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Ultrasound Assisted One-Pot Synthesis of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid Derivatives A Green Approach

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ABSTRACT

An efficient and convenient green approach for the synthesis of series of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives using Biginelli reaction under ultrasonic irradiation of 5-(4-isobutylphenyl)-5-oxopentanoic acid, thiourea and substituted aldehydes and K_2CO_3. The advantage of this reaction is shorter reaction duration, ease of product isolation, cleaner and mild reaction condition and simple work up procedure. K_2CO_3 is an efficient, inexpensive, readily available catalyst. The synthesized compounds were obtained in good yield. Their structures were confirmed by IR, ^{1}H NMR spectra, and elemental analysis. They have been found to have promising anti-inflammatory activity.

Keywords: Biginelli reaction; Ultrasound irradiation; Anti-inflammatory activity.

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INTRODUCTION

Multi-component reactions (MCRs) [1] are of increasing importance in organic and medicinal chemistry, because the strategies of MCRs offer significant advantages over conventional linear-type syntheses. MCRs allow the creation of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the creation of molecular diversity and complexity [2]. Multi-step reactions usually produce significant amount of waste, principally due to a series of complex isolation procedures which often involves toxic, hazardous and expensive solvents after each step. Thus, multi-component reactions (MCRs) constitute an efficient synthetic strategy for the rapid and effective laboratory organic transformations, because products are prepared in a one-pot and single step and the diversity can be obtained directly by changing the reacting components [3,4]. Nitrogen-containing heterocyclic compounds are widespread in natural products and medicinal agents [5], and their applications to biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important [6, 7]. The development of new efficient methods to synthesize N-heterocycles with structural diversity is one major interest of modern synthetic organic chemists [8–10]. Heterocyclic compounds have been reported for anti-inflammatory activity [11, 12].

This is continuation of our previous work wherein we report synthesis of the same under thermal condition promising anti-inflammatory activity [13]. The utilization of ultrasound energy in organic chemistry has been better known from the 1970s [14]. Ultrasonication, based on cavitation effects leading to mass transfer improvement, is an important technique that is widely used today in organic synthesis and has a profound impact on the way chemists approach organic and parallel synthesis. Reductions in reaction times, improved yields and suppression of side products, relative to traditional thermal heating, are benefits of this technology [15]. As increasing environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures. Ultrasound as a green synthetic approach has gradually been used in organic synthesis over the last three decades. Compared with the traditional methods, it is more convenient, easier to be controlled, and consumes less power. With use of ultrasound irradiation, a large number of organic reactions can be carried out in milder conditions with shorter reaction time and higher product yields [16]. Ultrasound-accelerated chemical reactions are well-known and proceed via the formation and adiabatic collapse of transient cavitation bubbles. Ultrasound irradiation has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to provide improved yields and increased selectivities [17]. Therefore, ultrasound irradiation has been established as an important technique in organic synthesis [18].

METHODS AND MATERIALS

All melting points were measured in open capillary and are uncorrected. The products were characterized byIR spectra, 1H NMR and elemental analysis. IR spectra were recorded on Perkin–Elmer FT-IR-1710 Instrument. 1H NMR was recorded on BrukerMSL-300 instrument

using TMS as an internal standard. Elemental analyses were determined by an elemental analyser (CHNS-O, EA 1108-elemental analyser, Carlo Erba instruments). For ultrasound assisted organic reactions, the ultrasonicator was used having the following specifications.
Electric supply: 230 v A.C. 50 Hz, 1phase.
Ultrasonic frequency: 36 ±3 KHz. Ultrasonic power: 100 watts.
All reagents were purchased from Merck and Loba and used without further purification.

General procedure

Preparation of 5-(4-isobutylphenyl)-5-oxopentanoic acid **(1)**: Isobutyl benzene (0.78 ml) and Glutaric anhydride (0.85 g) was placed in RBF provided with a reflux condenser and Calcium chloride guard tube. The reaction mixture was stirred and powdered anhydrous $AlCl_3$ was added (0.20 g) all at once. The reaction starts immediately. HCl was evolved and the mixture became hot. The reaction mixture was refluxed on oil bath at 70^0C, with continues stirring for 1 hr. The reaction mixture was allowed to cool, the flask was immersed in a bath of cold water and conc. HCl was slowly added. This leads to separation of the organic layer. The organic layer was separated and kept for overnight to form solid mass. The crude acid was dissolved in a solution of sodium carbonate by boiling it for 10–15 min. The solution was then filtered and washed with two portions of hot water to remove the small amount of aluminium hydroxide. The hot filtrate was treated with decolorizing carbon, it was then boiled for 5 min and filtered. The hot filtrate was cooled to about 5^0 C and cautiously acidified with conc. HCl and kept it for cooling to 0 ^{0}C in a freezing mixture of ice and salt. Thus the product obtained was filtered, washed thoroughly with cold water and dried to furnish colourless solid with 70% yield, M.P.130 ^{0}C.

