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Ultrasound-assisted three-component synthesis of 3-(5-amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-ones in water

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ABSTRACT

Indium(III) chloride was found to be an efficient catalyst for the synthesis of 3-(5-amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-ones by one-pot, three-component reaction of dimedone, 1*H*-pyrazol-5-amines and isatins in water under ultrasonic irradiation. The advantages of this method are the use of a readily available catalyst, easy workup, excellent yields, and the use of water as a solvent that is considered to be relatively environmentally benign.

1. Introduction

Recently published comprehensive books [1] and papers [2] indicate chemical applications of ultrasounds. "Sonochemistry", is a new trend in organic chemistry, offering a versatile and facile pathway for a large variety of syntheses. Thus, a large number of organic reactions can be carried out under ultrasonic irradiation in high yields, short reaction times and mild conditions [1,2].

Isatin and its derivatives have proved to be versatile starting materials for the synthesis of heterocyclic, and non-cyclic, natural products, and analogues, as well as for the synthesis of potentially important compounds with biological activities [3]. Oxindoles are well known amongst these compounds. Oxindoles are useful as antibacterial, antiinflammatory, and laxatives [4,5]. Furthermore, this heterocycle compounds were recently isolated from plant [6]. The 3,3-substituted oxindoles have been shown to possess mechanism-specific antiproliferative, antibacterial, antiprotozoal, and antiinflammatory activities [7–10]. Therefore, recently, few methods have been developed for the synthesis of 3,3-substituted oxindoles [4,11–14]. Similarly, heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically active compounds [15–17], among them such prominent drug molecules as Celecoxib, Pyrazofurine, and many others.

In recent years, indium(III) chloride has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various transformations under mild and convenient conditions, affording the corresponding products in excellent yields with high selectivity [18].

Considering the above reports and in continuation of our previous works on synthesis of heterocyclic compounds [19–31], herein, we report a simple and efficient method for the preparation of oxindole derivatives in water under ultrasonic irradiation. In fact, as clearly stated by Sheldon [32], it is generally recognized that "the best solvent is no solvent and if a solvent (diluent) is needed it should preferably be water". The use of water as the reaction medium represent a remarkable benefit since this green solvent is highly polar and therefore immiscible with most organic compounds; moreover the water soluble catalyst resides and operates in the aqueous phase and separation of the organic materials is thus easy.

2. Experimental

2.1. Chemicals and apparatus

The chemical used in this work were obtained from Fluka and Merck and were used without purification. Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102 MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating

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at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. ^{1}H and ^{13}C NMR spectra were obtained on solutions in DMSO-d_6 using TMS. Ultrasonication was performed in a EUROSONIC® 4D ultrasound cleaner with a frequency of 50 kHz and an output power of 350 W. The reaction flask was located in the maximum energy area in the cleaner, where the surface of reactants (reaction vessel) is slightly lower than the level of the water and the temperature of the water bath was controlled at 50 °C.

2.2. Typical procedure for the preparation of 3-(5-amino-1,3-diphenyl-1H-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-indolin-2-one (4a)

A 25 mL flask was charged with dimedone (1 mmol), 1,3-diphenyl-1*H*-pyrazol-5-amine (1 mmol), isatine (1 mmol), $InCl_3$ (10 mol%) and water (5 mL). The reaction mixture was sonicated at 50 °C for 2 h (TLC). After completion of reaction, the reaction mixture was filtered and the precipitate washed with water (10 mL) and recrystallized from EtOH to afford the pure product **4a** as white powder (91%). mp: 290 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3305 (NH_2, NH and OH), 3070, 1706 (C=O), 1618 (C=O). MS (EI, 70 eV) *m*/*z* (%): 504 (M^+, 10), 489 (10), 402 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.92 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.95 and 2.10 (2H, AB system, J = 16.1 Hz, CH_2), 2.56 (2H, s, CH_2), 6.48–7.60 (16H, m, H–Ar and NH_2), 9.79 (1H, s, NH), 9.99 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 27.3 (CH_3), 28.6 (CH_3), 32.4 ($C(CH_3)_2$), 41.4 (CH_2), 49.4 (C), 51.1 (CH_2), 101.9 (C=COH), 108.7 (NH_2–C=C), 109.1, 121.5, 123.6, 124.2, 127.6, 128.1, 128.2, 129.0, 129.9, 133.2, 137.4, 138.1, and 138.6 (Ar), 142.8 (C), 149.8 ($NH_{-2}CN$), 153.0 (NC=O), 179.9 (COH), 193.5 (CO). Anal. Calcd for $C_{31}H_{28}N_4O_3$: C, 73.79; H, 5.59; N, 11.10%. Found: C, 73.74; H, 5.55; N, 11.17%.

