RESEARCH PAPER

Nano-Fe_3O_4@SiO_2/$SnCl_4$ Promoted Synthesis of Indenopyrido[2,3-d] Pyrimidine Derivatives in Water

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ARTICLE INFO

Article History:
Received 12 April 2024
Accepted 26 June 2024
Published 01 July 2024

Keywords:
1,3-Indanedione
Indenopyrido[2,3-d] pyrimidines
6-Amino-2-(methylthio) pyrimidin-4(3H)-one
Multicomponent reaction
Nano-Fe_3O_4@SiO_2/$SnCl_4$

ABSTRACT

Pyrido[2,3-d]pyrimidine derivatives show variable biological activities such as anticancer, antitumor, antiviral, antihistaminic, anti-inflammatory and antibacterial. In this work, an efficient and environment friendly method for one-pot synthesis of indenopyrido[2,3-d]pyrimidine derivatives was developed in the presence of nano-Fe_3O_4@SiO_2/$SnCl_4$ nanoparticles in water. Indenopyrido[2,3-d]pyrimidines were synthesized via three-component couplings of 6-amino-2-(methylthio)pyrimidin-4(3H)-one, aldehydes and 1,3-indanedione under heating or ultrasound irradiation conditions in water. The structure of the obtained products was approved by FT-IR, ^{1}H NMR and ^{13}C NMR techniques. The mild reaction conditions, green and cost-effective catalyst, excellent yields, and easy work-up procedures, which avoid the use of large volumes of hazardous organic solvents, make it a useful protocol.

How to cite this article
Araqi R., Basharnavaz H., Mirjalili B., Bamoniri A. Nano-Fe_3O_4@SiO_2/$SnCl_4$ Promoted Synthesis of Indenopyrido[2,3-d] Pyrimidine Derivatives in Water. J Nanostruct, 2024; 14(3):963-970. DOI: 10.22052/JNS.2024.03.024

INTRODUCTION

Pyridopyrimidines are nitrogen-bearing heterocyclic compounds which have various pharmaceutical applications. In particular, pyrido[2,3-*d*]pyrimidine derivatives show variable biological activities such as anticancer agents inhibiting dihydrofolate reductases or tyrosine kinases [1], antitumor [2], antiviral [3], antihistaminic [4], anti-inflammatory [5], antibacterial [6], and also act as cyclin-dependent kinase 4 inhibitors [7]. This structural moiety is present in ramastine (anti-allergic) [8] and pirenperone (tranquilizer) [9]. As a result, the compounds of this class have attracted considerable interest for research. Several MCR methods have been reported for the synthesis of pyrido[2,3-*d*]pyrimidines [10]. Although most of these methods offer distinct advantages, some of them still have their own limitations in terms of yields, longer reaction times and difficult work-ups. In some cases, the used catalysts are harmful to the environment and cannot be reused. Therefore, an efficient method for the preparation of pyrido[2,3-*d*]pyrimidine derivatives is still desirable. In this work, we wish to report an efficient and eco-friendly procedure for the preparation of indenopyrido[2,3-*d*]pyrimidine in the presence of nano-Fe_3O_4@SiO_2/$SnCl_4$ [11,12].

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MATERIALS AND METHODS

Materials and apparatus

Chemicals and solvents were purchased from

Merck and Aldrich Companies. FT-IR spectra were recorded as KBr pellet on a Bruker, Equinox 55 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker DRX-400 in DMSO-d_6 as solvent and TMS as an internal standard. Melting points were obtained with a Buchi melting point B-540 B.V.CHI apparatus. Ultrasonic irradiations were done using Elmasonic S 40H ultrasonic cleaning.

General procedure for the synthesis of indenopyrido[2,3-d]pyrimidines

A mixture of 6-amino-2-(alkylthio) pyrimidin-4(3*H*)-one (1 mmol), 1, 3-indanedione (1 mmol), aldehydes (1 mmol), nano-Fe_3O_4@SiO_2/$SnCl_4$ (0.03 g) and 8 ml of water was heated under reflux or ultrasonic cleaning unit at 70 ºC. The progress of the reaction was monitored by TLC (EtOAc: petroleum ether, 7:3). After completion of the reaction, the catalyst was separated by an external magnet and reused for the next experiment. The reaction mixture was cooled to room temperature and then poured in to cold water. The solid product was filtered and washed with boiling water and recrystallized from ethanol to give the pure product in excellent yield.

Spectral data for selected compounds

5-(4-Chlorophenyl)-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6(5*H*, 11*H*)-dione (4a).