General procedure for synthesis of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives **(4a-4j):**

A mixture of 5-(4-isobutylphenyl)-5-oxopentanoic acid **1** (1mmol), thiourea **2** (2mmol), aldehyde **3**(1mmol) and K_2CO_3 in 4 ml ethanol the mixture sonicated in the water bath of an ultrasonic cleaner, the completion of reaction was monitored by thin layer chromatography. The reaction mixture was cooled and the solid obtained was filtered. The solid was dissolved in hot water and filtered. The filtrate was neutralized with acetic acid. The solid obtained was filtered, dried to furnish the desired product. The results are given in Table (4a–4j).

RESULTS AND DISCUSSION

We report a simple and efficient one pot synthesis of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives by condensation of 5-(4-isobutylphenyl)-5-oxopentanoic acid, thiourea and substituted aldehydes and K_2CO_3 as a catalyst under ultrasound irradiation (Scheme-2). However, 5-(4-isobutylphenyl)-5-oxopentanoic acid **1** was synthsied by exploiting Friedal Craft reaction (Scheme-1). In all cases, aromatic aldehydes substituted with either electron-donating or electron-with drawing groups underwent the reaction smoothly and gave the products in good to excellent yields. The results

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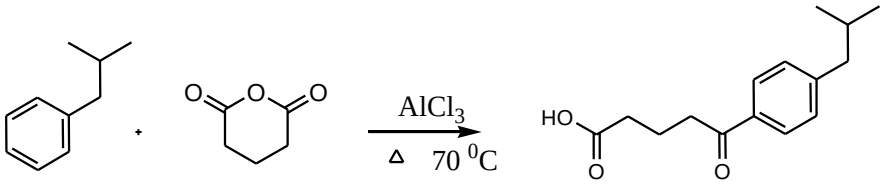
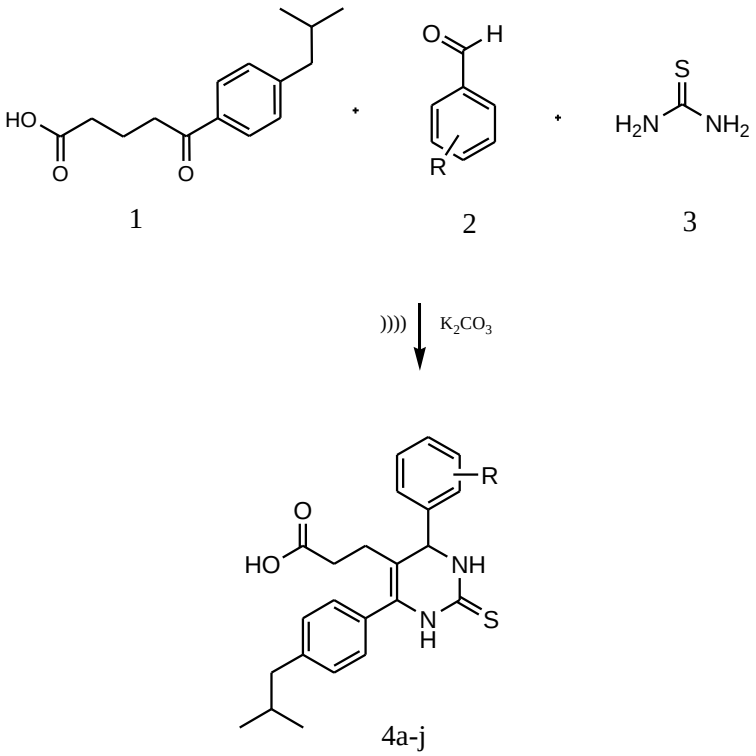
are shown in Table 1.The probable mechanism of the reaction is depicted in Scheme-3. The process was promoted by directly immersing of standard glass reaction vessels with the reaction mixture into the ultrasonic cleaning bath which provides a fairly even distribution of energy into the reaction medium. The reaction was completed within 40-115min, as compared to 8-12 hrs under thermal conditions with a substantial increase in the yield of product. This is an efficient and environmentally benign methodology for the synthesis of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives.



Scheme 1. Synthesis of 5-(4-isobutylphenyl)-5-oxopentanoic acid.



Scheme 2. Synthesis of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives.