2.2.1. 3-(5-Amino-1,3-diphenyl-1H-pyrazol-4-yl)-5-bromo-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-one (4b)

Cream powder (86%); mp: 240 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3219 (NH_2, NH and OH), 2957, 1714 (C=O), 1616 (C=O). MS (EI, 70 eV) *m*/*z* (%): 582 (M^+–1, 7), 564 (5), 482 (100), 402 (45). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.98 (6H, s, $2CH_3$), 1.98 (2H, s, CH_2), 2.58 (2H, s, CH_2), 6.40–7.65 (15H, m, H–Ar and NH_2), 9.90 (1H, s, NH), 9.94 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 27.6 (CH_3), 28.2 (CH_3), 32.5 ($C(CH_3)_2$), 41.3 (CH_2), 49.5 (C), 50.8 (CH_2), 101.2 (C=COH), 108.1 (NH_2–C=C), 111.0, 113.0, 124.5, 126.3, 127.8, 128.2, 128.3, 128.9, 129.9, 130.4, 133.0, 137.4, 138.0 and 140.7 (Ar), 142.1 (C), 149.8 ($NH_{-2}CN$), 153.5 (NC=O), 179.6 (COH), 193.7 (C=O). IR (KBr) cm^{-1}: 3219.4, 2957.49 and 2859.91,1714.69, 1616.47. Anal. Calcd for $C_{31}H_{27}BrN_4O_3$: C, 63.81; H, 4.66; N, 9.60%. Found: C, 63.87; H, 4.61; N, 9.66%.

2.2.2. 3-(5-Amino-1,3-diphenyl-1H-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-5-nitroindolin-2-one (4c)

Light brown powder (92%); mp: 215 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3224 (NH_2, NH and OH), 2952, 1735 (C=O), 1617 (C=O). MS (EI, 70 eV) *m*/*z* (%): 549 (M^+, 5), 529 (20), 419 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.99 (6H, s, $2CH_3$), 2.05 (2H, s, CH_2), 2.51 and 2.65 (2H, AB system, J = 24.7 Hz, CH_2), 6.58–8.03 (15H, m, H–Ar and NH_2), 10.03 (1H, s, NH), 10.55 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 27.8 (CH_3), 28.0 (CH_3), 32.6 ($C(CH_3)_2$), 41.2 (CH_2), 49.3 (C), 50.7 (CH_2), 100.8 (C=COH), 107.6 (NH_2–C=C), 109.0, 118.8, 124.5, 125.4, 127.9, 128.2, 128.5, 129.0, 129.9, 132.8, 137.9, 139.1, 142.2 and 149.4 (Ar), 149.8 (C), ($NH_{-2}CN$), 154.2 (NC=O), 180.6 (COH), 193.9 (C=O). Anal. Calcd for $C_{31}H_{27}N_5O_5$: C, 67.75; H, 4.95; N, 12.74%. Found: C, 67.70; H, 4.89; N, 12.68%.

2.2.3. 3-(5-Amino-1,3-diphenyl-1H-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-1-methylindolin-2-one (4d)

Cream powder (82%); mp: 294 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3333 (NH_2 and OH), 3051, 1691 (C=O), 1624 (C=O). MS (EI, 70 eV) *m*/*z* (%): 500 (M^+–H_20, 50), 416 (100), 426 (26), 387 (45). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.97 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.93 and 2.06 (2H, AB system, J = 24.3 Hz, CH_2), 2.60 (2H, s, CH_2), 2.62 (3H, s, CH_3), 6.58–7.65 (16H, m, H–Ar and NH_2), 9.93 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 25.9 (NCH_3), 27.3 (CH_3), 28.6 (CH_3), 32.5 ($C(CH_3)_2$), 41.4 (CH_2), 48.8 (C), 50.9 (CH_2), 102.0 (C=COH), 107.7 (NH_2–C=C), 108.2, 122.2, 123.8, 124.1, 127.6, 127.9, 128.0, 128.1, 128.9, 129.9, 133.0, 137.5 and 138.1 (Ar), 143.6 (C), 149.7 ($NH_{-2}CN$), 153.5 (NC=O), 178.2 (COH), 193.4 (C=O). Anal. Calcd for $C_{32}H_{30}N_4O_3$: C, 74.11; H, 5.83; N, 10.80%. Found: C, 74.17; H, 5.77; N, 10.87%.

