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A clean and highly efficient synthesis of oxindole substituted pyrrolo[2,3-*d*]pyrimidines under ultrasound irradiation

Seyyedeh Cobra Azimi*, Kurosh Rad-Moghadam

Department of Chemistry, Faculty of Sciences, University of Guilan, Rasht, Iran

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Abstract

A practical and new method for the synthesis of oxindole substituted pyrrolo[2,3-*d*]pyrimidines by the condensation of isatin, acetophenone and 6-amino-uracil under ultrasound irradiation conditions at 60 °C was described. The reaction was developed via a sequential tandem process to afford the oxindole substituted pyrrolo[2,3-*d*]pyrimidines in good to excellent yields. All reactions performed efficiently under ultrasound irradiation and results were compared with conventional heating method. In this field, several types of acetophenones, amino-uracils, and isatins were rapidly changed to the corresponding derivatives. The remarkable features of the new procedure are shorter reaction time, excellent yields, cleaner reaction profile, and simple experimental and workup procedure.

Keywords: 6-Amino-uracils; ultrasounic irradiation; pyrrolo[2,3-*d*]pyrimidines; isatin; acetophenone.

Introduction

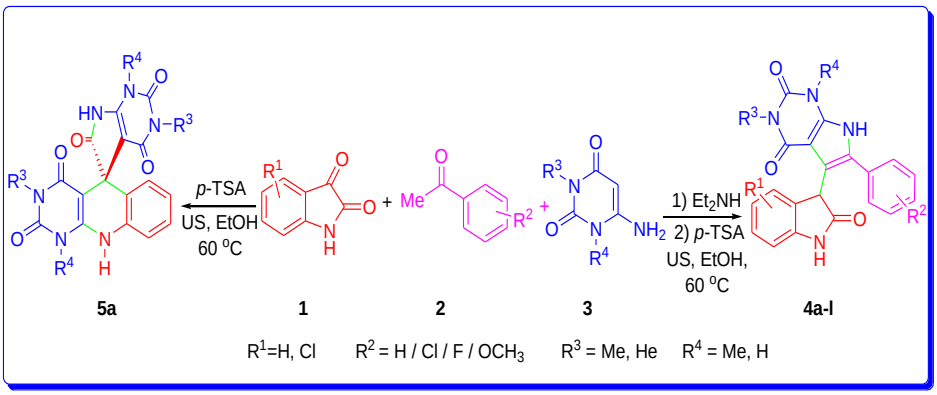
The discovery of novel synthetic methodologies and improved reactions to facilitate the preparation of organic compounds, especially the heterocycles is a pivotal focal point of research activity in the field of modern medicinal and combinatorial chemistry [1]. One of the primary motivating goals of this research is the development of cleaner, more efficient transformations to synthesize the complex organic molecules without isolating and purifying the intermediates resulting in substantial minimization of waste, labour, time and cost. The tandem reactions are effective methods in heterocyclic scaffolds for the creation of different chemical libraries of drug-like advanced compounds in organic and medicinal chemistry. Moreover, sequential tandem reactions are to combine two or more distinct reactions into a single transformation. In the mainstream of current interest, one-pot sequential tandem reactions have attracted considerable attention due to significant advantages such as convergence, elegance, atom economy, one-pot operation with maximization of molecular complexicity and rapid target-oriented synthesis [2-6].

Pyrrolo[2,3-*d*]pyrimidines-containing compounds, also known as 7-deazapurines, have been a source of research interest that represent diverse biological activities in part due to their

*Corresponding author: Seyyedeh Cobra Azimi
Tel: +98 (131) 2233271, Fax: +98 (131) 2233271
E-mail: cobra.azimi@gmail.com

resemblance to pyrimidines and purines [7,8]. A number of pyrrolo[2,3-*d*]pyrimidine derivatives have shown antibacterial [9], antiviral [10], protein kinase inhibitory [11] as well as potential anticancer activities. Naturally occurring toyocamycin, tubercidin, and sangivamycin also possess a pyrrolo[2,3-*d*]pyrimidine moiety that also includes anti-tumor [12-14], cytotoxic [15-17], antibiotic [18], and antiviral activities [19]. In addition, oxindoles are attractive targets in organic synthesis because of their significant biological activities as well as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceuticals [20-22]. Despite numerous diverse approaches toward the synthesis of pyrrolo[2,3-*d*]pyrimidine developed so far [23,24], it is still challenging to prepare 5-(2-oxindolin-3-yl) derivatives from readily available building blocks.

