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Microwave assisted catalyst free synthesis of 3-hydroxy-2-oxidoles by aldol condensation of acetophenones with isatins

H. M. Meshram*, N. Nageswara Rao, N. Satish Kumar and L. Chandrasekhara Rao

Discovery Laboratory, Organic Chemistry Division – I, Indian Institute of Chemical Technology, Hyderabad – 500 007, India

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ABSTRACT

An efficient and catalyst free method is described for the synthesis of oxindole by the reaction of isatin with ketones under microwave irradiation. The method is applicable for a variety of isatins and ketones and avoids the use of organic solvent. Some new oxindoles are prepared in good yield.

Key Words: Acetophenone, Isatin, Microwave irradiation, Oxindole.

INTRODUCTION

The Indole (1) moiety constitutes a core structural unit of many bioactive natural products as well as pharmaceuticals. Particularly, the 3-substituted hydroxy indoline-2-one unit was found in some drug candidates like, convolutainydines, dinzonamide A, TMC-95s, dioxibrassinine and witindolinone (2). Due to distinct medicinal properties of indoline containing molecules, there is growing interest to devise a rapid and clean method for the synthesis of indolines. 3-Hydroxy oxindoles are commonly synthesized by the nucleophilic addition of a nucleophile to isatin in the presence of base. Some of the methods require metal complexes or chiral catalyst (3). Recently, catalyst free condensation of alkyl ketones with isatin has been reported in the presence of molecular sieve in DMF (4). According to reported protocol, DMF acts as a weak base and the reaction did not complete without molecular sieves. Other reported methods involve the use of metallic base or complexes. In addition to this some of the methods require high boiling solvent (DMF) which is detrimental to the environment and recovery of product is troublesome. Consequently, the reported methods (3) (4) uses either base or organic solvent or additive for the synthesis of 3-hydroxy-2-oxindoles. In this context of green chemistry, there is a scope to devise a practically catalyst or additive free method in environmentally benign solvent.

Water is obviously the cleanest and safest available solvent, but it is not commonly used as most organic compounds are poorly water soluble (5). By heating water above 100 ^{0}C under microwave irradiation, the chemical and physical properties of water can be altered and it behaves both as a pseudo-organic solvent and an acid (6). Due to this effect without any catalyst, a lot of the acid-catalyzed transformations have been reported (7). Microwave irradiation is an alternate source of heating and it has been proven recently that microwave heating improves the efficiency (7) of the reaction and reduces the reaction time for severally. Due to environmental benefit of water and alternative source of heating, we envision promoting the reaction by microwave irradiation. Herein we wish to report the results of condensation of acetophenone with isatin in catalyst free condition under microwave irradiation.

MATERIALS AND METHODS

Experimental Part

Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300W. Reactions were performed in glass vessels (capacity 10 mL) equipped with a magnetic stirring bar and sealed with a septum. The target temperature was set and fixed during the irradiation. Settings and readings for power (W) and pressure were taken from the instrument. Melting points were determined in open capillary tubes using a Electro Thermal 9100 series apparatus. Column chromatography (CC): silica gel (SiO_2; BDH 60 – 120 mesh). Thin layer chromatography (TLC): silica gel GF254 (Merck) plates. IR Spectra: Perkin Elmer RX1 FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: Varian Gemini 200 MHz spectrometer; DMSO as solvent; at 200 MHz and 70 MHz, resp. ESI-MS: LC-MSD Trap-SL spectrometer.

General procedure for the synthesis of 3-hydroxy oxindoles. A sealed 10 mL glass tube containing acetophenone (1.1 equiv.), isatin (1 equiv.) and water (2 mL) was placed in the cavity of a microwave reactor and irradiated for an appropriate time, at 100^{0}C (temperature monitored by in built infrared sensor), and power 140 W. After cooling to room temperature by an air-flow, the tube was removed from the rotor. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were then dried over Na_2SO_4 and after removal of the solvent, the mixture was purified by short column chromatography (hexane/AcOEt as eluent) to give pure 3-hydroxy oxindole products **(Table 1)**.

Data of All Representative Compounds.