Red Powder; M.P. >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3251, 3126, 3037, 2926, 1646, 1543, 1498, 1452, 1355, 1274, 1185, 1086, 902, 834, 746, 713; ^{1}H NMR (ppm): δ 2.60 (s, 3H, CH_3), 4.82 (s, 1H, CH), 7.30–7.25 (m, 5H, Ar-H), 7.36 (t, 1H, *J* = 7.40 Hz, Ar-H), 7.45 (t, 1H, *J* = 7.40 Hz, Ar-H), 7.79 (d, 1H, *J* = 7.20 Hz, Ar-H), 11.13 (brs, 1H, NH), 12.60 (brs, 1H, CO–NH); ^{13}C NMR (ppm): δ 13.3 (Me), 34.2 (CH), 99.9, 107.9, 120.4, 120.9, 128.4, 130.1, 130.8, 131.2, 132.4, 133.6, 136.6, 137.5, 144.8, 153.5, 155.8, 161.5 (CONH), 191.1 (C=O).

5-(4-Bromophenyl)-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6(5*H*, 11*H*)-dione (4b).

Red Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3220, 3125, 3032, 2926, 1644, 1543, 1497, 1450, 1353, 1272, 1185, 1074, 966, 901, 834, 711; ^{1}H NMR (ppm): δ 2.60 (s, 3H, CH_3), 4.80 (s, 1H, CH), 7.21 (d, 2H, *J* = 7.60 Hz, Ar-H), 7.26 (d, 1H, *J* = 6.80 Hz, Ar-H), 7.35 (t, 1H, *J* = 7.20 Hz, Ar-H), 7.42 (m, 3H, Ar-H), 7.79 (d, 1H, *J* = 6.80 Hz, Ar-H), 11.12 (br s, 1H, NH), 12.58 (br s, 1H, CO–NH); ^{13}C NMR (ppm): δ 13.3 (Me), 34.3 (CH), 99.9, 107.8, 119.7, 120.4, 120.9, 129.6, 130.5, 130.8, 131.3, 132.4, 133.6, 136.6, 145.2, 155.8, 162.1 (CONH), 191.1 (C=O).

5-(4-Fluorophenyl)-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6(5*H*, 11*H*)-dione (4c).

Red Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3117, 3026, 2923, 2850, 1644, 1542, 1499, 1455, 1358, 1276, 1225, 1187, 962, 902, 842, 711; ^{1}H NMR (ppm): δ 2.60 (s, 3H, CH_3), 4.83 (s, 1H, CH), 7.07–7.01 (m, 4H, Ar-H), 7.26 (d, 2H, *J* = 6.40 Hz, Ar-H), 7.35 (t, 1H, *J* = 7.40 Hz, Ar-H), 7.45 (t, 1H, *J* = 7.20 Hz, Ar-H), 7.79 (d, 1H, *J* = 7.20 Hz, Ar-H), 11.10 (br s, 1H, NH), 12.56 (br s, 1H, CO–NH); ^{13}C NMR (ppm): δ 13.3 (Me), 34.0 (CH), 99.6, 108.1, 114.9 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 120.3, 120.7, 129.9 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 130.6, 132.1, 133.9, 136.8, 142.6, 153.3, 156.1, 158.9, 160.6 (d, $^1J_{C\text{-}F}$ = 240.0 Hz), 191.0 (C=O).

5-(2-Bromophenyl)-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6(5*H*, 11*H*)-dione (4d).

Red Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3230, 3123, 3048, 2936, 2849, 1645, 1549, 1499, 1455, 1349, 1273, 1188, 1038, 963, 890, 768, 712; ^{1}H NMR (ppm): δ 2.60 (s, 3H, CH_3), 5.24 (s, 1H, CH), 7.06 (dt, 1H, *J* = 8.40 Hz, 2.20 Hz, Ar-H), 7.28–7.21 (m, 3H, Ar-H), 7.35 (t, 1H, *J* = 7.40 Hz, Ar-H), 7.48–7.43 (m, 2H, Ar-H), 7.80 (d, 1H, *J* = 7.20 Hz, Ar-H), 11.11 (br s, 1H, NH), 12.26 (br s, 1H, CO–NH); ^{13}C NMR (ppm): δ 13.3 (Me), 35.7 (CH), 100.0, 107.8, 120.4, 120.7, 123.4, 128.1, 128.4, 130.7, 132.0, 132.2, 132.8, 133.6, 136.6, 136.7, 144.9, 153.7, 155.6, 162.1 (CONH), 190.7 (C=O).

5-(2-Chlorophenyl)-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6(5*H*, 11*H*)-dione (4e).