2.2.4. 3-(5-Amino-1,3-diphenyl-1H-pyrazol-4-yl)-5-bromo-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-1-methylindolin-2-one (4e)

Cream powder (80%); mp: 294 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3224 (NH_2 and OH), 2957, 1722 (C=O), 1618 (C=O). MS (EI, 70 eV) *m*/*z* (%): 598 (M^++2, 50), 596 (M^+, 50), 580 (30), 496 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.99 (3H, s, CH_3), 1.01 (3H, s, CH_3), 2.03 (2H, s, CH_2), 2.49 (2H, s, CH_2), 2.61 (3H, s, CH_3), 6.55–8.31 (13H, m, H–Ar and NH_2), 9.98 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 26.0 (NCH_3), 27.7 (CH_3), 28.2 (CH_3), 32.6 ($C(CH_3)_2$), 41.2 (CH_2), 48.9 (C), 50.7 (CH_2), 101.3 (C=COH), 107.7 (NH_2–C=C), 109.7, 113.9, 124.4, 126.0, 127.8, 128.2, 128.5, 128.8, 129.9, 130.5, 132.8, 137.4, 138.0 and 139.6 (Ar), 143.0 (C), 149.6 ($NH_{-2}CN$), 153.8 (NC=O), 177.9 (COH), 193.8 (C=O). Anal. Calcd for $C_{32}H_{29}BrN_4O_3$: C, 64.32; H, 4.89; N, 9.38%. Found: C, 64.20; H, 4.82; N, 9.31%.

2.2.5. 3-(5-Amino-1,3-diphenyl-1H-pyrazol-4-yl)-1-ethyl-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-one (4f)

White powder (83%); mp: 235 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3214 (NH_2 and OH), 2866, 1713 (C=O), 1608 (C=O). MS (EI, 70 eV) *m*/*z* (%): 532 (M^+, 5), 514 (M^+–H_2O, 10), 430 (100), 471 (40). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.78 (3H, t, J = 6.1 Hz, CH_3), 0.97 (3H, s, CH_3), 1.01 (3H, s, CH_3), 2.07 (2H, s, CH_2), 2.59 (2H, s, CH_2), 3.06 (1H, m, CH_2), 3.30 (1H, m, CH_2), 6.53–7.60 (14H, m, H–Ar and NH_2), 9.86 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 11.9 (CH_3), 27.2 (CH_3), 28.6 (CH_3), 31.1 (NCH_2), 32.5 ($C(CH_3)_2$), 41.3 (CH_2), 48.8 (C), 50.9 (CH_2), 101.8 (C=COH), 108.0 (NH_2–C=C), 108.6, 122.0, 123.5, 124.2, 127.7, 127.9, 128.0, 128.2, 128.9, 129.9, 133.2, 137.4, 137.8 and 138.1 (Ar), 143.2 (C), 149.7 ($NH_{-2}CN$), 153.1 (NC=O), 177.7 (COH), 193.6 (C=O). Anal. Calcd for $C_{33}H_{32}N_4O_3$: C, 74.41; H, 6.06; N, 10.52%. Found: C, 74.49; H, 6.01; N, 10.45%.