***3-hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one*(3a)**. mp.177-178 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3376, 3293, 2896, 1726, 1672, 1620, 1471, 1392, 1356, 1334, 1220, 7560. ^{1}H NMR(DMSO, 300MHz): δ 10.11 (s, 1H, N-H), 7.85 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.1 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.21 (d, J = 7.3 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.84 (t, J = 6.6 Hz, 2H), 5.88 (br s, 1H), 3.89 (d, J = 17.3 Hz, 1H), 3.61 (d, J = 17.3 Hz, 1H); ^{13}C NMR(DMSO, 75MHz): δ 195.3, 178.0, 141.9, 135.6, 132.3, 130.5, 128.3, 127.6, 127.2, 122.7, 120.8, 109.2, 95.2, 72.8, 45.0; MS: m/z= 268[M+1]$^{+\cdot}$.

***3-hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl)indolin-2-one*(3b).** mp. 186-188 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3382, 3059, 2963, 1725, 1668, 1603, 1509, 1343, 1261, 1230, 1174, 749. ^{1}H NMR(DMSO, 300MHz): δ 10.09 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 7.1 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.82-6.88 (m, 4H), 5.82 (s, 1H), 3 .82 (s, 3H), 3.81 (d, J = 16.9 Hz, 1H), 3.5 (d, J = 16.9 Hz, 1H); ^{13}C NMR(DMSO, 75MHz): δ 193.5, 177.7, 162.3, 141.7, 130.5, 129.2, 128.5, 127.8, 122.4, 120.3, 112.5, 108.8, 72.5, 54.2, 44.3; MS: m/z= 320[M+23]$^{+\cdot}$.

***3-hydroxy-5-nitro-3-(2-oxo-2-phenylethyl)indolin-2-one*(3c).** mp. 228-229 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3250, 2926, 1716, 1680, 1625, 1523, 1455, 1333, 1216, 1183, 746. ^{1}H NMR(DMSO, 300MHz): δ 10.82 (s, 1H), 8.09-8.12 (m, 2H), 7.86 (d, J = 6.9 Hz, 2H), 7.52 (d, J = 6.9 Hz, 1H), 7.41-7.47 (m, 2H), 6.97 (d, J = 7.9 Hz, 1H), 6.22 (s, 1H), 4.05 (d, J = 17.8 Hz, 1H), 3.72 (d, J = 17.8 Hz, 1H); ^{13}C NMR(DMSO, 75MHz): δ 194.4, 176.7, 147.8, 140.1, 133.8, 131.5, 130.9, 126.6, 126.0, 124.3, 117.5, 107.5, 93.7, 70.7, 44.0; MS: m/z= 335[M+23]$^{+\cdot}$.

***3-hydroxy-5-nitro-3-(2-(4-nitrophenyl)-2-oxoethyl)indolin-2-one*(3d)**. mp. 197-198 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3246, 1712, 1649, 1626, 1521, 1415, 1336, 1226, 1184, 725. ^{1}H NMR(DMSO, 300MHz): δ 10.94 (s, 1H), 8.28 (d, J = 8.4 Hz, 2H), 8.08-8.21 (m, 4H), 7.02 (d, J = 8.4 Hz, 1H), 6.38 (s, 1H), 4.23 (d, J = 17.7 Hz, 1H), 3.83 (d, J = 17.7 Hz, 1H); ^{13}C NMR(DMSO, 75MHz): δ 193.5, 176.8, 148.4, 147.8, 140.5, 138.6, 130.8, 127.8, 124.4, 121.8, 118.0, 107.8, 94.1, 70.9, 44.7; MS: m/z=380 ([M$^+$+23]$^{+\cdot}$.

***3-(2-(3-aminophenyl)-2-oxoethyl)-3-hydroxy-5-nitroindolin-2-one*(3e)**. mp. 210-212 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3569, 3459, 3388, 3124, 1734, 1663, 1624, 1460, 1336, 1309, 1187, 748. ^{1}H NMR(DMSO, 300MHz): δ 10.90 (s, 1H), 8.13 (d, J = 6.7 Hz, 2H), 7.04-7.11 (m, 3H), 7.01 (d, J = 9.2 Hz, 1H), 6.78 (d, J = 6.7 Hz, 1H), 6.30 (s, 1H), 4.89 (s, 2H), 4.07 (d, J = 17.9 Hz, 1H), 3.71 (d, J = 17.9 Hz, 1H); ^{13}C NMR (DMSO, 75MHz): δ 195.3, 177.7, 148.4, 146.9, 141.1, 135.5, 131.6, 127.9, 124.9, 118.1, 115.4, 112.2, 108.4, 94.7, 71.7, 45.0; EI-MS: m/z= 328 (M+1)$^{+\cdot}$.