Red Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3238, 3142, 3067, 2975, 2924, 2851, 1648, 1544, 1491, 1440, 1349, 1265, 1186, 1043, 961, 900, 825, 757; ^{1}H NMR (ppm): δ 2.60 (s, 3H, CH_3), 5.24 (s, 1H, CH), 7.15 (d, 1H, *J* = 7.20 Hz, Ar-H), 7.21 (t, 2H, *J* = 7.40 Hz, Ar-H), 7.29 (d, 2H, *J* = 7.20 Hz,Ar-H), 7.35 (t, 1H, *J* = 7.20 Hz, Ar-H), 7.44 (t, 1H, *J* = 7.20 Hz, Ar-H), 7.79 (d, 1H, *J* = 7.20 Hz, Ar-H), 11.10 (br s, 1H, NH), 12.49 (br s, 1H, CO–NH); ^{13}C NMR

(ppm): δ 13.3 (Me), 33.3 (CH), 99.9, 107.6, 120.4, 120.7, 127.4, 128.1, 129.5, 130.7, 131.9, 132.2, 132.9, 133.6, 136.6, 143.1, 153.7, 155.9, 162.1 (CONH), 190.7 (C=O).

5-(2,4-Dichlorophenyl)-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6(5*H*,11*H*)-dione (4g).

Red Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3432, 3149, 3068, 2928, 1650, 1548, 1502, 1452, 1352, 1274, 1188, 1050, 967, 901, 856, 763, 706; ^{1}H NMR (ppm): δ 2.60 (s, 3H, CH_3), 5.22 (s, 1H, CH), 7.23 (d, 1H, *J* = 6.40 Hz, Ar-H), 7.37–7.27 (m, 3H, Ar-H), 7.47–7.44 (m, 2H, Ar-H), 7.80 (d, 1H, *J* = 7.20 Hz, Ar-H), 11.13 (br s, 1H, NH), 12.52 (br s, 1H, CO–NH); ^{13}C NMR (ppm): δ 13.3 (Me), 33.0 (CH), 99.4, 107.1, 120.5, 120.7, 127.6, 128.7, 130.8, 131.7, 132.2, 133.0, 133.5, 133.9, 142.3, 136.6, 153.8, 156.0, 162.0 (CONH), 190.7 (C=O).

5-(2-Hydroxyphenyl)-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6(5*H*,11*H*)-dione (4h).

Orang Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3377, 3131, 3068, 2931, 1694, 1646, 1619, 1556, 1500, 1443, 1405, 1353, 1277, 1223, 1193, 970, 899, 763, 711; ^{1}H NMR (ppm): δ 2.59 (s, 3H, CH_3), 4.98 (s, 1H, CH), 6.72–6.69 (m, 2H, Ar-H), 7.03–7.0 (m, 2H, Ar-H), 7.25 (d, 1H, *J* = 6.80 Hz, Ar-H), 7.35 (t, 1H, *J* = 7.40 Hz, Ar-H), 7.45 (t, 1H, *J* = 7.40 Hz, Ar-H), 7.79 (d, 1H, *J* = 7.20 Hz, Ar-H), 9.58 (br s, 1H, NH), 11.12 (s, 1H, OH), 12.73 (br s, 1H, CO–NH); ^{13}C NMR (ppm): δ 13.3 (Me), 29.6 (CH), 100.0, 107.9, 117.5, 120.0, 120.2, 120.8, 127.9, 130.0, 130.6, 132.3, 133.8, 136.8, 136.9, 154.8, 155.0, 156.4, 156.5, 163.9 (CONH), 191.1 (C=O).

5-Phenyl-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6(5*H*,11*H*)-dione (4i).

Red Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3433, 3024, 2922, 2848, 1719, 1647, 1541, 1497, 1453, 1357, 1275, 1189, 966, 902, 744, 701; ^{1}H NMR (ppm): δ 2.60 (s, 3H, CH_3), 4.82 (s, 1H, CH), 7.15–7.11 (m, 1H, Ar-H), 7.26–7.21 (m, 4H, Ar-H), 7.34 (t, 2H, *J* = 7.40 Hz, Ar-H), 7.44 (t, 1H, *J* = 7.60 Hz, Ar-H), 7.78 (d, 1H, *J* = 7.20 Hz, Ar-H), 11.07 (br s, 1H, NH), 12.55 (br s, 1H, CO–NH); ^{13}C NMR (ppm): δ 13.3 (Me), 34.5 (CH), 100.0, 108.5, 120.3, 120.8, 126.6, 127.4, 128.2, 128.5, 130.6, 132.3, 133.7, 136.7, 146.0, 153.3, 155.7, 162.5 (CONH), 191.1 (C=O).

5-(p-Tolyl)-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6 (5*H*,11*H*)-dione (4j).