2.2.6. 3-(5-Amino-1,3-diphenyl-1H-pyrazol-4-yl)-5-bromo-1-ethyl-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-one (4g)

Cream powder (85%); mp: 330 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3437 (NH_2 and OH), 2945, 1691 (C=O), 1626 (C=O). MS (EI, 70 eV) *m*/*z* (%): 612 (M^++2, 15), 610 (M^+, 15), 592 (43), 416 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 0.77 (3H, s, CH_3), 0.99 (6H, s, $2CH_3$), 2.02 (2H, s, CH_2), 2.59 (2H, s, CH_2), 3.05 (1H, m, CH_2), 3.34 (1H, bs, CH_2), 6.58–7.63 (13H, m, H–Ar and NH_2), 9.94 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C (ppm) 11.7 (CH_3), 27.6 (CH_3), 28.3 (CH_3), 32.5 (NCH_2), 34.3 ($C(CH_3)_2$), 41.2 (CH_2), 48.9 (C), 50.7 (CH_2), 101.0 (C=COH), 107.9 (NH_2–C=C), 109.9, 113.7, 124.4, 126.3, 127.8, 128.2, 128.3, 128.9, 129.9, 130.6, 133.0, 137.5, 138.0 and 138.3 (Ar), 142.5 (C), 149.6 ($NH_{-2}CN$), 153.6 (NC=O), 177.4 (COH), 193.7 (C=O). Anal. Calcd for $C_{33}H_{31}BrN_4O_3$: C, 64.81; H, 5.11; N, 9.16%. Found: C, 64.71; H, 5.02; N, 9.07%.

2.2.7. 3-(5-Amino-1-(4-nitrophenyl)-3-phenyl-1H-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-one ***(4h)***

Yellow powder (83%); mp: 294 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3419 (OH), 3219 (NH_2 and NH), 1705 (C=O), 1609 (C=O). MS (EI, 70 eV) *m/z* (%): 549 (M^+, 25), 531 (40), 368 (70), 57 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 1.00 (3H, s, CH_3), 1.02 (3H, s, CH_3), 1.99 and 2.09 (2H, AB system, J = 15.0 Hz, CH_2), 2.50 (2H, bs, CH_2), 6.47–8.48 (11H, m, H–Ar and NH_2), 7.92 (2H, d, J = 8.6 Hz, H–Ar), 8.42 (2H, d, J = 8.4 Hz, H–Ar), 9.82 (1H, s, NH),9.93 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C 27.3 (CH_3), 28.5 (CH_3), 32.5 ($C(CH_3)_2$), 41.4 (CH_2), 49.2 (C), 51.0 (CH_2), 103.0 (C=COH), 109.1 (NH_2–C=C), 109.2, 121.6, 123.6, 124.2, 125.5, 127.7, 127.9, 128.5, 128.9, 132.6, 138.0, 138.2, 142.8 and 143.1 (Ar), 146.0 (C), 151.5 ($NH_{-2}CN$), 152.8 (NC=O), 179.6 (COH), 193.7 (C=O). Anal. Calcd for $C_{31}H_{27}N_5O_5$: C, 67.75; H, 4.95; N, 12.74%. Found: C, 67.63; H, 4.86; N, 12.68%.

2.2.8. 3-(5-Amino-1-(4-nitrophenyl)-3-phenyl-1H-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-1-methylindolin-2-one ***(4i)***

Yellow powder (89%); mp: >320 °C. IR (KBr) (ν_{max}/cm^{-1}): 3465 (OH), 3219 (NH_2), 1714 (C=O), 1601 (C=O). MS (EI, 70 eV) *m/z* (%): 563 (M^+, 10), 538 (40), 368 (70), 57 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.99 (3H, s, CH_3), 1.02 (3H, s, CH_3), 1.95 and 2.09 (2H, AB system, J = 15.7 Hz, CH_2), 2.61 (5H, s, CH_2 and CH_3), 6.58–7.27 (11H, m, H–Ar and NH_2), 7.94 (2H, d, J = 8.8 Hz, H–Ar), 8.43 (2H, d, J = 8.9 Hz, H–Ar), 10.01 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C 25.9 (NCH_3), 27.4 (CH_3), 28.5 (CH_3), 32.6 ($C(CH_3)_2$), 41.4 (CH_2), 48.7 (C), 50.9 (CH_2), 103.0 (C=COH), 107.9 (NH_2–C=C), 108.7, 122.3, 123.4, 124.2, 125.5, 127.8, 128.1, 128.6, 128.8, 132.4, 137.2, 137.9, 143.1 and 143.6 (Ar), 146.1 (C), 151.4 ($NH_{-2}CN$), 153.2 (NC=O), 177.9 (COH), 193.8 (C=O). Anal. Calcd for $C_{32}H_{29}N_5O_5$: C, 68.19; H, 5.19; N, 12.43%. Found: C, 68.13; H, 5.24; N, 12.49%.