Utilization of ultrasound in the field of organic chemistry has got considerable attention in the last three decades [25,26]. Ultrasonic irradiation makes to the acceleration of numerous catalytic reactions in homogeneous and heterogeneous systems [27,28]. Ultrasound-assisted organic method as a green and clean synthetic method is a powerful technique that is being employed more and more to improve organic reactions and practical syntheses [29,30]. As part of our continuing efforts on the development of new routes in the synthesis of heterocyclic compounds [31-41], herein, we report a novel and efficient method for the preparation of 5-(2-oxoindolin-3-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidines 4a-l under ultrasound irradiation (Scheme 1).



Scheme 1. Synthesis of 5-(2-oxoindolin-3-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidines **4a-l** under ultrasound irradiation

Experimental

General

All of the solvents and reagents were purchased from Fluka and Merck chemical companies. Melting points were measured on an Electrothermal apparatus. IR spectra were obtained in KBr disks on a Shimadzu IR-470 spectrometer. ^{1}H- and ^{13}C NMR spectra were measured with Brucker DRX-400 AVANCE spectrometer. Mass spectra were recorded on a Shimadzu QP1100EX mass spectrometer operating at an ionization potential of 70 eV. Ultrasound assisted reactions were carried out using a EUROSONIC® 4D ultrasound cleaner with a frequency of 50 kHz and a nominal 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 60 °C.

Typical procedure for the preparation of (4a-l)

1- Conventional heating procedure

A mixture of isatin (0.147 g, 1 mmol), acetophenone (0.116 mL, 1 mmol), and diethylamine (0.015 mL, 0.15 mmol) in ethanol (95.5%, 1 mL) was heated at 60 ºC for about 15 min. To the solid obtained at this stage was added 6-amino-1,3-dimethyluracil (0.155 g, 1 mmol), *p*-toluenesulfonic acid monohydrate (0.076 g, 0.04 mmol), and EtOH (95.5%, 2 mL). The mixture was stirred and heated gently at 60 ºC. After completion of the reaction (150 minutes), as monitored by TLC using 5:1 ratio of ethyl acetate/n-hexane, the reaction mixture was cooled to room temperature and then filtered. The separated solid were filtered and the precipitate were washed with water (2×5 mL) and EtOH (95.5%, 2×5 mL) to afford the pure product **4a**.

2- Ultrasound irradiation procedure

A mixture of isatin (0.147 g, 1 mmol), acetophenone (0.116 mL, 1 mmol), and diethylamine (0.015 mL, 0.15 mmol) in ethanol (95.5%, 1 mL) was sonicated at 60 ºC for about 10 min. To the solid obtained at this stage was added 6-amino-1,3-dimethyluracil (0.155 g, 1 mmol), *p*-toluenesulfonic acid monohydrate (0.076 g, 0.04 mmol), and EtOH (95.5%, 2 mL). The mixture was stirred and heated gently at 60 ºC. After completion of the reaction, the reaction mixture was filtered and the precipitate were washed with water (2×5 mL) and EtOH (95.5%, 2×5 mL) to afford the product **4a**.

The Selected spectral data

1,3-Dimethyl-5-(2-oxoindolin-3-yl)-6-phenyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**4a**): White powder; mp 350 °C decomp. IR (KBr) (ν_{max} /cm^{-1}): 3356, 3108, 3035, 1682, 1643, 1551. MS (EI, 70 eV) m/z (%): 386 (M$^+$, 17), 381 (17), 368 (58), 313 (50), 260 (77), 236 (56), 183 (37), 152 (41), 83 (64), 57 (100). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 3.04 (3H, s, CH_3), 3.49 (3H, s, CH_3), 4.60 (1H, s, CH), 6.83 (1H, t, *J* = 7.2 Hz, ArH), 6.83 (1H, d, *J* = 7.6 Hz, ArH), 7.14 (1H, t, *J* = 7.6 Hz, ArH), 7.43 (1H, t, *J* = 7.4 Hz, ArH), 7.53 (2H, t, *J* = 7.6 Hz, ArH), 7.62 (2H, d, *J* = 7.2 Hz, ArH), 10.37 (1H, s, NH), 11.88 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_c (ppm) 27.8 (CH_3), 31.0 (CH_3), 44.2, 97.8, 109.5, 111.3, 121.2, 123.4, 127.7, 128.2, 128.3, 128.8, 129.3, 131.0, 131.2, 140.2, 144.0, 151.1, 157.8, 178.0.