Red Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3490, 3227, 3126, 3027, 2925, 1647, 1539, 1545, 1499, 1450, 1355, 1272, 1186, 963, 788, 710; ^{1}H NMR (ppm): δ 2.21 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 4.77 (s, 1H, CH), 7.03 (d, 2H, *J* = 7.20 Hz,Ar-H), 7.12 (d, 2H, *J* = 7.20 Hz, Ar-H), 7.25 (d, 1H, *J* = 6.40 Hz, Ar-H), 7.34 (t, 1H, *J* = 7.20 Hz, Ar-H), 7.44 (t, 1H, *J* = 7.20 Hz, Ar-H), 7.77 (d, 1H, *J* = 6.80 Hz, Ar-H), 11.04 (br s, 1H, NH), 12.54 (br s, 1H, CO–NH); ^{13}C NMR (ppm): δ 13.3 (Me), 21.0 (Me), 34.1 (CH), 100.2, 108.7, 120.2, 120.8, 128.0, 128.4, 129.0, 130.6, 132.3, 133.7, 135.6, 136.8, 143.1, 153.2, 155.5, 162.4 (CONH), 191.1 (C=O).

5-(4-Methoxyphenyl)-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6(5*H*,11*H*)-dione (4k).

Red Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3212, 2920, 2853, 1675, 1639, 1605, 1551, 1489, 1437, 1349, 1262, 1218, 1187, 1146, 1020, 967, 901, 837, 768, 704; ^{1}H NMR (ppm): δ 2.59 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 4.76 (s, 1H, CH), 6.79 (d, 2H, *J* = 8.20 Hz, Ar-H), 7.14 (d, 2H, *J* = 8.20 Hz, Ar-H), 7.26 (d, 1H, *J* = 7.20 Hz, Ar-H), 7.35 (t, 1H, *J* = 7.20 Hz,Ar-H), 7.44 (t, 1H, *J* = 7.40 Hz, Ar-H), 7.78 (d, 1H, *J* = 6.80 Hz, Ar-H), 11.03 (br s, 1H, NH), 12.53 (br s, 1H, CO–NH); ^{13}C NMR (ppm): δ 13.3 (Me), 33.6 (CH), 55.4 (MeO), 95.0, 108.7, 112.8, 113.9, 120.2, 120.8, 129.1, 130.6, 132.3, 133.7, 136.8, 138.2, 155.4, 158.1, 161.5 (CONH), 191.2 (C=O).

5-(3,4-Dimethoxyphenyl)-2-(methylthio)-3*H*-indeno[5,6:1′,2′]pyrido[2,3-*d*]pyrimidine-4,6 (5*H*,11*H*)-dione (4l).

Red Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3390, 3233, 3141, 3063, 2933, 2845, 1656, 1602, 1553, 1505, 1451, 1345, 1268, 1180, 1140, 1025, 963, 899, 766, 712; ^{1}H NMR (ppm): δ 2.60 (s, 3H, SCH_3), 3.67 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.79 (s, 1H, CH), 6.64 (d, 1H, *J* = 8.40 Hz, Ar-H), 6.74 (d, 1H, *J* = 8.40Hz, Ar-H), 6.95 (s, 1H, Ar-H), 7.27 (d, 1H, *J* = 6.80 Hz, Ar-H), 7.34 (t, 1H, *J* = 7.20 Hz, Ar-H), 7.43 (t, 1H, *J* = 7.20 Hz, Ar-H), 7.77 (d, 1H, *J* = 7.20 Hz, Ar-H), 11.01 (br s, 1H, NH), 12.54 (br s, 1H, CO–NH); ^{13}C NMR (ppm): δ 13.3 (Me), 33.9 (CH), 55.9 (MeO), 56.0 (MeO), 100, 108.5, 112.3, 112.6, 119.8, 120.2, 120.8, 130.6, 132.3, 133.7, 136.7, 138.6, 147.8, 148.6, 155.4, 162.5 (CONH), 191.2 (C=O).

5-(4-Hydroxy-3-methoxyphenyl)-2-(methylthio)-3*H*-indeno[2',1':5,6]pyrido[2,3-*d*]pyrimidine-4,6(5*H*,11*H*)-dione (4m).