***3-hydroxy-5-nitro-3-(2-oxo-2-(thiophen-2-yl)ethyl)indolin-2-one*(3f).** mp. 221-222 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3240, 2928, 1717, 1649, 1521, 1409, 1333, 1179, 720. ^{1}H NMR(DMSO, 300MHz): δ 10.87 (s, 1H), 8.16 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 2.8 Hz, 1H), 7.68 (d, J = 4.6 Hz, 1H), 7.13 (t, J = 4.6 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.33 (s, 1H), 3.97 (d, J = 16.8 Hz, 1H), 3.66 (d, J = 16.8 Hz, 1H); ^{13}C NMR (DMSO, 75MHz): δ 187.1, 176.5, 147.6, 141.1, 140.1, 132.9, 131.8, 130.6, 126.5, 124.3, 117.7, 107.6, 93.7, 70.6, 44.1; MS: m/z= 341 **[**M+23]$^{+\cdot}$.

***3-hydroxy-3-(2-(5-methylfuran-2-yl)-2-oxoethyl)-5-nitroindolin-2-one*(3g)**. mp. 211-212 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3245, 3121, 1717, 1666, 1517, 1333, 1191, 801, 749. ^{1}H NMR(DMSO, 300MHz): δ 10.93 (s, 1H), 8.10-8.20 (m, 2H), 7.28 (s, 1H), 6.97 (d, J = 7.9 Hz, 1H), 6.35 (s, 1H), 6.25 (s, 1H), 3.87 (d, J = 16.8 Hz, 1H), 3.39 (d, J = 16.8 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR(DMSO, 75MHz): δ 181.4, 176.5, 156.0, 147.5, 140.1, 132.6, 130.5, 124.3, 118.7, 117.7, 107.6, 107.3, 70.7, 43.0, 11.8; MS: m/z=339 [M+23]$^{+\cdot}$.

***5-bromo-3-hydroxy-3-(2-oxo-2-phenylethyl) indolin-2-one*(3h)**. mp. 216-218 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3222, 1700, 1618, 1348, 1218, 1181, 825, 734. ^{1}H NMR(DMSO, 300MHz): δ 10.34 (s, 1H), 7.87 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.1 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.37 (s, 1H), 7.26 (d, J = 9.6 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.12 (s, 1H), 4.01 (d, J = 17.7 Hz, 1H), 3.66 (d, J = 17.7 Hz, 1H); ^{13}C NMR (DMSO, 75MHz): δ 196.4, 177.5, 142.4, 134.6, 132.5, 131.7, 129.1, 127.5, 126.4, 113.1, 111.4, 71.7, 45.4; MS: m/z= 346 [M]$^{+\cdot}$.

***5-bromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one*(3i)**. mp.167-169 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3577, 3240, 1700, 1615, 1477, 1336, 1185, 826, 729. ^{1}H NMR(DMSO, 300MHz): δ 10.22 (s, 1H), 7.43-7.49 (m, 2H), 6.66 (d, J = 7.9 Hz, 1H), 5.94 (s, 1H), 3.20 (d, J = 16.8 Hz, 1H), 3.01 (d, J = 16.8 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR(DMSO, 75MHz): δ 203.6, 192.8, 141.4, 136.6, 133.0, 131.3, 111.2, 95.0, 72.0, 49.4, 29.7; MS: m/z= 282 [M]$^{+\cdot}$.

***3-hydroxy-5-iodo-3-(2-oxo-2-phenylethyl)indolin-2-one*(3j)**. mp. 218-220 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3342, 2921, 2851, 1672, 1437, 1328, 1210, 1173, 1067, 821, 724. ^{1}H NMR(DMSO, 300MHz): δ 10.30 (s, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.41-7.58 (m, 5H), 6.70 (d, J = 8.4 Hz, 1H), 6.06 (s, 1H), 3.94 (d, J = 17.7 Hz, 1H), 3.68 (d, J = 17.7 Hz, 1H); ^{13}C NMR(DMSO, 75MHz): δ 194.2, 175.9, 141.1, 135.4, 134.3, 131.4, 130.2, 126.7, 126.1, 110.2, 93.9, 81.6, 71.1, 44.1; MS: m/z= 394 [M+23]$^{+\cdot}$.