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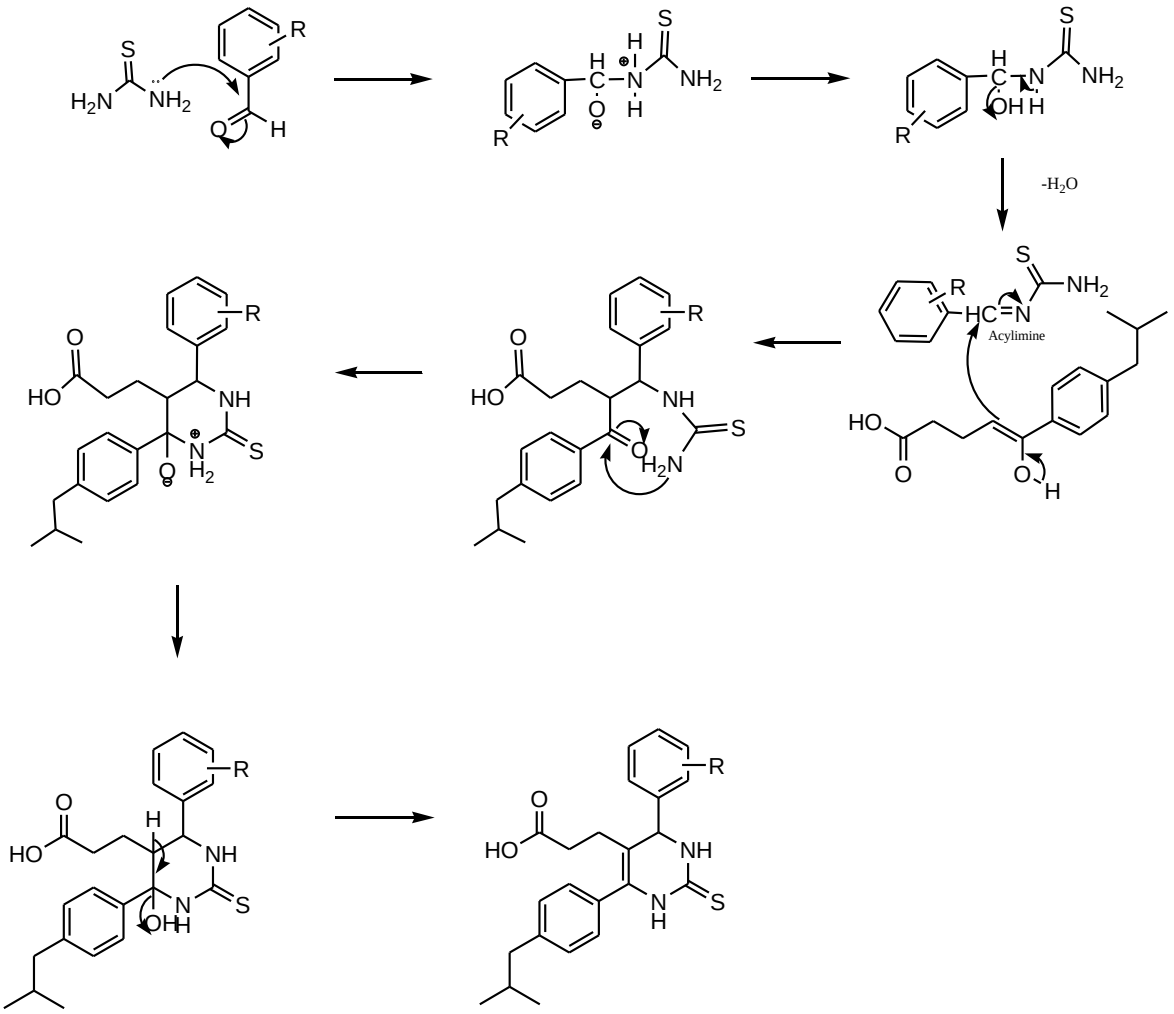

Scheme. 3: A probable mechanism of formation of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimi din-5-yl) propanoic acid derivatives.

Table. 1. Synthesis of 3-(4, 6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives under ultrasound irradiation in ethanol as solvent.

