m, 1H), 5.01-4.59(m, 1H), 1.76*(d, 3H, *J* = 7.0 Hz), 1.38(d, 1H, *J* = 7.0 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.1, 175.8*, 142.1, 141.8*, 133.3, 132.7*, 130.7, 130.4*, 127.7, 127.2, 113.9, 113.4*, 112.4*, 112.1*, 86.2, 85.4*, 75.8, 75.9*, 13.7, 12.5* ppm; MS(ESI): *m*/*z* = 323 $[M+Na]^+$; Anal. Calcd for $C_{10}H_9BrN_2O_4$: C, 39.89; H, 3.01; N, 9.30. Found: C, 39.99; H, 3.02; N, 9.35%.

5-Fluoro-3-hydroxy-3-(1-nitroethyl)-1,3-dihydro-2*H*-indolin-2-one

(3h, Table 1, Entry 8): Pale yellow solid. M.p. 128−130 °C; IR (KBr, cm^{-1}): 3361, 3277, 2927, 1731, 1617, 1558, 1480, 1377, 1192, 749; ^{1}H NMR (300 MHz, DMSO-d_6) (diastereomeric ratio, *threo:erythro* 67:33, * denotes minor diastereomer peaks): δ 10.47(br s, 1H), 10.39*(br s 1H), 7.17(d, 1H, *J* = 7.0 Hz), 7.07*(d, 1H, *J* = 6.2 Hz), 7.01-6.96(m 1H), 6.84-6.81(m 1H), 6.78(br s, 1H), 6.78*(br s, 1H), 5.01-4.95(m, 1H), 1.72*(d, 3H, *J* = 6.2 Hz), 1.35(d, 3H, *J* = 6.2 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.28*, 175.61, 159.60, 159.51*, 156.42, 156.34*, 138.67*, 138.51, 128.81*, 128.77*, 128.41, 128.31, 116.54, 116.33*, 116.14, 116.01*, 113.71, 113.33, 112.74*, 112.41*, 111.01*, 110.91*, 110.85, 110.84, 86.38, 85.41*, 76.01, 75.21*, 13.64, 12.44; MS(ESI): *m*/*z* = 263 $[M+Na]^+$; Anal. Calcd for $C_{10}H_9FN_2O_4$: C, 50.01; H, 3.78; N, 11.66. Found: C, 50.14; H, 3.80; N, 11.70%.

3-Hydroxy-5-iodo-3-(1-nitroethyl)-1,3-dihydro-2*H*-indolin-2-one

(3i, Table 1, Entry 9): White solid. M.p. 278−280 °C; IR (KBr, cm^{-1}): 3381, 3248, 2934, 1733, 1614, 1552, 1472, 1357, 1188, 816; ^{1}H NMR (300 MHz, DMSO-d_6) (diastereomeric ratio, *threo:erythro* 91:9, * denotes minor diastereomer peaks): δ 10.55(br s, 1H), 10.49*(br s, 1H), 7.67(d, 1H, *J* = 1.5 Hz), 7.55(dd, 1H, *J* = 8.1, 1.5, Hz), 6.7(br s, 1H), 6.68(d, 1H, *J* = 8.1 Hz), 4.99-4.92(m, 1H), 1.75*(d, 3H, *J* = 7.0 Hz), 1.38(d, 3H, *J* = 7.0 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.51*, 174.83, 142.32*, 142.27, 138.38, 133.15, 132.56*, 129.80*, 129.45, 112.36*, 112.30, 86.19, 85.18*, 84, 83.6*, 75.34, 74.64*, 13.5, 12.3* ppm; MS(ESI): *m*/*z* = 371 $[M+Na]^+$; Anal. Calcd for $C_{10}H_9IN_2O_4$: C,

34.50; H, 2.61; N, 8.05. Found: C, 34.64; H, 2.63; N, 8.09%.