6-(4-Chlorophenyl)-1,3-dimethyl-5-(2-oxoindolin-3-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine 2,4(3*H*,7*H*)-dione (**4b**): Cream powder; mp 355 °C decomp. IR (KBr) (ν_{max} /cm^{-1}): 3362, 3296, 3138, 3050, 1693, 1642, 1535. MS (EI, 70 eV) m/z (%): 422 (M$^+$, ^{37}Cl, 4), 421 (3), 420 (M$^+$, ^{35}Cl, 13), 386 (24), 368 (36), 339 (20), 313 (52), 260 (76), 236 (72), 196 (25), 149 (44), 109 (40), 83 (82), 57 (100). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 3.03 (3H, s, CH_3), 3.49 (3H, s, CH_3), 4.61 (1H, s, CH), 6.81-6.86 (2H, m , ArH), 6.89 (1H, d, *J* = 7.2 Hz, ArH), 7.14 (1H, t, *J* = 7.6 Hz, ArH), 7.58 (2H, d, *J* = 8.8 Hz, ArH), 7.63 (2H, d, *J* = 8.8 Hz, ArH), 10.39 (1H, s, NH), 11.91 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_c (ppm) 27.8 (CH_3), 31.0 (CH_3), 44.1, 97.9, 109.5, 112.0, 121.2, 123.4, 127.9, 128.3, 129.3, 129.9, 130.4, 130.8, 132.9, 140.3, 144.0, 151.0, 157.8, 177.9.

6-(4-Fluorophenyl)-1,3-dimethyl-5-(2-oxoindolin-3-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**4c**): White powder; mp 338 °C decomp. IR (KBr): 3361, 3104, 3047, 2898, 1683, 1645, 1550, 1230, 744. MS (EI, 70 eV) m/z:404 (M$^+$, 60), 386 (21), 261 (43),

245 (100), 196 (52), 152 (39), 105 (14). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.03 (3H, s, CH_3), 3.48 (3H, s, CH_3), 4.57 (1H, s, CH), 6.82 (1H, t, J = 7.4 Hz, ArH), 6.83 (1H, d, J = 7.6 Hz, ArH), 6.90 (1H, d, J = 7.6 Hz, ArH), 7.13 (1H, t, J = 7.8 Hz, ArH), 7.38 (2H, t, J = 8.6 Hz, ArH), 7.64 (2H, d.d, J_{HH} = 8.6 Hz, J_{HF} = 5.6 Hz, ArH), 10.39 (1H, s, NH), 11.90 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_c (ppm) 27.8 (CH_3), 31.0 (CH_3), 44.1, 97.8, 109.5, 111.4, 116.3 (d, 2JCF = 22 Hz), 121.2, 123.4, 127.4 (d, 4J = 1 Hz) 127.8, 130.2, 130.92 (d, 3JCF = 8.3 Hz), 130.93, 140.1, 144.0, 151.1, 157.8, 161.0 (d, 1JCF = 243 Hz), 178.0.

5-(5-Chloro-2-oxoindolin-3-yl)-1,3-dimethyl-6-phenyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**4d**): Cream powder; mp 335 °C decomp. IR (KBr): 3295, 3198, 1690, 1637, 1527, 1478. MS (EI, 70 eV) m/z :422 (M^+, ^{37}Cl, 6), 421 (M^++1, 9), 420 (M^+, ^{35}Cl, 16), 368 (25), 313 (39), 260 (43), 236 (54), 167 (20), 149 (55), 123 (24), 83 (63), 57 (100). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H 3.04 (3H, s, CH_3), 3.49 (3H, s, CH_3), 4.67 (1H, s, CH), 6.82 (1H, d, J = 8.4 Hz, ArH), 6.88 (1H, s broad, ArH), 7.18 (1H, dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, ArH), 7.43 (1H, t, J = 7.2 Hz, ArH), 7.53 (2H, t, J = 7.6 Hz, ArH), 7.60 (2H, d, J = 7.2 Hz, ArH), 10.52 (1H, s, NH), 11.92 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_c 27.8 (CH_3), 31.0 (CH_3), 44.3, 97.8, 110.4, 110.8, 123.3, 125.1, 127.7, 128.4, 128.9, 129.3, 131.0, 131.5, 133.3, 140.2, 143.0, 151.0, 157.9, 177.8.