Product	R	With Ultrasound	
		Time (min)	Yield (%)
4a	3,4,5-$(OCH_3)_3C_6H_2$	41	85%
4b	2-OH C_6H_4	88	70%
4c	4-$N(CH_3)_2C_6H_4$	91	75%
4d	4-$OCH_3C_6H_4$	96	73%
4e	4-OH C_6H_4	56	75%
4f	4-$NO_2C_6H_4$	97	88%
4g	2-$NO_2C_6H_4$	115	65%
4h	2- Cl- C_6H_4	84	63%
4i	3-NO_2-C_6H_5	58	78%
4j	C_2H_2-C_6H_6	58	70%

The Spectral Data:

3-(1,2,3,4-tetrahydro-6-(4-isobutylphenyl)-4-(3,4,5-trimethoxyphenyl)-2-thioxopyrimidin-5-yl)propanoicacid (4a).

m.p 130-134 , Yield:(85%)IR (KBr): cm-1 3010, 3354, 1693,1546,1718 1HNMR (300 MHz,CDCl3)0.9(d, 2CH3), 1.9(m, CH), 2.0(t, CH2), 2.4(m, 2CH2), 2.9(m,CH2), 4.0 (s,3OCH3), 5.8(s,1H),7.1(d,2CH), 7.3(s,2CH), 8.2(brs,NH), 8.6(brs,NH), 9.9(brs,OH) Anal. Calc. for C26H31N2O5S C, 64.44; H,6.66; N, 5.78;S, 6.62 Found C, 64.50; H, 6.73; N, 5.83; S, 6.66.

3-(1,2,3,4-tetrahydro-4-(2-hydroxyphenyl)-6-(4-isobutylphenyl)-2-thioxopyrimidin-5-yl) propanoicacid (4b).

m.p 110-115, Yield:(70%)IR (KBr): cm-1 1510, 3352, 1680, 1705 1HNMR (300MHz, CDCl3) 0.9(d,2CH3), 1.9 (m,CH), 2.0(t,CH2), 2.5(m,2CH2), 3.1(t,CH2), 5.7(s,1H), 6.5(brs,OH), 7.2(d,4CH),7.9(d,2CH), 8.3(brs,NH), 8.7(brs,NH)10.5(brs,OH) Anal.Calc.for C23H25N2O3S C, 67.29; H, 6.38; N, 6.82;S, 7.81 Found C, 67.33; H, 6.40; N, 6.88; S, 7.85.

3-(4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-(4-isobutylphenyl)-2-thioxopyrimidin-5-yl) propanoic acid (4c).

m.p 140-142, Yield:(75%)IR (KBr): cm-1 1500, 3334, 1670, 1705 1HNMR (300MHz , CDCl3)0.9(d,2CH3), 1.9(m,CH), 2.1(t,CH2), 2.6(m,2CH2), 3.1(s,2CH3), 5.8(s,1H), 6.7(d,2CH),7.2(d,2CH),7.7(d,2CH), 7.9(d,2CH), 8.3(brs,NH), 8.6(brs,NH) ,9.8(s,brsOH) Anal.Calc.for C25H30N3O2S C, 68.62; H,7.14; N, 9.60; S, 7.33 Found C, 68.66 H, 7.15; N, 9.61; S, 7.36.

3-(1,2,3,4-tetrahydro-6-(4-isobutylphenyl)-4-(4-methoxyphenyl)-2-thioxopyrimidin-5-yl)propanoic acid (4d).

m.p 120-125,Yield:(73%) IR (KBr): cm-1 1508,3394,1708,1716 1HNMR (300MHz,CDCl3) 0.9(d,2CH3), 1.9(m,CH),2.0(t,CH2), 2.4(m,2CH2), 3.9(s,OCH3), 5.9(s.1H), 6.9(d,2CH), 7.1(d,2CH), 7.7(d,2CH),7.89(d,2CH),8.2(brs,NH),8.6(brs,NH),9.9(s,brsOH)Anal.Calc.for C24H27N2O3S C, 67.90; H, 6.65; N, 6.60; S, 7.55 Found C, 67.95; H, 6.66; N, 6.63; S, 7.57.

3-(1,2,3,4-tetrahydro-4-(4-hydroxyphenyl)-6-(4-isobutylphenyl)-2-thioxopyrimidin-5-yl) propanoic acid(4e).

m.p 120-125, Yield:(75%) IR (KBr): cm-1 1546,3379,1650,1726 1HNMR (300 MHz, CDCl3) 0.9(d,2CH3), 1.9(m, CH), 2.0(t, CH2), 2.4(m, 2CH2), 4.5(s,brs-OH), 5.8(s.1H) ,7.2(d,2CH), 7.8(d,2CH),8.1(d,2CH), 8.4(d,2CH), 8.3(brs,NH), 8.8(brs,NH), 10.1(s,brsOH) Anal.Calc.for C23H25N2O3S C, 67.29; H,6.38; N, 6.82; S, 7.81 Found C, 67.31; H, 6.42; N, 6.85; S, 7.88