3-Hydroxy-1-methyl-3-(1-nitroethyl)-1,3-dihydro-2*H*-indolin-2one

(3j, Table 1, Entry 10): White solid. M.p. 140−142 °C; IR (KBr, cm^{-1}): 3316, 2939, 1703, 1616, 1551, 1468, 1385, 1355, 1113, 1061, 759; ^1H NMR (300 MHz, DMSO-d_6) (diastereomeric ratio, *threo:erythro* 63:37, * denotes minor diastereomer peaks): δ 7.44*(s, 1H), 7.42*(s, 1H), 7.35(s, 1H), 7.33(s, 1H), 7.12-7.0(m, 1H), 6.88(d, 1H, *J* = 3.5 Hz), 6.85*(d, 1H, *J* = 3.2 Hz), 6.68*(br s, 1H), 6.63(br s, 1H), 5.05-4.98(m, 1H), 3.18*(s, 3H), 3.17(s, 3H), 1.76*(d, 3H, *J* = 6.8 Hz), 1.37(d, 3H, *J* = 6.8 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.83*, 174.4, 144.3*, 144.09, 130.43, 130.13*, 127.4*, 126.9, 124.24, 123.8*, 122.7, 122.3*, 108.9*, 108.57, 78.4, 77.8*, 72.75, 71.6*, 26.17, 25.3*, 13.9, 12.8* ppm; MS(ESI): *m*/*z* = 259 $[M+Na]^+$; Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.11; N, 11.86. Found: C, 56.05; H, 5.13; N, 11.90%.

3-Hydroxy-3-(1-nitroethyl)-1-pheny-1,3-dihydro-2*H*-indolin-2-one

(3k, Table 1, Entry 11): White solid. M.p. 102−105 °C; IR (KBr, cm^{-1}): 3331, 2923, 1711, 1619, 1569, 1471, 1374, 1087, 769; ^1H NMR (300 MHz, DMSO-d_6) (diastereomeric ratio, *threo:erythro* 72:28, * denotes minor diastereomer peaks): δ 7.56-7.37(m, 6H), 7.26(t, 1H, *J* = 7.4 Hz), 7.19-7.15*(m, 1H), 7.10(t, 1H, *J* = 7.5 Hz), 7.06-7.01*(m, 1H), 6.91(br s, 1H), 6.89*(br s, 1H), 6.74(d, 1H, *J* = 7.4 Hz), 5.19-5.09 (m, 1H), 1.84*(d, 3H, *J* = 6.9 Hz), 1.57(d, 3H, *J* = 6.9 Hz) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.4*, 173.3, 143.9*, 143.6, 133.8*, 133.7, 130.0*, 129.4, 128.2*, 128.1, 128.03, 127.9*, 126.5*, 126.3, 125.2, 124.9*, 122.92, 122.79*, 109.18*, 109.05, 86.93, 85.7*, 74.7*, 74.6, 13.58, 12.2* ppm; MS(ESI): *m*/*z* = 321 $[M+Na]^+$; Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.53; H, 4.74; N, 9.44%.

3-Hydroxy-1-(hydroxymethyl)-5-iodo-3-(1-nitroethyl)-1,3-dihydro-2*H*-indolin-2-one

(3l, Table 1, entry 12): White solid. M.p. 151−153 °C; IR (KBr, cm^{-1}): 3341, 2982, 1731, 1604, 1537, 1480, 1333, 1194, 1029, 965, 810; ^1H NMR (300 MHz, DMSO-d_6) (diastereomeric ratio, *threo:erythro* 88:12, * denotes minor diastereomer peaks) δ 7.75(d, 1H, *J* = 7.5 Hz), 7.66(dd, 1H, *J* = 8.3, 1.7 Hz), 7.61*(dd, 1H, *J* = 8.3, 1.7 Hz), 6.95(d, 1H, *J* = 8.1 Hz), 6.9(br s, 1H), 6.8*(br s, 1H), 6.2(br s, 1H), 5.1(s, 2H), 5.04-4.9(m, 1H), 1.76*(d, 1H, *J* = 7.0 Hz), 1.37(d, 1H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 173.5*, 172.9, 142.3, 138.6, 133.6, 132.7*, 129.0*, 128.6, 112.4, 86.35, 85.6, 85.4, 85.3*, 75.1, 74.6*, 62.8, 13.52, 12.4*; MS(ESI): *m*/*z* = 379 $[M+H]^+$; Anal. Calcd for $C_{11}H_{11}IN_2O_5$: C, 34.94; H, 2.93; N, 7.41. Found: C, 35.09; H, 2.94; N, 7.45%.

CONCLUSION

In this, we have developed a simple, convenient and efficient protocol for synthesis of substituted indolin-2-one derivatives using catalytic amount of piperidine under proper stirring conditions at RT. In addition, using commercially available, easy to handle, inexpensive reagents and the very mild reaction conditions make this process a simple and convenient approach to obtain substituted indolin-2-one derivatives with high yields.

