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AN EFFICIENT ROUTE TO THE SYNTHESIS OF PYRIMIDINE-2-ONES UNDER ULTRASOUND IRRADIATION

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Chalcone derivatives have been prepared by condensation of various substituted aryl aldehydes and acetophenone in alkaline ethanol, while pyrimidine-2-one derivatives have been prepared by the combination of chalcones and urea under conventional and ultrasonic conditions. A beneficial ultrasound effect was observed and high yields of the products were obtained after 15–30 min sonication. Characterization and structural elucidation of the products have been done on the basis of chemical, analytical and spectral analysis. The results demonstrate clearly, that to achieve a high efficiency of ultrasonic systems in chemical processes

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1. Introduction

Heterocyclic rings have played an important role in medicinal chemistry, serving as key templates central to the development of numerous important therapeutic agents [1]. Pyrimidine derivatives have found application in a wide range of medicinal chemistry because of their diverse biological activities, such as antimicrobial [2], antitumor and antifungal activities [3], also these compounds are considered to be important for drugs and agricultural chemicals [4-6]. These chemotherapeutic applications of pyrimidine derivatives prompted us to the synthesis of some substituted pyrimidines in a facil pathway. Recently, several methods have been reported for the synthesis of pyrimidine derivatives. In one method aldehydes, β-dicarbonyl compounds, and urea/thiourea were reacted in the presence of a catalytic amount of tetrachlorosilane in DMF at normal ambient temperature [7]. The synthesis of 2-thiopyrimido benzimidazole derivatives under condensation of 4-isothiocyanato-4-methyl-2-pentanone and 3,3-diaminobenzidine in absolute methanol under refluxing conditions is the other method [8]. Pyrimidine derivatives also can be prepared by reaction of certain amides with carbonitriles under electrophilic activation of the amide with 2-chloro-pyridine and trifluoromethanesulfonic anhydride [9]. However, these methods suffer from drawbacks, such as longer reaction time, complicated workup, and low yield. The present investigation describes the synthesis of pyrimidine-2-one derivatives under conventional and ultrasonic irradiation by the reaction of chalcones and urea. Ultrasound effects on organic reactions are attributed to cavitations, a physical process that create, enlarge, and implode gaseous and vaporous cavities in an irradiated liquid [10]. Cavitations induces very high local temperatures and pressure inside the bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer [11]. Ultrasonic Irradiation in some organic reactions proceeds with facile reactions to provide high yields within a very short reaction time periods [12-14].

2. Experimental

General: All melting points are uncorrected and were determined in capillary tube on Boetius melting point microscope. FT-IR spectra were recorded on a Nicolet Magna 550 spectrometer (KBr). 1H-NMR spectra were obtained on Bruker 400 MHZ spectrometer with

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DMSO-d_6 as a solvent using tetramethylsilane (TMS) as an internal standard; the chemical shift values are in δppm. Sonication was performed in an ELO-150 ultrasonic cleaner with a frequency of 46 kHz and a nominal power of 200 W. All reactions were followed and checked by T.L.C. using n-hexane/ethylacetat (7:3) and spots were examined by UV lamp. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer.

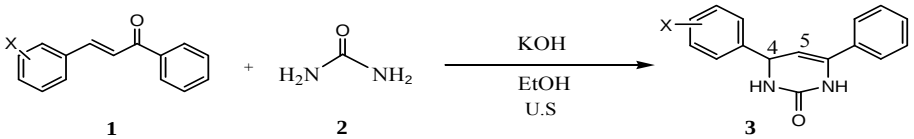
General Procedure for the preparation of Pyrimidine-2-one derivatives 3(a-h).

Method A: A mixture of chalcones (0.005 mol), urea (0.005 mol) and potassium hydroxide (0.5 g) in ethanol (20 ml) was refluxed on oil bath at 70-80 ºC for 6 h. Then the reaction mixture was left for overnight and then was concentrated under reduced pressure. The residue was filtered, washed with water and recrystallised from ethanol.

Method B: All contents were taken in ultrasonic bath for 30 min, at 20-30 °C and workup similarly as mentioned in method A.

3. Results and discussion

In these research chalcone derivatives 1 was reacted with urea 2 in the presence of potassium hydroxide in ethanol to produce the pyrimidine-2-one derivatives 3. The reaction was carried out in two steps, at first the conjugate addition take placed on the ß-position of carbonyl group and then the nucleophilic attack to carbonyl group followed by dehydration lead to six member ring products [15-17] (Scheme1).



3a: X = H
3b: X = 2-CH_3
3c: X = 3- CH_3
3d: X = 4-CH_3
3e: X = 2-OCH_3
3f: X = 4-OCH_3
3g: X = 2,4-OCH_3
3h: X = $N(Me)_2$

Scheme1. Approach to the synthesis of Pyrimidine-2-ones under ultrasound irradiation.