***3-hydroxy-5-iodo-3-(2-(4-nitophenyl)-2-oxoethyl)indolin-2-one*(3k).** mp. 213-215 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3573, 3246, 1698, 1616, 1476, 1442, 1339, 1184, 1066, 825, 731. ^{1}H NMR(DMSO, 300MHz): δ 10.23 (s, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.74-7.85 (m, 1H), 7.43-7.51 (m, 3H), 6.66 (d, J = 7.9 Hz, 2H), 5.94 (s, 1H), 3.22 (d, J = 16.8 Hz, 1H), 3.02 (d, J = 16.8 Hz, 1H); ^{13}C NMR(DMSO, 75MHz): δ 183.1, 177.2, 142.3, 137.1, 132.1, 127.8, 127.1, 120.3, 11.7, 109.0, 95.3, 72.7, 44.6; MS: :m/z= 438 [M+1]$^{+\cdot}$.

***3-hydroxy-5-iodo-3-(2-oxo-2-(thiophen-2-yl)ethyl)indolin-2-one*(3l).** mp. 201-203 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3246, 2925, 1701, 1663, 1616, 1515, 1210, 1025, 822. ^{1}H NMR(DMSO, 300MHz): δ 10.31 (s, 1H), 7.46-7.54 (m, 1H), 7.12 (s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.17 (s, 1H), 6.04 (s, 1H), 3.65 (d, J = 16.4 Hz, 1H), 3.33 (d, J = 16.4 Hz, 1H); ^{13}C NMR(DMSO, 75MHz): δ 183.1, 177.2, 142.3, 137.1, 127.8, 127.1, 120.3, 111.7, 109.0, 95.3, 79.1, 72.7, 44.6; MS: 422[M+23]$^{+\cdot}$.

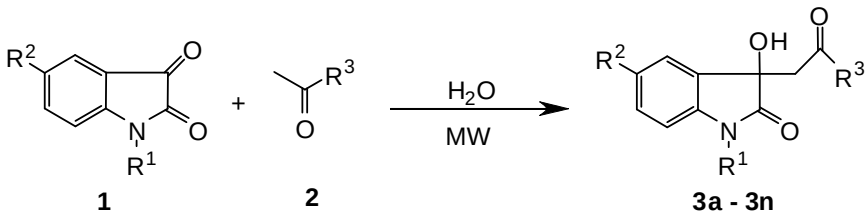
***1-benzyl-3-hydroxy-3-(2-(4-nitrophenyl)-2-oxoethyl)indolin-2-one*(3m)**. mp. 135-137 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3372, 3060, 2946, 2879, 1684, 1613, 1490, 1467, 1349, 1178, 1006, 756. ^{1}H NMR(DMSO, 300MHz): δ 7.45 (d, J = 7.1 Hz, 2H), 7.22-7.34 (m, 5H), 7.07-7.18 (m, 3H), 6.89 (t, J = 7.3 Hz, 1H), 6.82 (d, J = 6.7 Hz, 1H), 6.60 (d, J = 7.5 Hz, 1H), 6.08 (s, 1H), 4.92 (s, 2H), 3.93 (d, J = 17.1 Hz, 1H), 3.74 (d, J = 17.1 Hz, 1H), 3.16 (s, 2H); ^{13}C NMR(DMSO, 75MHz): δ 194.4, 174.9, 145.6, 141.7, 135.0, 134.4, 129.3, 127.1, 126.9, 126.4, 125.2, 121.2, 120.0, 119.9, 117.6, 114.7, 111.7, 106.9, 93.7, 70.8, 44.1, 41.1; MS: 395 [M+23]$^{+\cdot}$.

***3-hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl)-1-methylindolin-2-one*(3n)**. mp. 191-192 ^{0}C. IR (KBr) ν_{max}(cm^{-1}): 3365, 3080, 2952, 1694, 1672, 1600, 1265, 1169, 754. ^{1}H NMR(DMSO, 300MHz): δ 7.86 (d, J = 7.5 Hz, 2H), 7.25-7.30 (m, 2H), 6.96-6.99 (m, 4H), 6.11 (s, 1H), 4.06 (d, J = 17.7 Hz, 1H), 3.82 (s, 3H), 3.60 (d, J = 17.7 Hz, 1H), 3.14 (s, 3H); ^{13}C NMR(DMSO, 75MHz): δ 194.6, 176.6, 163.2, 144.0, 131.6, 129.8, 129.1, 123.0, 121.6, 113.6, 108.4, 72.5, 55.4, 45.2, 25.8; MS: m/z= 334 [M+23]$^{+\cdot}$.