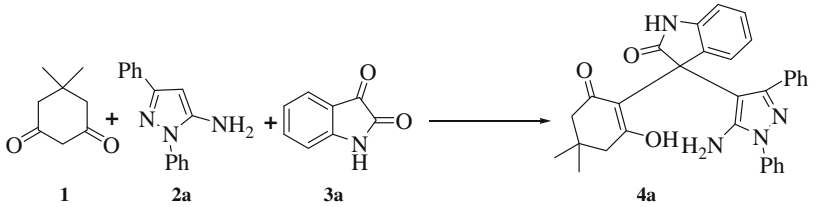
2.2.9. 3-(5-Amino-1-(4-nitrophenyl)-3-phenyl-1H-pyrazol-4-yl)-1-ethyl-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-one ***(4j)***

Yellow powder (87%); mp: 294 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3435 (OH), 3214 (NH_2), 1714 (C=O), 1606 (C=O). MS (EI, 70 eV) *m/z* (%): 577 (M^+, 10), 552 (40), 368 (70), 57 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.78 (3H, bs, CH_3), 0.99 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.93 and 2.06 (2H, AB system, J = 24.3 Hz, CH_2), 2.54 (2H, bs, CH_2), 3.06 (2H, s, CH_2), 6.56–7.24 (11H, m, H–Ar and NH_2), 7.93 (2H, bs, H–Ar), 8.40 (2H, bs, H–Ar), 9.99 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C 11.8 (CH_3), 27.3 (CH_3), 28.5 (CH_3), 32.5 ($C(CH_3)_2$), 34.2 (NCH_2), 41.4 (CH_2), 48.7 (C), 50.8 (CH_2), 102.8 (C=COH), 108.0 (NH_2–C=C), 108.9, 122.1, 123.6, 124.2, 125.4, 127.8, 128.1, 128.5, 128.8, 132.6, 137.5, 138.0, 143.1 and 143.2 (Ar), 146.0 (C), 151.4 ($NH_{-2}CN$), 152.9 (NC=O), 177.5 (COH), 193.7 (C=O). Anal. Calcd for $C_{33}H_{31}N_5O_5$: C, 68.62; H, 5.41; N, 12.12%. Found: C, 68.71; H, 5.34; N, 12.04%.

2.2.10. 3-(5-Amino-1-(4-nitrophenyl)-3-phenyl-1H-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-5-nitroindolin-2-one ***(4k)***

Cream powder (90%); mp: 299 °C dec. IR (KBr) (ν_{max}/cm^{-1}): 3415 (OH), 3256 (NH_2 and NH), 1710 (C=O), 1626 (C=O). MS (EI, 70 eV) *m/z* (%): 594 (M^+, 10), 576 (40), 57 (100). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.97 (3H, s, CH_3), 1.02 (3H, s, CH_3), 2.03 (2H, bs, CH_2), 2.51 (2H, bs, CH_2), 6.53–7.25 (10H, m, H–Ar and NH_2), 7.94 (2H, bs, H–Ar), 8.38 (2H, bs, H–Ar), 9.81 (1H, s, NH), 9.99 (1H, s, OH). ^{13}C NMR (DMSO-d_6): δ_C 27.5 (CH_3), 28.7 (CH_3), 32.4 ($C(CH_3)_2$), 41.4 (CH_2), 48.6 (C), 50.4 (CH_2), 101.9 (C=COH), 108.1 (NH_2–C=C), 108.4, 122.0, 123.7, 124.0, 125.4, 127.6, 128.3, 128.5, 129.4, 132.5, 137.1, 138.5, 143.3 and 143.8 (Ar), 146.1 (C), 151.9 ($NH_{-2}CN$), 152.3 (NC=O), 177.8 (COH), 193.4 (C=O). Anal. Calcd for $C_{31}H_{26}N_6O_7$: C, 62.62; H, 4.41; N, 14.13%. Found: C, 62.54; H, 4.49; N, 14.19%.