5-(5-Chloro-2-oxoindolin-3-yl)-6-(4-chlorophenyl)-1,3-dimethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**4e**): White powder; mp 370 °C decomp. IR (KBr): 3301, 3178, 1697, 1682, 1636, 1558. MS (EI, 70 eV) m/z: 458 (3), 457 (7), 456 (M^+, ^{35}Cl, ^{37}Cl, 42), 455 (M^++1, ^{35}Cl, ^{35}Cl, 18), 454 (M^+, ^{35}Cl, ^{35}Cl, 61), 420 (28), 368 (17), 313 (36), 245 (86), 196 (44), 167 (36), 149 (82), 83(61), 57 (100). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H 3.04 (3H, s, CH_3), 3.48 (3H, s, CH_3), 4.68 (1H, s, CH), 6.84 (1H, d, J = 8.4 Hz, ArH), 6.88 (1H, s broad, ArH), 7.18 (1H, dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, ArH), 7.60 (4H, s), 10.53 (1H, s, NH), 11.95 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ_c 27.8 (CH_3), 31.0 (CH_3), 44.2, 97.8, 110.8, 111.1, 123.4, 125.2, 127.7, 129.3, 129.9, 130.2, 130.6, 133.0, 133.2, 140.4, 143.0, 151.0, 157.9, 177.6.

5-(5-Chloro-2-oxoindolin-3-yl)-6-(4-fluorophenyl)-1,3-dimethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*) dione (**4f**): White powder; mp 300 °C decomp. IR (KBr): 3307, 3104, 3053, 1698, 1682, 1634, 1553, 1223, 740. MS (EI, 70 eV) m/z:440 (M^+, ^{37}Cl, 5), 439 (M^++1, ^{35}Cl, 6), 438 (M^+, ^{35}Cl, 14), 368 (40), 329 (35), 285 (18), 264 (21), 245 (49), 167 (22), 149 (56), 83 (62), 57 (100). ^{1}H NMR (400 MHz, DMSO-d$_6$): δ_H 3.04 (3H, s, CH_3), 3.48 (3H, s, CH_3), 4.63 (1H, s, CH), 6.83 (1H, d, J = 8.4 Hz, ArH), 6.89 (1H, s broad, ArH), 7.18 (1H, dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, ArH), 7.38 (2H, t, J = 8.8 Hz, ArH), 7.63 (2H, dd, J_{HH} = 8.8 Hz, J_{HF} = 5.6 Hz, ArH), 10.53 (1H, s, NH), 11.93 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_c (ppm) 27.8 (CH_3), 31.0 (CH_3), 44.2, 97.6, 110.5, 110.8, 116.2 (d, 2JCF = 21.5 Hz), 123.4, 125.2, 127.5 (d, 4JCF = 1 Hz), 127.7, 130.5, 131.1 (d, $^3J_{CF}$ 8.3 Hz), 133.2, 140.2, 143.0, 151.0, 157.9, 162.3 (d, 1JCF = 244 Hz), 177.7 (amidic C=O). Anal. Calcd for $C_{22}H_{16}ClFN_4O_3$: C, 60.21; H, 3.67; N, 12.77%. Found: C, 60.14; H, 3.62; N, 12.82%.

6-(4-Methoxyphenyl)-1,3-dimethyl-5-(2-oxoindolin-3-yl)-1*H*-

pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**4g**): White powder; mp 360 °C decomp. IR (KBr): 3348, 3122, 3047, 1684, 1643, 1547, 1316, 1249 cm^{-1}. MS (EI, 70 eV) m/z: 417 (M^++1, 4), 385 (7), 278 (38), 255 (19), 221 (44), 193 (23), 149 (43), 129 (41), 111 (37), 97 (36), 71 (46), 43 (100). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 3.03 (3H, s, CH_3), 3.48 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 4.55 (1H, s, CH), 6.81-6.85 (2H, m, ArH), 6.90 (1H, d, *J* = 7.2 Hz, ArH), 7.09 (2H, d, *J* = 8.6 Hz, ArH), 7.15 (1H, d, *J* = 7.2 Hz, ArH), 7.53 (2H, d, *J* = 8.6 Hz, ArH), 10.36 (1H, s, NH), 11.80 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 27.7 (CH_3), 31.0 (CH_3), 44.2, 55.7 (CH_3), 97.7, 109.5, 110.4, 114.8, 121.2, 123.4, 123.6, 127.8, 130.2, 131.0, 131.1, 139.8, 143.9, 151.1, 157.8, 159.5, 178.1.