Application of ultrasound shortened the reaction time of the generation of pyrimidines from 6 h under classical conditions to 30 min (Table). Also the yields of products were improved 20–30% in compared with the thermal heating method. In the view of the interesting green chemistry for the synthesis organic compounds we could describe an optimized procedure for the preparation pyrimidine-2-one derivatives. We carried out these reactions under milder and cleaner conditions. While the thermal heating should be take placed for 6 h at 70-80 °C, but our new method carried out in room temperature.

*Table. Preparation of Pyrimidine-2-ones (**3**) under Conventional and Ultrasound Conditions*

Entry	Conventional Conditions		Ultrasound Irradiation	
	Time (h)	Yield (%)	Time (min)	Yield (%)
3a	6.5	65	24	82
3b	6	55	22	78
3c	6	54	21	80
3d	6	58	24	76
3e	5.5	60	28	78
3f	5.5	61	25	75
3g	5	65	22	73
3h	5.5	55	29	75

It was determined here that ultrasound promoted reactions of chalcones and urea to produce the pyrimidine-2-one derivatives. This procedure has the advantages of shorter reaction time relative to common methods with an efficient yield.

Spectral data for compounds

4,6-di-(phenyl)-3,4-dihydropyrimidine-2(1H)-one (3a). Yellow crystal; m.p. 182-184 °C. FT-IR (KBr): ν 3173 (NH), 1644 (C=N), 1559, 1478 (C=C), 1680 (C=O). ^{1}H-NMR (DMSO-d_6): δ 4.86 (d, 1H, 4-CH), 5.15 (d, 1H, 5-CH C=CH), 6.78-7.29 (m, 10H, Ar-H), 8.85 (bs, 1H, NH), 9.60 (bs, 1H, NH). ^{13}C-NMR (DMSO-d_6): 55.1, 101.6, 126.3, 126.8, 127.25, 128.85, 129.16, 129.31, 133.77, 134.8, 144.54, 178.4. Anal. Calcd. For $C_{16}H_{14}N_2O$: C 72.18, H 5.1, N 9.77. Found C 72.25, H 5.20, N 9.91.

4-(2′-methylphenyl)-6-(phenyl)-3,4-dihydropyrimidine-2-(1H)-one(3b). Yellow crystal; m.p. 177-179 °C. FT-IR (KBr): ν 3235(NH), 1642 (C=N), 1566, 1480 (C=C), 1682 (C=O). ^{1}H-NMR (DMSO): δ 2.1 (s, 3H, CH_3), 4.87 (d, 1H, 4-CH) 5.12 (d, 1H, 5-CH C=CH), 6.91-7.30 (m, 9H, Ar-H), 8.85 (bs, 1H, NH), 9.60 (bs, 1H, NH). ^{13}C-NMR (DMSO-d_6): 22.3, 56, 101.8, 125.45, 125.8, 127.5, 127.9, 128.7, 129.2, 133.4, 133.8, 134.7, 137.5, 144.3, 177.2. Anal. Calcd. For $C_{17}H_{16}N_2O$: C 72.85, H 5.71, N 10.00. Found C 72.75, H 5.80, N 10.15.

4-(3′-methylphenyl)-6-(phenyl)-3,4-dihydro pyrimidine -2(1H)-one (3c).

Yellow crystal; mp 183-185 °C. FT-IR (KBr, cm^{-1}):ν 3169(NH), 1640 (C=N), 1575, 1482 (C=C), 1682 (C=O). ^{1}H-NMR (DMSO-d_6): δ 2.08 (s, 3H, CH_3), 4.85 (d, 1H, 4-CH) 5.15 (d, 1H, 5-CH), 6.83-7.31 (m, 9H, Ar-H), 8.85 (bs, 1H, NH), 9.64 (bs, 1H, NH). ^{13}C-NMR (DMSO-d_6): 21.6, 55.1, 101.7, 124, 126.2, 127.3, 127.9, 128.6, 129.1, 129.3, 133.75, 134.6, 138.2, 144.5, 177.3 Anal. Calcd. For $C_{17}H_{16}N_2O$: C 72.85, H 5.71, N 10.00. Found C 72.88, H 5.77, N 10.10.

4-(4′-methylphenyl)-6-(phenyl)-3,4-dihydropyrimidine-2(1H)-one(3d).