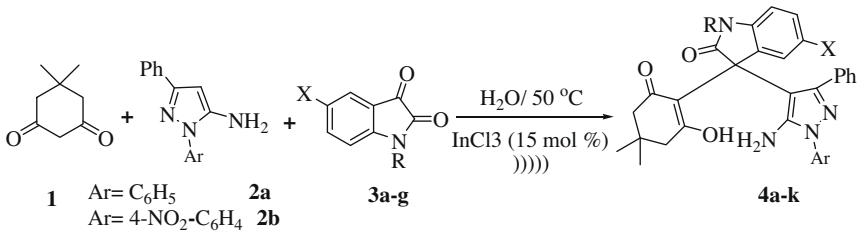
Table 1
Model reaction, conditions, and yield.[a]



1 **2a** **3a** **4a**

Entry	Conditions (°C)	Method	Catalyst (mol%)	Yield (%)
1	H_2O/50	Ultrasound	HOAc (15)	Trace
2	H_2O/50	Ultrasound	$ZnCl_2$ (15)	Trace
3	H_2O/50	Ultrasound	$LiClO_4$ (15)	55
4	H_2O/50	Ultrasound	*p*-TSA (15)	43
5	H_2O/50	Ultrasound	None	Trace
6	H_2O/50	Ultrasound	$InCl_3$ (10)	68
7	H_2O/50	Ultrasound	$InCl_3$ (15)	90
8	H_2O/50	Ultrasound	$InCl_3$ (20)	91
9	H_2O/30	Ultrasound	$InCl_3$ (15)	47
10	H_2O/40	Ultrasound	$InCl_3$ (15)	70
11	H_2O/50	High speed stirring	$InCl_3$ (15)	<30
12	THF/50	Ultrasound	$InCl_3$ (15)	75
13	THF/50	High speed stirring	$InCl_3$ (15)	<30
14	EtOH/50	Ultrasound	$InCl_3$ (15)	65
15	EtOH/50	High speed stirring	$InCl_3$ (15)	<30
16	CH_3CN/50	Ultrasound	$InCl_3$ (15)	69
17	CH_3CN/50	High speed stirring	$InCl_3$ (15)	<30

[a] 1*H*-pyrazol-5-amine (1 mmol), dimedone (1 mmol), isatin (1 mmol); reaction times = 2 h.



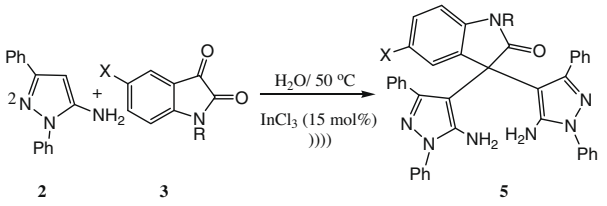
Scheme 1.

Table 2
Synthesis of oxindoles **4**.

Product **4**	R	*X*	Ar	Time (h)	Yield (%)[a]
a	H	H	C_6H_5	2	90
b	H	Br	C_6H_5	1.7	86
c	H	NO_2	C_6H_5	1.5	92
d	Me	H	C_6H_5	2	82
e	Me	Br	C_6H_5	1.8	80
f	Et	H	C_6H_5	2	83
g	Et	Br	C_6H_5	2	85
h	H	H	4-NO_2–C_6H_4	1.2	83
i	Me	H	4-NO_2–C_6H_4	1.5	89
j	Et	H	4-NO_2–C_6H_4	1.5	87
k	H	NO_2	4-NO_2–C_6H_4	1	90

[a] Isolated yields.

Table 3
Synthesis of 3,3-bis(5-amino-1*H*-pyrazol-4-yl)indolin-2-one **5**.



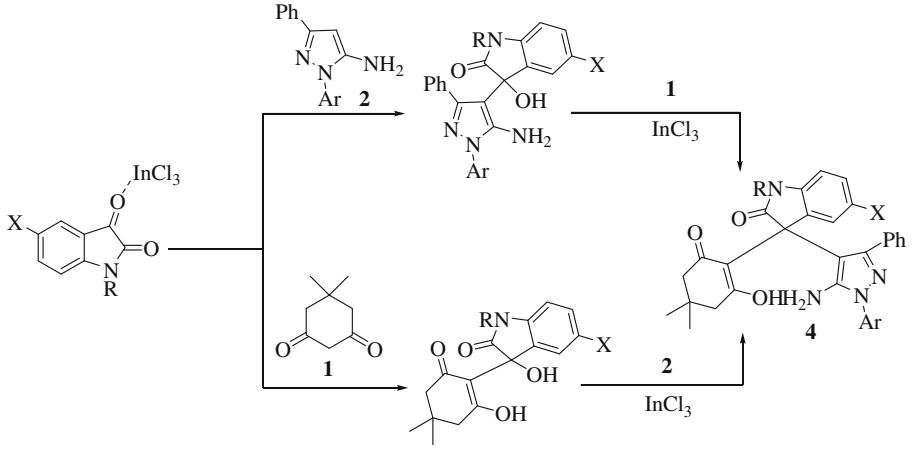
Product **5**	R	*X*	Time (h)	Yield (%)
a	H	H	50	85
b	Me	H	60	82
c	Et	H	60	80
d	H	Br	30	88
e	Me	Br	40	84
f	H	NO_2	30	91