5-(5-Chloro-2-oxoindolin-3-yl)-6-(4-methoxyphenyl)-1,3-dimethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*) -dione (**4h**): Cream powder; mp 350 °C decomp. IR (KBr): 3335, 3292, 1699, 1681, 1647, 1558, 1246, 1029, 741. MS (EI, 70 eV) m/z: 452 (M^+, ^{37}Cl, 27), 451 (M^+ +1, ^{35}Cl, 23) 450 (M^+, ^{35}Cl, 100), 421 (24), 337 (15), 315 (13), 259 (12), 190 (21), 134 (43), 91 (45), 57 (62), 41 (53). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.04 (3H, s, CH_3), 3.48 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 4.61 (1H, s, CH), 6.83 (1H, d, *J* = 8.4 Hz, ArH), 6.86 (1H, s broad, ArH), 7.10 (2H, d, *J* = 8.6 Hz, ArH), 7.17 (1H, dd, ^3J = 8.4 Hz, 4*J* = 1.2 Hz, ArH), 7.52 (2H, d, *J* = 8.6 Hz, ArH), 10.50 (1H, s, NH), 11.84 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_c 27.8 (CH_3), 31.0 (CH_3), 44.3, 55.7 (OCH_3), 97.5, 109.6, 110.8, 114.8, 123.3, 123.4, 125.1, 127.7, 130.3, 131.5, 133.4, 139.9, 143.0, 151.1, 157.9, 159.6, 177.8.

5-(2-Oxoindolin-3-yl)-6-phenyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**4i**): White powder; mp 360 °C decomp. IR (KBr): 3284, 3189, 1702, 1681, 1646, 1618, 1560, 1314, 1177. MS (EI, 70 eV) m/z: 358 (M^+, 15), 327 (6), 259 (4), 180 (10), 135 (13), 127 (40), 105 (45), 97 (24), 84 (37), 55 (86), 43 (100). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.58 (1H, s, CH), 6.80-6.84 (2H, m, ArH), 6.89 (1H, d, *J* = 7.6 Hz, ArH), 7.12 (1H, t, *J* = 7.6 Hz, ArH), 7.38 (1H, t, *J* = 7.2 Hz, ArH), 7.48 (2H, t, *J* = 7.6 Hz, ArH), 7.57 (2H, d, *J* = 7.8 Hz, ArH), 10.23 (1H, s, NH), 10.34 (1H, s, NH), 11.49 (1H, s, NH), 11.72 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_c 44.2, 109.4, 110.7, 121.2, 123.4, 127.8, 128.0, 128.2, 128.5, 129.2, 130.6, 131.1, 131.4, 140.2, 144.0, 151.5, 159.0, 178.1.

6-(4-Chlorophenyl)-5-(2-oxoindolin-3-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**4j**): White powder; mp 370 °C decomp. IR (KBr): 3160, 3030, 2825, 1737, 1702, 1654, 1623, 1587, 1465. MS (EI, 70 eV) m/z: 392 (M^+-2, ^{37}Cl, 5), 391 (3), 390 (M^+-2, ^{35}Cl, 16), 279 (14), 180 (15), 139 (55), 111 (47), 91 (16), 64 (33), 44 (100). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.57 (1H, s, CH), 6.78-6.82 (2H, m, ArH), 6.88 (1H, d, *J* = 7.6 Hz, ArH), 7.12 (1H, t, *J* = 7.6 Hz, ArH), 7.53 (2H, d, *J* = 8.8 Hz, ArH), 7.57 (2H, d, *J* = 8.8 Hz, ArH), 10.26 (1H, s, NH), 10.35 (1H, s, NH), 11.53 (1H, s, NH), 11.80 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_c 44.1, 98.3, 109.4, 111.3, 121.2, 128.1, 129.2, 129.4, 129.6, 130.1, 130.2, 131.0, 132.6, 140.4, 144.0, 151.5, 159.0, 178.0.

6-(4-Fluorophenyl)-5-(2-oxoindolin-3-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**3k**): White powder; mp 360 °C decomp. IR

(KBr): 3188, 3103, 3048, 2821, 1721, 1698, 1665, 1576, 1459, 1218, 832. MS (EI, 70 eV) m/z: 376 (M^+, 14), 374 (M^+-2, 22), 345 (9), 279 (10), 180 (21), 153 (13), 123 (100), 95 (74), 75 (23), 44 (27). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.52 (1H, s, CH), 6.79-6.83 (2H, m, ArH), 6.88 (1H, d, *J* = 7.2 Hz, ArH), 7.12 (1H, t, *J* = 7.6 Hz, ArH), 7.32 (2H, t, *J* = 8.8 Hz, ArH), 7.58 (2H, dd, $^3J_{HH}$ = 8.8 Hz, $^3J_{HF}$ = 5.4 Hz, ArH), 10.24 (1H, s, NH), 10.35 (1H, s, NH), 11.51 (1H, s, NH), 11.75 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 44.1, 97.8, 109.4, 110.7, 116.1 (d, 2*J*CF = 21.5 Hz), 121.2, 123.4, 127.7, 128.5 (d, 4*J*CF = 1 Hz), 129.7, 130.7, (d, 3*J*CF = 8.2 Hz), 131.1, 140.2, 144.0, 151.5, 159.0, 162.6 (d, 1*J*CF = 236 Hz), 178.1.