3-(1,2,3,4-tetrahydro-6-(4-isobutylphenyl)-4-(4-nitrophenyl)-2-thioxopyrimidin-5-yl)propanoic acid (4f).

m.p 125-130, Yield:(88 %) IR (KBr): cm-1 1532, 3344,1671,1654,1392 1HNMR (300MHz,CDCl3)0.9(d,2CH3), 1.9(m,CH), 2.0(t,CH2), 2.4(m,2CH2), 5.7(s.1H), 6.9(d,2CH), 7.2(d,2CH), 7.8(d,2CH),7.9(d,2CH), 8.4(brs,NH), 8.7(brs,NH), 9.9(s,brs-OH)Anal.Calc.for C23H24N3O4S C, 62.85; H, 5.73; N,9.56; S, 7.30 Found C, 62.88; H, 5.79; N, 9.60; S, 7.35.

3-(1,2,3,4-tetrahydro-6-(4-isobutylphenyl)-4-(2-nitrophenyl)-2-thioxopyrimidin-5-yl) propanoic acid(4g).

m.p 100,105 Yield: (65%) IR (KBr): cm-1 1510, 3364,1692,1674,1386 1HNMR (300MHz,CDCl3)0.9(d,2CH3), 1.9(m,CH), 2.0(t,CH2), 2.4(m,2CH2), 5.8(s.1H7.3(m,CH), 7.8(d,3CH), 7.9(d,2CH),8.2(d,2CH), 8.5(brs,NH), 8.8(brs,NH), 10.4(s,brsOH) Anal.Calc.for C23H24N3O4S C, 62.85; H, 5.73; N,9.56; S, 7.30 Found C, 62.89; H, 5.76; N, 9.57; S, 7.37.

3-(4-(2-chlorophenyl)-1,2,3,4-tetrahydro-6-(4-isobutylphenyl)-2-thioxopyrimidin-5-yl) propanoic acid(4h).

m.p112-115,Yield:(63%)IR(KBr):cm-11537,3378,1692,1725,734 1HNMR (300MHz, CDCl3)1HNMR0.9(d,2CH3),1.8(m,CH),2.0(t,CH2),2.4(m,2CH2),5.6(s.1H), 7.3(m,CH), 7.8(d,3CH) 7.9(d,2CH),8.3(d,2CH), 8.5(brs,NH), 8.8(brs,NH),Anal.Calc.for C23H24ClN2O2S C, 64.40; H, 5.87; Cl, 8.26; N, 6.53; S, 7.4 Found C, 64.41 H, 5.88; Cl, 8.30; N, 6.56; S, 7.48.

3-(1,2,3,4-tetrahydro-6-(4-isobutylphenyl)-4-(3-nitrophenyl)-2-thioxopyrimidin-5-yl) propanoic acid(4i).

m.p 120-123, Yield:(78 %)IR (KBr): cm-1 1532, 3340, 1660, 1702, 1343 1HNMR (300MHz,CDCl3)0.9(d,2CH3), 1.9(m,CH), 2.0(t,CH2), 2.4(m,2CH2), 5.7(s.1H), 7.2(m,CH), 7.9(d,3CH), 8.4(d,2CH),8.6(d,2CH), 8.9(brs,NH), 9.2(brs,NH), 10.2(s,brsOH)Anal.Calc.for C23H24N3O4S C, 62.85; H, 5.73; N,9.56; S, 7.30 Found C, 62.90; H, 5.79; N, 9.59; S, 7.37.

3-(1,2,3,4-tetrahydro-6-(4-isobutylphenyl)-4-styryl-2-thioxopyrimidin-5-yl)propanoic acid (4j).

m.p 103-108,Yield:(70%) IR (KBr): cm-1 1512,3360,1377,1701, 1HNMR (300MHz,CDCl3) 0.9(d,2CH3),1.9(m,CH), 2.0(t,CH2), 2.4(m,2CH2), 5.6(s.1H), 6.4(m,CH), 6.5(m,CH), 7.2(m,2CH), 7.7(m,3CH),8.7(m,2CH), 8.8(d,2CH), 8.7(brs,NH), 9.0(brs,NH),9.7(s,brsOH) Anal.Calc.for C25H27N2O5S C, 71.40; H,6.71; N, 6.66; S, 7.62 Found C, 71.46; H, 6.74; N, 6.76; S, 7.67

CONCLUSION

This is a green protocol for the synthesis of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives with promising anti-inflammatory activity. The method is simple; required accessible commercial materials, the advantage of this new

method is operational simplicity, good yields, short reaction times and easy work-up. There is scope for further innovation in structural modification to achieve series of new anti-inflammatory drugs.

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