Red Powder; M.p.: >300 °C; FT-IR (KBr, ῡ, cm^{-1}): 3341, 3067, 2924, 2843, 1690, 1651, 1567, 1505, 1453, 1340, 1273, 1243, 1219, 1170, 1149, 1040, 956, 898, 792, 709; ^{1}H NMR (ppm): δ 2.60 (s, 3H, SCH_3), 3.72 (s, 3H, OCH_3), 4.74 (s, 1H, CH), 6.51 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.63 (d, 1H, *J* = 8. 0 Hz, Ar-H), 6.91 (s, 1H, Ar-H), 7.27 (d, 1H, *J* = 7.20 Hz, Ar-H), 7.35 (t, 1H, *J* = 7.40 Hz, Ar-H), 7.44 (t, 1H, *J* = 7.20 Hz, Ar-H), 7.77 (d, 1H, *J* = 7.20 Hz, Ar-H), 8.76 (s, 1H, OH), 11.01 (br s, 1H, NH), 12.55 (br s, 1H, CO–NH); ^{13}C NMR (ppm): *δ* 13.3 (Me), 33.8 (CH), 56.1 (MeO), 100, 108.7, 112.9, 115.6, 120.0, 120.2, 120.8, 130.6, 132.3, 133.7, 136.8, 137.1, 145.5, 147.4, 155.4, 162.1 (CONH), 191.3 (C=O).

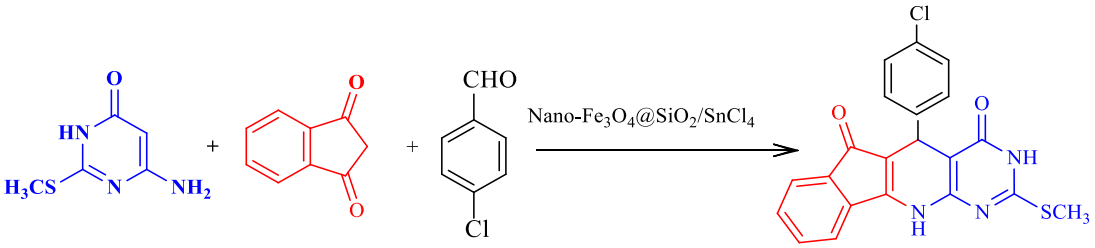
RESULTS AND DISCUSSION

Following our continued studies in the development of benign methods [11-20], we have examined the synthesis of indenopyrido[2,3-*d*] pyrimidine in the presence of nano-Fe_3O_4@SiO_2/$SnCl_4$. For this purpose, multi-component condensation reactions of 6-amino-2-(methylthio) pyrimidin-4(3*H*)-one, aryl aldehydes and 1, 3-indanedione were done.

To optimize the desired reaction conditions, the preparation of 5-(4-chlorophenyl)-2-(methylthio)-3*H*-indeno[2,1:5,6]pyrido[2,3-*d*]pyrimidine-4,6-(5*H*,11*H*)-dione (4a) was selected as the model reaction. In initial experiments, the effects of solvents and reaction temperature were evaluated for this model reaction in the presence of nano-Fe_3O_4@SiO_2/$SnCl_4$, and results are summarized in tables 1. It is evident from the results that using nano-Fe_3O_4@SiO_2/$SnCl_4$ as catalyst in water at 70 ˚C is the most effective condition producing the higher yield product (4a, 90%) in lower reaction time (Table 1, Entry 4).

Using the best obtained reaction condition, we have also established the amount of the catalyst required for the model reaction in water (Table 2). The obtained results showed that, in the absence of a catalyst, no significant product was obtained, and in the presence of nano-Fe_3O_4@SiO_2/$SnCl_4$, the reaction was carried out with high yields. For example, the synthesis of a model compound under ultrasound irradiation in the presence of 0.01 g nano-Fe_3O_4@SiO_2/$SnCl_4$ per 1 mmol of any substrate produced a high yield (90%) of product in H_2O at 70 ºC after 4 min. Increasing the amount of catalyst to 0.02 g and 0.03 g resulted in increasing the yield to 94% and 98% after 3 and

Table 1. Synthesis of 5-(4-chlorophenyl)-2-(methylthio)-3H-indeno[2',1':5,6]pyrido[2,3-d]pyrimidine-4,6-(5H,11H)-dione (model compound) using various solvents under reflux or ultrasound irradiation. [a]



Entry	Solvent	Method I (Δ)		Method II (US)	
		T (°C)/Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	H_2O	25/70	60	12	70
2	H_2O	50/60	75	7	85
3	H_2O	60/50	80	5	90
4	H_2O	70/40	85	4	90
5	H_2O	80/40	85	4	90
6	EtOH	70/70	75	7	82
7	MeOH	60/80	60	8	70
8	Acetone	50/70	50	10	60
9	CH_3CN	80/90	40	12	50
10	DMF	120/50	70	6	80
11	HOAc	110/60	70	7	75
12	Solvent-free	120/60	80	6	85

[a] 4-Cl-benzaldehyde (1 mmol), 1,3-indanedione (1 mmol), 6-amino-2-(methylthio)pyrimidin-4(*3H*)-one (1 mmol), and nano-Fe_3O_4@SiO_2/$SnCl_4$ (0.01 g). [b] Isolated yields.