6-(4-Methoxyphenyl)-5-(2-oxoindolin-3-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione (**4l**): White powder; mp 360 °C decomp. IR (KBr): 3365, 3178, 3033, 2837, 1697, 1658, 1255, 742 cm^{-1}. MS (EI, 70 eV) m/z: 388 (M^+, 6), 386 (M^+-2, 16), 357 (3), 257 (61), 186 (32), 171 (28), 155 (26), 135 (100), 92 (29), 77 (48), 44 (39). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 3.78 (3H, s, CH_3), 4.52 (1H, s, CH), 6.79-6.85 (2H, m, ArH), 6.88 (1H, d, *J* = 7.2 Hz, ArH), 7.05 (2H, d, *J* = 8.8 Hz, ArH), 7.11 (1H, t, *J* = 7.6 Hz, ArH), 7.48 (2H, d, *J* = 8.8 Hz, ArH), 10.20 (1H, s, NH), 10.33 (1H, s, NH), 11.42 (1H, s, NH), 11.62 (1H, s, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 44.2, 55.7, 98.0, 109.8, 113.6, 114.6, 121.2, 123.8, 127.7, 129.3, 129.9, 130.6, 131.3, 139.9, 144.0, 151.5, 159.0, 159.3, 178.3.

Results and discussion

To achieve suitable conditions for the synthesis of 1,3-dimethyl-5-(2-oxoindolin-3-yl)-6-phenyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione **4a**, various reaction conditions and catalysts have been investigated in the reaction of isatin **1a**, acetophenone **2a** and 6-amino-1,3-dimethyluracil **3a** as a model reaction. The two-component reaction of isatin **1a** and 6-amino-1,3-dimethyluracil **3a** in acidic conditions provides the 1,1',3,3'-tetramethyl-1*H*-spiro[pyrimido[4,5-*b*]quinoline-5,5'-pyrrolo[2,3-*d*]pyrimidine]-2,2',4,4',6'(1'*H*,3*H*,3'*H*,7'*H*,10*H*)-pentaone **5a** (Scheme 1) [35]. Moreover, under mild basic conditions the reaction of isatin **1a** and acetophenone **2a** afford the intermediate of 3-hydroxy-3-benzoylmethylindolin-2-one **6** (Scheme 2). Observing the above results, we consider the three components into a sequential tandem reaction in one pot to synthesize the oxindole substituted pyrrolo[2,3-*d*]pyrimidines simply by changing the pH of the reaction medium. In the first stage of the procedure we have a quick base-catalyzed addition of acetophenone on isatin which goes to complete in a few minutes. After changing the reaction from basic to acidic conditions, the condensation of oxindole intermediate with 6-amino-1,3-dimethyluracil **3a** to give the 5-(2-oxoindolin-3-yl)-1*H*-pyrrolo[2,3-*d*] pyrimidine **4a**. Therefore, the reaction condition for a successful tandem synthesis is very important. The results were collected in Table 1. It could be seen that the best yield of the product is obtained by the sequential use of diethylamine (15 mol%) and *p*-toluenesulfonic acid (*p*-TSA, 40 mol%) under ultrasound irradiation in ethanol at 60 ºC (Table 1, entry 8). When this reaction was carried out without *p*-toluenesulfonic acid or other catalysts such as, CH_3COOH, HCl, HOAc, the yield of the expected product was very low (Table 1, Entries 15-18). Similarly, the yields of the

reaction were unsatisfactory when it was run in ionic liquids such as [BMIm]BF_4, [BMIm]Cl and [BMIm]HSO_4 without any additional solvents or catalysts (Table 1, Entries 12-14). To study the effect of temperature on this synthesis, we also performed experiments in 30, 40, 50, and 60 ^oC under ultrasonic irradiation (Table 1). It was observed that a lower reaction temperature led to a lower yield. Also, this reaction was performed using various amounts of *p*-toluenesulfonic acid. Initially, 20 mol% *p*-toluenesulfonic acid was used to perform the reaction. But it requires slightly long reaction time. Therefore, the loading of the catalyst was gradually increased from 20 mol% to 50 mol%. It was found that 40 mol% of *p*-toluenesulfonic acid is optimal to afford the oxindole substituted pyrrolo[2,3-*d*]pyrimidine **4a** in excellent yield. The use of excess of catalyst did not alter either reaction time or yield of the product (Table 1, Entry 21). To delineate the role of ultrasound and solvent effect, the reaction was investigated with ultrasonic irradiation at 60 ^oC in various solvents. Table 1 demonstrates that ethanol is the best choice of solvent and the use of ultrasound radiation in ethanol improves the yield of the product.