Yellow crystal; mp 183-185 °C. FT-IR (KBr): ν 3198 (NH), 1640 (C=N), 1566, 1480 (C=C), 1682 (C=O).^{1}H-NMR (DMSO-d_6): δ 2.03 (s, 3H, CH_3), 4.86 (d, 1H, 4-CH) 5.14 (d, 1H, 5-CH), 6.87-7.29 (m, 9H, Ar-H), 8.85 (bs, 1H, NH), 9.64 (bs, 1H, NH). C-NMR (DMSO-d_6): 21.2, 56, 102.8, 127.45, 127.95, 128.53, 129.51, 130.4, 130.7, 134.9, 138.4, 142.2, 178.1. Anal. Calcd. For $C_{17}H_{16}N_2O$: C 72.85, H 5.71, N 10.00. Found C 72.92, H 5.80, N 10.14.

4-(2′-methoxyphenyl)-6-(phenyl)-3,4-dihydropyrimidine-2(1H)-one(3e). White crystal; mp 173-175°C. FT-IR (KBr): ν 3152 (NH), 1642 (C=N), 1555, 1479 (C=C), 1682 (C=O). ^{1}H-NMR (DMSO-d_6): δ 3.6 (s, 3H -OCH_3), 5.13 (m, 2H, 4-CH, 5-CH), 6.93-7.23 (m, 9H, Ar-H), 8.75 (bs, 1H, NH), 9.71 (bs, 1H, NH). ^{13}C-NMR (DMSO-d_6): 50.17, 56.03, 100.8, 111.55, 121.13, 126.22, 126.93, 128.83, 129.13, 129.21, 132.11, 133.82, 134.80, 155.73, 177.3. Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C 68.91, H 5.40, N 9.45. Found C 68.99, H 5.50, N 9.39.

4-(4′-methoxyphenyl)-6-(phenyl)-3,4-dihydropyrimidine-2(1H)-one(3f).

White crystal; mp 176-177°C (lit.[17] m.p. 175-177 °C). FT-IR (KBr): ν 3149 (NH), 1644 (C=N), 1555, 1479 (C=C), 1682 (C=O). ^{1}H-NMR (DMSO-d_6): δ 3.6 (s, 3H -OCH_3), 5.13 (m, 2H, 4-CH, 5-CH), 6.79-7.25 (m, 9H, Ar-H), 8.62 (bs, 1H, NH), 9.60 (bs, 1H, NH). ^{13}C-NMR (DMSO-d_6): 50.2, 56.03, 100.81, 111.56, 121.13, 126.22, 128.83, 129.12, 129.21, 132.12, 134.82, 155.76, 178.21. Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C 68.91, H 5.40, N 9.45. Found C 69.02, H 5.51, N 9.41.

4-(2′,4′-dimethoxyphenyl)-6-(phenyl)-3,4dihydropyrimidine-2(1H)-one(3g). White crystal; mp 180-182°C. FT-IR (KBr): ν 3195(NH), 1642 (C=N), 1581, 1465 (C=C), 1680 (C=O). ^{1}H-NMR (DMSO-d_6): δ 3.6 (s, 6H 2′,4′-OCH_3), 5.13 (m, 2H, 4-CH, 5-CH), 6.83-7.25 (m, 8H, Ar-H), 8.60 (bs, 1H, NH), 9.63 (bs, 1H, NH). ^{13}C-NMR (DMSO-d_6): 51.12, 58.23, 101.2, 111.23, 121.18, 125.22, 125.9, 127.31, 129.1, 129.8, 132.6, 134.8, 153.7, 154.6, 177.11. Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C 66.25, H 5.52, N 8.58. Found C 66.29, H 5.43, N 8.67.

4-(4′-N,N-dimethyl)-6-(phenyl)-3,4-dihydropyrimidine-2(1H)-one(3h).

Yellow crystal; mp 162-164°C. FT-IR (KBr): ν 3196(NH), 1640 (C=N), 1552, 1475 (C=C), 1680 (C=O). ^{1}H-NMR (DMSO-d_6): δ 2.74 (s, 6H, $N(Me)_2$), 5 (m, 2H, 4-CH, 5-CH), 6.83-7.25 (m, 8H, Ar-H), 8.64 (bs, 1H, NH), 9.60 (bs, 1H, NH). ^{13}C-NMR (DMSO-d_6): 56.52, 79.67, 102.04, 112.22,

125.64, 126.26, 127.98, 128.19, 130.29, 134.46, 138.7,150.54, 176.12. Anal. Calcd. for $C_{18}H_{19}N_3O$: C 69.91, H 6.14, N 13.9. Found C 70.03, H 6.19, N 13.95.

4. Conclusions

In summary, we have described an optimized procedure for the preparation of pyrimidine-2-one derivatives under milder and cleaner conditions. The advantages of ultrasound in chemical reactions such as shorter reaction time and higher yields and milder conditions could be of use in industrial application in pharmaceutical or fine chemical industry.

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