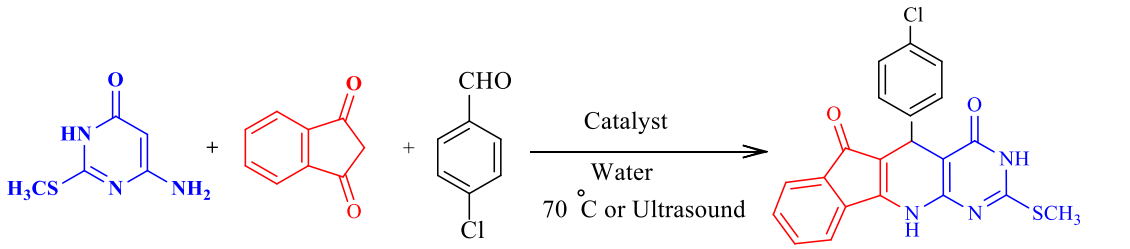
2 min respectively. Therefore, the best result was obtained using 0.03 g nano-Fe_3O_4@SiO_2/$SnCl_4$ and 1 mmol of any substrate. Notably, the increase of the catalyst in reflux and ultrasound irradiation conditions did not show any significant changes in yield or time of reaction (Entry 9, Table 2).

Using the optimal conditions described in this report, several derivatives of indenopyrido[2,3-*d*] pyrimidines (4a–m) were prepared in high yields (94–99 %) and short reaction times (1.5–3 min) (Fig. 1 and Table 3).

No obvious effect of the electronic nature of the substituent in the aromatic aldehydes ring was observed. Aromatic aldehydes containing electron-donating groups (such as methoxy and methyl groups) or electron-withdrawing groups (such as halides and nitro groups) were employed and reacted to give the corresponding products 4a–m in high yield under the optimized reaction conditions. The structure of all products was established by spectroscopic methods (IR, ^{1}H NMR and ^{13}C NMR).

In all cases, when the reactions were carried out under ultrasound irradiation, the times of

Table 2. Synthesis of 5-(4-chlorophenyl)-2-(methylthio)-3*H*-indeno[2′,1′:5,6]pyrido[2,3-*d*] pyrimi dine-4,6-(5*H*,11*H*)-dione (model compound) using nano-Fe_3O_4@SiO_2/$SnCl_4$ under heating (I) and ultrasound irradiation (II) in water [a].



Entry	Method I (Δ)		Method II (US)	
	Catalyst (g)		Catalyst (g)	
	Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	none		none	
	120	35	20	40
2	Fe_3O_4@SiO_2 (0.10)		Fe_3O_4@SiO_2 (0.10)	
	30	55	10	60
3	nano-Fe_3O_4 (0.10)		nano-Fe_3O_4 (0.10)	
	30	70	10	75
4	$SnCl_4$/SiO_2 (0.10)		$SnCl_4$/SiO_2 (0.10)	
	50	60	12	70
5	Fe_3O_4@SiO_2/$SnCl_4$ (0.005)		Fe_3O_4@SiO_2/$SnCl_4$ (0.005)	
	45	75	7	80
6	Fe_3O_4@SiO_2/$SnCl_4$ (0.01)		Fe_3O_4@SiO_2/$SnCl_4$ (0.01)	
	40	85	4	90
7	Fe_3O_4@SiO_2/$SnCl_4$ (0.02)		Fe_3O_4@SiO_2/$SnCl_4$ (0.02)	
	30	85	3	94
8	Fe_3O_4@SiO_2/$SnCl_4$ (0.03)		Fe_3O_4@SiO_2/$SnCl_4$ (0.03)	
	20	88	2	98
9	Fe_3O_4@SiO_2/$SnCl_4$ (0.04)		Fe_3O_4@SiO_2/$SnCl_4$ (0.04)	
	20	88	2	98

[a] 4-Cl-benzaldehyde (1 mmol), 1,3-indanedione (1 mmol), 6-amino-2-(methylthio)pyrimidin-4(3*H*)-one (1 mmol) and water (8 mL) at 70 °C. [b]Isolated yields.

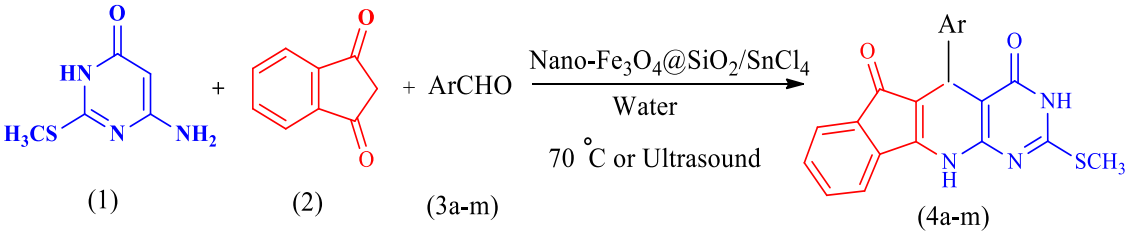


Fig. 1. Synthesis of indenopyrido[2,3-d]pyrimidine derivatives

Table 3. Synthesis of indenopyrido[2,3-*d*]pyrimidine derivatives under heating (method I) and sonication (method II) conditions [a].