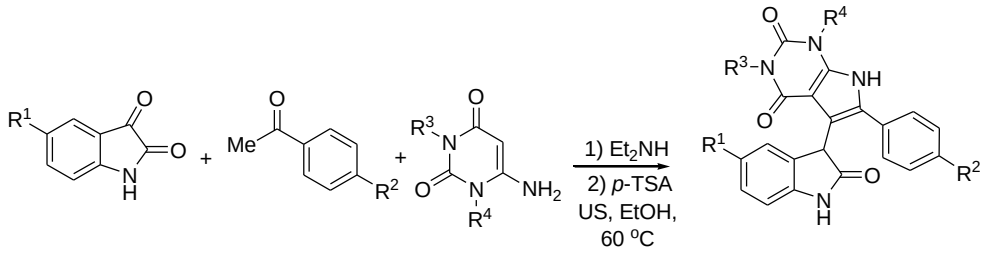
Table 1. The model reaction, conditions, and the resulting yields [a]

Entry	Conditions	Method	Catalyst (X mol%)	Yield (%)[a]
1	H_2O/ 30 ^oC	Ultrasound	*p*-TSA (40 mol%)	Trace
2	H_2O/ 40 ^oC	Ultrasound	*p*-TSA (40 mol%)	<30
3	H_2O/ 50 ^oC	Ultrasound	*p*-TSA (40 mol%)	45
4	H_2O/ 60 ^oC	Ultrasound	*p*-TSA (40 mol%)	67
5	EtOH/ 30 ^oC	Ultrasound	*p*-TSA (40 mol%)	<35
6	EtOH/ 40 ^oC	Ultrasound	*p*-TSA (40 mol%)	52
7	EtOH/ 50 ^oC	Ultrasound	*p*-TSA (40 mol%)	69
8	EtOH/ 60 ^oC	Ultrasound	*p*-TSA (40 mol%)	95
9	THF/ 60 ^oC	Ultrasound	*p*-TSA (40 mol%)	<30
10	H_2O/ EtOH/ 60 ^oC	Ultrasound	*p*-TSA (40 mol%)	79
11	CH_3CN/ 60 ^oC	Ultrasound	*p*-TSA (40 mol%)	<20
12	Solvent-free/ 60 ^oC	Ultrasound	[BMIm]BF_4 (5 mol%)	<30
13	Solvent-free/ 60 ^oC	Ultrasound	[BMIm]Cl (5 mol%)	<20
14	Solvent-free/ 60 ^oC	Ultrasound	[BMIm]HSO_4 (5 mol%)	<42
15	EtOH/ 60 ^oC	Ultrasound	HCl (5 mol%)	<30
16	EtOH/ 60 ^oC	Ultrasound	CH_3COOH (5 mol%)	<45
17	EtOH/ 60 ^oC	Ultrasound	HOAc (5 mol%)	<35
18	EtOH/ 60 ^oC	Ultrasound	-	-
19	EtOH/ 60 ^oC	Ultrasound	*p*-TSA (20 mol%)	46[b]
20	EtOH/ 60 ^oC	Ultrasound	*p*-TSA (30 mol%)	78
21	EtOH/ 60 ^oC	Ultrasound	*p*-TSA (50 mol%)	95
22	EtOH/ 60 ^oC	Reflux	*p*-TSA (40 mol%)	82[c]
23	H_2O/EtOH/ 60 ^oC	Reflux	*p*-TSA (40 mol%)	72[c]
24	H_2O/ 60 ^oC	Reflux	*p*-TSA (40 mol%)	56[c]

[a]Isatin 1a (1 mmol), acetophenone 2a (1 mmol) and 6-amino-1,3-dimethyluracil 3a (1 mmol); reaction time= 15 min.
[b]Reaction time= 180 min.
[c]Reaction time= 150 min.