RESULTS AND DISCUSSION

In continuation of our work on the development of clean and green methodologies (8), in this article we wish to describe a catalyst free, rapid and practical method for the synthesis of 3-hydroxy-2-oxindoles in the aqueous medium under microwave irradiation **(Scheme1)**.

Scheme 1: Synthesis of 3-hydroxy oxindole derivatives



1 **2** **3a - 3n**

R^1 = H, Me, $PhCH_2$ R^2 = H, NO_2, Br, I.

R^3= Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 3-$NH_2C_6H_4$, 2-Thienyl, 5-Me-2-Furanyl, Me.

Table 1 : Catalyst Free Synthesis Of Oxindole Under Microwave Irradiation

Entry	R^1	R^2	R^3	Product[a)]	Time(min)	Yield[b)][%]
1	H	H	Ph	**3a**	4	90
2	H	H	4-MeO-C_6H_4	**3b**	5	92
3	H	NO_2	Ph	**3c**	4	90
4	H	NO_2	4-NO_2-C_6H_4	**3d**	6	85
5	H	NO_2	3-NH_2-C_6H_4	**3e**	8	93
6	H	NO_2	2-Thienyl	**3f**	7	87
7	H	NO_2	5-Me-2-Furanyl	**3g**	9	85
8	H	Br	Ph	**3h**	5	88
9	H	Br	Me	**3i**	6	80
10	H	I	Ph	**3j**	6	85
11	H	I	4-NO_2-C_6H_4	**3k**	7	85
12	H	I	2-Thienyl	**3l**	6	87
13	$PhCH_2$	H	3-NH_2-C_6H_4	**3m**	10	85
14	Me	H	4-MeO-C_6H_4	**3n**	9	90

[a)]The structures of the products were deduced from their spectral(IR, ^{1}H-, ^{13}C-NMR and MS) and analytical data. [b)] Yields of isolated pure products after column chromatography.

Thus, the initial reaction of isatin (1 mmol) with acetophenone (1.1 mmol) in aqueous medium at 60 ^{0} for 10 h afforded low yield (30%) of oxindole. As it is well documented that microwave irradiation improves the efficiency of reactions, the same reaction mixture was irradiated with microwave. To our surprise, the reaction was completed in 4 min. and **3a** was isolated in high yield (***Table 1)***. After irradiation, the temperature of the mixture was 100 ^{0}. To confirm the effect of microwave irradiation, a blank experiment was conducted. When the same reaction mixture was heated in a preheated conventional oil bath (100 ^{0}), the reaction was completed after 10 h. These observations clearly indicated that the driving force for the reaction was not purely thermal but because of generated microwave. It is presumed (6) that the reaction may occur due to the change of properties of H_2O during microwave irradiation. This result encouraged us for further screening of reaction with other ketones. Interestingly, various aromatic and heteroaromatic ketones reacted smoothly with isatin under similar conditions to give the desired products in high yield. Aromatic ketones like, acetophenone (***Table 1***, *Entries 3a and 3c*), 4-nitoacetophenoe (***Table 1***, *Entries 3d and 3k*), amino acetophenone (***Table 1***, *Entries 3e and 3m*), methoxy acetophenone (***Table 1***, *Entries 3b and 3n*) reacted rapidly with isatin and afforded respective products in high yield whereas aliphatic ketone (***Table 1***, *Entry 3i*) such as acetone afforded expected product in moderate yield. We have not observed substantial effect of any substituents on the benzene ring. The heterocyclic ketones such as, 2-Acetyl furan (***Table 1***, *Entry 3g*) and 2-acetyl thiophene (***Table 1***, *Entries 3f and 3l*) also reacted analogously with isatin and resulted in good yield of 3-hydroxy oxindoles, which have not been prepared previously (see ***Table 1***). The reaction was clean and products were obtained in high yield. We believe that the use of aqueous medium and rapid reactions are attractive alternative over earlier methods.

CONCLUSION

In conclusion, we have demonstrated a practically, catalyst free synthesis of 3-hydroxy-2-oxindoles in aqueous medium under microwave irradiation. The yields are high and the method is applicable for a variety of isatins as well as ketones like aromatic, heteroaromatic, aliphatic. The aqueous medium and rapid reaction makes the procedure more advantageous and eco-friendly.

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