Product	Ar	Time (min) / Yield (%)[b]	
		Method I (Δ)	Method II (US)
4a	4-ClC_6H_4	20 / 88	2 / 98
4b	4-BrC_6H_4	20 / 86	2 / 98
4c	4-FC_6H_4	18 / 90	1.50 / 99
4d	2-BrC_6H_4	24 / 88	2 / 97
4e	2- ClC_6H_4	24 / 89	2 / 97
4f	2- $NO_2C_6H_4$	24 / 88	2 / 96
4g	2,4-$Cl_2C_6H_3$	20 / 89	2 / 98
4h	2-OHC_6H_4	28 / 84	2.5 / 95
4i	C_6H_5	30 / 80	3 / 94
4j	4-MeC_6H_4	28 / 85	2.5 / 95
4k	4-$OMeC_6H_4$	28 / 85	2.5 / 96
4l	3,4-$OMe_2C_6H_3$	27 / 86	2.5 / 97
4m	4-OH-3-$OMeC_6H_3$	27 / 86	2.5 / 96

[a] Arylaldehyde (1 mmol), 1,3-indanedione (1 mmol), 6-amino-2-(mrthylthio)pyrimidin-4(3*H*)-one (1 mmol), water (8 mL) and nano-Fe_3O_4@SiO_2-$SnCl_4$ (0.01 g) at 70 ºC, [b] Isolated yields.