3. Results and discussion

To achieve suitable conditions for the synthesis of 3-(5-amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-ones **4**, various reaction conditions and catalysts have been investigated in the reaction of dimedone **1**, 1,3-diphenyl-1*H*-pyrazol-5-amine **2a**, and isatin **3a** as a model reaction (Table 1). As could be seen in Table 1, the best result was obtained with a 15 mol% of $InCl_3$ as the catalyst in water at 50 °C under ultrasonic irradiation (entry 7). Using lower amount of catalyst resulted in lower yields, while higher amount of catalyst did not affect reaction times and yields (Table 1). When this reaction was carried out without $InCl_3$ or with other catalysts such as, $ZnCl_2$, $LiClO_4$, *p*-TSA, HOAc, the yield of the expected product was very low (Table 1).

To study the effect of temperature on this synthesis, we also performed three experiments in 30, 40, and 50 °C under ultrasonic irradiation (Table 1). It was observed that a lower reaction temperature led to a lower yield. To delineate the role of ultrasound and solvent effect, the reaction was investigated with and without ultrasonic irradiation at the same temperature (50 °C) in various solvents. In all reactions it was found that the use of ultrasound irradiation leads to a higher yield. Table 1 demonstrates that water is the best choice of solvent and the use of ultrasound radiation in water improves the yield of the product.

Therefore, the one-pot, three-component condensation reaction of dimedone **1**, 1*H*-pyrazol-5-amines **2a and b**, and various isatines 3a–g in the presence of $InCl_3$ (15 mol%) proceeded rapidly in water at 50 °C under ultrasonic irradiation and were complete after 1–2 h to afford 3-(5-amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-ones **4a–k**, in good yields (Scheme 1 and Table 2). ^1H and ^{13}C NMR spectra of the crude products clearly indicated the formation of oxindol **4**.



Scheme 2.

The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Compounds **4a–k** are stable solids whose structures were established by IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

To the best of our knowledge, this new procedure provides the first example of an efficient and three-component method for the synthesis of 3-(5-amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-ones. This method, based on three-component $InCl_3$-catalyzed reaction in water under ultrasonic irradiation, is the most simple and convenient and would be applicable for the synthesis of different types of oxindoles.

We have not established an exact mechanism for the formation of 3-(1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-one **4**, however, a reasonable possibility is shown in Scheme 2.

Very recently [33], we have prepared 3,3-bis(5-amino-1*H*-pyrazol-4-yl)indolin-2-ones **5** via a reaction of 1,3-diphenyl-1*H*-pyrazol-5-amine **2** with isatins **3** in the presence of *p*-TSA in refluxing water within 4–8 h. To further explore the potential of $InCl_3$-catalyzed reaction under ultrasonic irradiation for oxindoles synthesis, we investigated reaction of 1,3-diphenyl-1*H*-pyrazol-5-amine **2** with isatins **3** under similar conditions ($InCl_3/H_2O$/US) and obtained 3,3-bis(5-amino-1*H*-pyrazol-4-yl)indolin-2-ones **5** in good yields for 30–60 min (Table 3). As could be seen in Table 1, the use of ultrasound irradiation leads to a higher yield.

4. Conclusion

In conclusion, we have developed a facile, one-pot and three-component procedure for the preparation of oxindole derivatives in water under ultrasound radiations in the presence of $InCl_3$ as a nontoxic and available catalyst. The method is simple, starts from readily accessible commercial starting materials, and provides biologically interesting oxindol derivatives in good yields.

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