In order to apply this reaction to a library synthesis, we have extended the reaction of isatin derivatives, acetophenones, and amino-uracils under similar conditions (ethanol/60 °C/ultrasound/*p*-TSA), furnishing the respective 5-(2-oxoindolin-3-yl)-1*H*-pyrrolo[2,3-*d*]pyrimidines **4a-l** in good yields (Table 2). To the best of our knowledge, this new procedure provides the first example of an efficient method for the synthesis of oxindole substituted pyrrolo[2,3-*d*]pyrimidines under ultrasound irradiation. On the other hand, when comparing the results obtained using conventional heating with ultrasound assisted method, we can conclude that the main advantages of ultrasound are the significant decrease of reaction times and improvement of yields (Table 2). The structures of compounds **4a-l** were confirmed by IR, ^{1}H and ^{13}C NMR and Mass spectroscopy. The IR spectrum of compound **4b**, for example, show absorption bands at 3362, 3296, 3138, 3050, 1693, 1642, and 1535 cm^{-1} indicating the presence of N-H and C=O groups in this molecule. In ^{1}H NMR spectrum **4b**, aromatic protons of this compound were seen at δ 6.81-7.63 with proper integrals and splittings. Aliphatic region of this spectrum exhibits two singlet peaks at δ 3.03, and 3.49 arising from protons of the methyl groups along with the characteristic sharp signal of the methine proton at δ 4.61. In addition, there are two singlet signals appeared at δ 10.39 and 11.91 in the spectrum accounting for the presence of two N-H groups in the molecule. The ^{13}C NMR spectrum of **4b** displays 20 distinct lines with appropriate chemical shifts corresponding to the structure of this compound.

Table 2. Synthesis of the pyrrolo[2,3-*d*]pyrimidines **4a-l** [a]

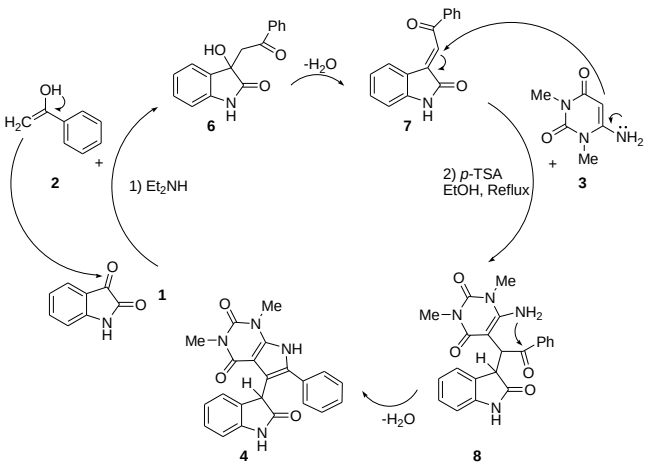


Product	R^1	R^2	R^3	R^4	Ultrasound Time (min)/ Yield (%)	Conventional heating[b] Time (min)/ Yield (%)
4a	H	H	Me	Me	15/95	150/82
4b	H	Cl	Me	Me	20/90	150/83
4c	H	F	Me	Me	20/91	130/88
4d	Cl	H	Me	Me	15/89	140/81
4e	Cl	Cl	Me	Me	20/85	150/79
4f	Cl	F	Me	Me	15/92	140/89
4g	H	OCH_3	Me	Me	20/93	140/87
4h	Cl	OCH_3	H	H	15/91	150/89

4i	H	H	H	H	15/90	160/84
4j	H	Cl	H	H	20/96	150/86
4k	H	F	H	H	15/94	140/87
4l	H	OCH_3	H	H	15/92	145/88

[a]Isolated yields.
[b]Conventional heating 60 ºC.
[c]Reaction time= 150 min.

The possible mechanism for the synthesis of 5-(2-oxoindolin-3-yl)-pyrrolo[2,3-*d*] pyrimidine-2,4(3*H*,7*H*)-diones **4a-l** is outlined in Scheme 2. The first step is believed to be the base-catalyzed nucleophilic addition of acetophenones onto isatins to afford 3-hydroxy-3-aroylmethylindolin-2-ones **6** undergo dehydration to give 3-aryloylmethylideneindolin-2-one **7**. The 6-amino-1,3-dimethyluracil **3** attacks to the adduct **7** in a michael-type fashion to produce intermediate **8**. This intermediate undergoes intramolecular cyclization by the reaction of nucleophilic amino function to carbonyl group followed by dehydration to form product **4**.



Scheme 2. A reasonable path for formation of the 5-(2-oxoindolin-3-yl)-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione **4a**

Conclusion

In conclusion, we have described an expedient and new method for the synthesis of 5-(2-oxoindolin-3-yl)-pyrrolo[2,3-*d*] pyrimidine-2,4(3*H*,7*H*)-dione. This procedure has the advantage of shorter reaction time relative to common methods with an efficient yield.

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