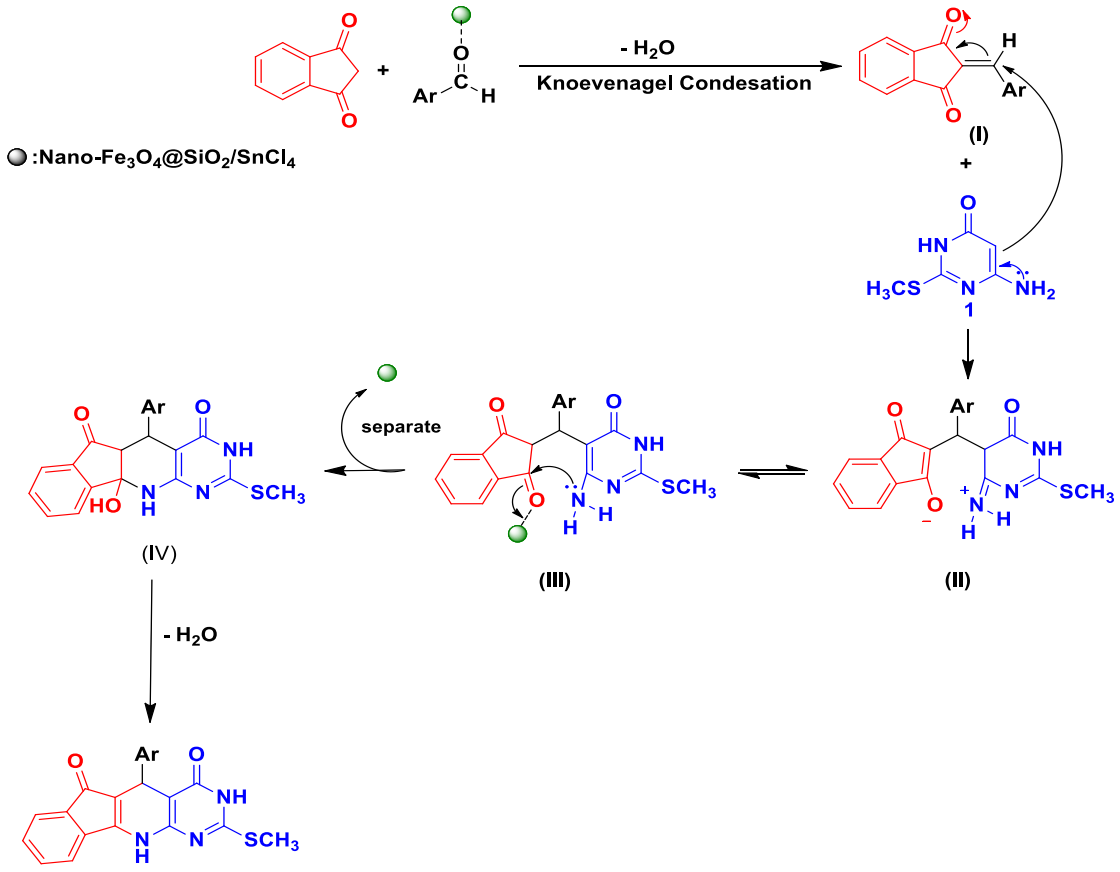


Fig. 2. Proposed mechanism for the synthesis of indenopyrido[2,3-*d*]pyrimidines in the presence of nano-Fe_3O_4@SiO_2/$SnCl_4$

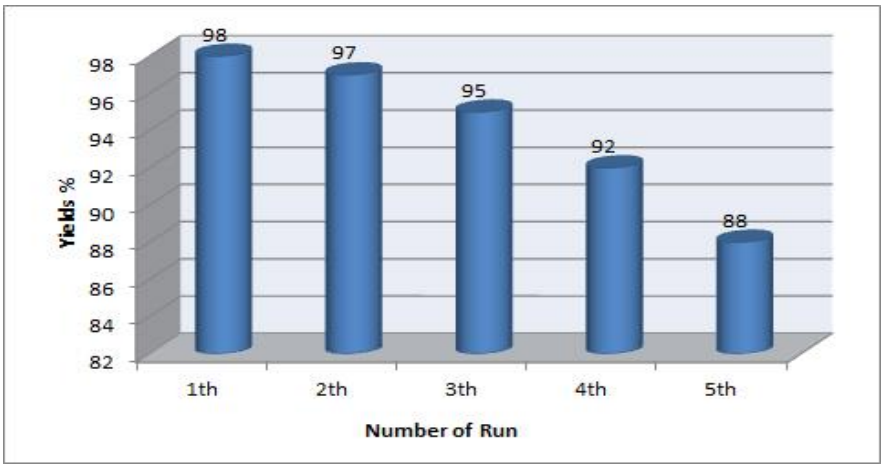


Fig. 3. Reusability study of nano-Fe_3O_4@SiO_2/$SnCl_4$

the reactions were shorter and the yields of the products were higher than with the heating method.

A proposed mechanism for the synthesis of indenopyrido[2,3-d]pyrimidines in the presence of Fe_3O_4@SiO_2-$SnCl_4$, as a Lewis acid catalyst is shown in scheme 2. The carbonyl oxygen of aldehyde coordinates with the Lewis acid moiety, increasing the electrophilicity of the carbonyl group and thereby making it possible to carry out the reaction in a short time. In a plausible mechanism, it is assumed that the reaction may proceed initially through the Knoevenagel condensation between arylaldehydes and 1, 3-indanedione to form intermediate (I). Next, michael addition of 6-amino-2-(methylthio)-pyrimidin-4(3*H*)-one to intermediate (I) affords (II). Intermediate (II) converts to (III) after tautomerization. Then, Intermediate (III) converts to intermediate (IV) *via* cyclization. Finally, the desired product (V) is obtained after tautomerization of (IV) (Fig. 2).

Consequently, it is essential for the solid acid to maintain strong acidity even after recycling, which has the most important benefits for commercial applications. The catalyst was also recycled and reused in the preparation of 4a as a model compound. After completion of the reaction, nano-Fe_3O_4@SiO_2/$SnCl_4$ is easily separated by an external magnet. The recovered catalyst was washed with ethanol (15 mL) and dried at room temperature without further purification for use in the next run in the current reaction under identical conditions. The result showed that after five successive runs, catalytic activity of the catalyst was retained without significant loss of activity (Fig. 3).

CONCLUSION

In summary, for the first time, we have shown that nano-Fe_3O_4@SiO_2/$SnCl_4$ was an effective heterogeneous catalyst for the one-pot synthesis of indenopyrido[2,3-*d*]pyrimidine derivatives from 6-amino-2-(methylthio)-pyrimidin-4(3*H*)-one, aryl aldehyde and 1,3-indanedione under reflux and ultrasound irradiation conditions in water. The mild reaction conditions, green and cost-effective catalyst, excellent yields, and easy work-up procedures, which avoid the use of large volumes of hazardous organic solvents, make it a useful alternative to previously reported procedures. Compared with a nonmagnetic nanoparticle catalytic system, the present protocol combines the advantages of solid Lewis acid and magnetic nanoparticles and offers great potential for the rapid synthesis of indenopyrido[2,3-*d*]pyrimidine derivatives.

ACKNOWLEDGEMENTS

The authors are grateful to the Research Council of Yazd University for financial support of this work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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