REFERENCES

1. Gourhari M, Utpal K, Rajiv K & Bhattacharya R N, *Indian J Chem*, 52B, 2013, 122.
2. Reddy B V S, Reddy M R, Rao Y G, Yadav J S & Srighar B, *Org Lett*, 15, 2013, 464.
3. Anxionnat B, Pardo D G, Ricci G, Rossen K & Cossy J, *Org Lett*, 15, 2013, 3876.
4. Zhao Y, Li D, Zhao L & Zhang J, *Synthesis*, 2011, 873.
5. Gogoi A, Guin S, Rout S K & Patel B K, *Org. Lett.*, 15, 2013, 1802.

6. Pasquini S, Mugnaini C, Ligresti A, Tafi A, Brogi S, Falciani C, Pedani V, Pesco N, Guida F, Luongo L, Varani K, Borea P A, Maione S, Marzo V D & Corelli F, *J Med Chem*, 55, 2012, 5391.
7. Matthias L, Ludwig J , Bovens S, Brauch C & Elfringhoff A S, *J Med Chem*, 49, 2006, 2611.
8. Sachin M, Sandip B , Sudhakar M, Prashant J, Sonali S B, Paul R J, Ram A V & Bhabatosh C, *J Med Chem*, 57, 2014, 9658.
9. Zhang N X, Zhu J, Turpoff A, Chen G, Morrill C, Huang S, Lennox W, Ramesh K, Ronggang L, Chunshi Li, Hongyu R, Neil A, Srikanth V, Njoroge G F, Zhengxian Gu , Valerie C, Jason G, Stephen P J, Yingcong Z, Joseph M C, Fred L, Josephine S, Anna M, Marla W, Amin N & Gary M K, *J Med Chem*, 57, 2014, 2121.
10. Heinz Fretz, Anja Valdenaire , Julien Pothier , Kurt Hilpert , Carmela Gnerre , Oliver Peter , Xavier Leroy & Markus A. Riederer, *J Med Chem*, 56, 2013, 4899.
11. Jeong U S, Sung P C, Tae Hun K, Cheol-Kyu J, Joo-Youn L, and Sang-Hun J & Geun T K, *Bioorg Med Chem Lett*, 25, 2015, and 1254.
12. Najahi E, Valentin A, Paul-Louis F, Reybier K & Nepveu F, *Eur J Med Chem,* 78, 2014, 269.
13. Bin Wu, Hui-Ling Wang, Victor J C, Brian A L, Thomas N, Liping P, Anthony B R, Ryan P W, Nadia G, Christine Sastri, Jeff Winston, Russell L, Matthew R L Christopher M, Kristin L A & Andrew S T, *Bioorg & Med Chem Lett*, 25, 2015, 775.
14. Qing Ye, Weili Mao, Yubo Zhou, Lei Xu, Qiu Li, Yuanxue Gao, Jing Wang, Chenhui Li, Yazhou Xu, Yuan Xu, Hong Liao, Luyong Zhang, Jianrong Gao, Jia Li, Tao Pang, *Bioorg & Med Chem*, 23, 2015, 1179.
15. Setterholm N A, McDonald F E, Boatright J H, Michael Iuvone P, *Tetrahedron Lett.*, 56, 2015, 3413.
16. Chauhan P, Singh S & Swapandeep Singh C, *Indian J Chem*, 52B, 2013, 245.
17. Narumiya S, Sugimoto Y & Ushikubi F, *Physiol Rev* 79, 1999, 1193.
18. Zafer A K, Ahmet O, Gilbert R & Gulhan TZ, *Eur J Med Chem,* 43, 2008, 125.
19. Sundberg R J, *The Chemistry of Indoles (*Academic press, NewYork*)*, pp 133, 1996.
20. Hubacher M H, Doernberg S, Horner A, *Am J Pharm Assoc,* 42, 1953, 23.
21. Gazit, A, Osherov N, Posner I, Yaish P, Poradosu E, Gilon C & Levitzki A.*J Med Chem*, 34, 1991, 1896.
22. Dilber S, Saban M, Jelaca J, Gelineo A, Arsenijevic L & Bogavac, M. *Pharmazie,* 44, 1989, 649.
23. Klumpp D A, Yeung K Y, Prakash G K S & Olah G A, *J Org Chem,* 63, 1998, 4481.