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Ultrasound-assisted synthesis of dihydropyrimidine-2-thiones

JAVAD SAFAEI-GHOMI* and MOHAMMAD ALI GHASEMZADEH

Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, 51167 Kashan, I. R. Iran

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Abstract: Chalcone derivatives were prepared by the condensation of various substituted aryl aldehydes and acetophenone in alkaline ethanol, while pyrimidine-2-thione derivatives were prepared by the combination of chalcones and thiourea under conventional and ultrasonic conditions. Advantages of the ultrasound effect were observed and high yields of the products were obtained after 20–30 min sonication. Characterization and structural elucidation of the products was realized based on chemical, analytical and spectral analyses. The results clearly demonstrated a high efficiency of the ultrasonic systems was achieved in the chemical processes.

Keywords: chalcone derivatives, ultrasound, pyrimidine-2-thione derivatives.

INTRODUCTION

Heterocyclic compounds have so far been synthesized mainly because of their wide range of biological activities. These compounds play 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 medical applications because of their diverse biological activities, such as antimicrobial,[2] antitumor and antifungal activities.[3] In addition, these compounds are considered to be important for drugs and agricultural chemicals.[4–6] These chemotherapeutic applications of pyrimidine derivatives prompted the present synthesis of some substituted pyrimidines in a facile pathway.

Multi-component reactions (MCRs) play an important role in combinatorial chemistry because they enable the synthesis of small drug-like molecules with several degrees of structural diversity. This reaction tool allows compounds to be synthesized in a few steps and usually in a one-pot operation. Another typical benefit from these reactions is the simplified purification, because all the reagents

* Corresponding author. E-mail: safaei@kashanu.ac.ir
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are incorporated into the final product. The Biginelli reaction is a multiple-component chemical reaction that creates dihydropyrimidine from ethyl acetoacetate, an aryl aldehyde and urea or thiourea.[7,8]

Recently, several methods have been reported for the synthesis of pyrimidine derivatives. One method involves the reaction of aldehydes, ß-dicarbonyl compounds and urea/thiourea in the presence of a catalytic amount of tetrachlorosilane in DMF at ambient temperature.[9] The synthesis of 2-thiopyrimido benzimidazole derivatives by the condensation of 4-isothiocyanato-4-methyl-2-pentanone and 3,3'-diaminobenzidine in absolute methanol under reflux is another method.[10] Pyrimidine derivatives can also be prepared by the reaction of certain amides with nitriles under electrophilic activation of the amide with 2-chloropyridine and trifluoromethanesulfonic anhydride.[11] However, these methods suffer from drawbacks, such as longer reaction times, complicated workup and low yields.

The present paper describes the synthesis of pyrimidine-2-thione derivatives under conventional and ultrasonic irradiation by the reaction of chalcones and thiourea. The effects of ultrasound on organic reactions are attributed to cavitations, a physical process that create, enlarge, and implode gaseous and vaporous cavities in an irradiated liquid.[12] The cavitations induce very high local temperatures and pressures inside the bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer.[13] In some reactions, ultrasonic irradiation allows the process to occur with ease to provide high yields within very short times.[14–16]

EXPERIMENTAL

All melting points are uncorrected and were determined in a capillary tube on a Boetius melting point microscope. The FTIR spectra were recorded on a Nicolet Magna 550 spectrometer (KBr). The ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Bruker 400 MHz spectrometer with DMSO-d_6 as the solvent using tetramethylsilane (TMS) as the internal standard. 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 TLC using *n*-hexane/ethyl acetate (7:3) as the mobile phase. The spots were visualized using a UV lamp. The elemental analyses (C, H, N) were obtained from a Carlo ERBA Model EA 1108 analyzer. The mass spectra were recorded on a Joel D-30 instrument at an ionization potential of 70 eV.

*General procedure for the preparation of pyrimidine-2-thione derivatives (**3a–h**)*

Conventional heating. A mixture of chalcone (0.005 mol), thiourea (0.005 mol) and potassium hydroxide (0.5 g) in ethanol (20 ml) was refluxed with stirring on an oil bath at 70––80 °C for the periods indicated in Table I. Subsequently, the reaction mixture was left overnight and then concentrated under reduced pressure. The solid residue was collected, washed with water and recrystallized from ethanol.

Ultrasound. All contents were placed in an ultrasonic bath for the periods indicated in Table I, at 20–25 °C and worked up as described above.

TABLE 1. Preparation of pyrimidines (**3**) under conventional and ultrasound conditions

Compound	Conventional conditions		Ultrasound irradiation	
	Time, h	Yield, %	Time, min	Yield, %
3a	5.5	65	20	82
3b	6	55	22	78
3c	6	54	22	80
3d	5.5	58	24	76
3e	6	60	26	78
3f	6	61	24	75
3g	6.5	65	25	73
3h	5.5	55	29	75

RESULTS AND DISCUSSION

Spectral data for the compounds

*4,6-Diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**3a**)*. Yellow crystals; m.p.: 182–184 °C (lit.[17] m.p. 184 °C). FTIR (KBr, cm^{-1}): 3173 (NH), 1644 (C=N), 1559, 1478 (C=C), 1183 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 4.86 (1H, *d*, *J* = 5.0 Hz, 4–CH), 5.15 (1H, *d*, *J* = 5.0 Hz, 5–CH), 6.78–7.29 (10H, *m*, Ar–H), 8.85 (1H, *bs*, NH), 9.60 (1H, *bs*, NH). ^{13}C-NMR (100 MHz, DMSO-d_6, δ / / ppm): 55.1, 101.6, 126.3, 126.8, 127.2, 128.85, 129.2, 129.3, 133.8, 134.8, 144.5, 175.4.

*4-(2-Methylphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**3b**)*. Yellow crystals; m.p.: 175–177 °C; Anal. Calcd. for $C_{17}H_{16}N_2S$: C 72.85, H 5.71, N 10.00 %. Found: C 72.75, H 5.80, N 10.15 %. FTIR (KBr, cm^{-1}): 3235 (NH), 1642 (C=N), 1566, 1480 (C=C), 1165 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / / ppm): 2.10 (3H, *s*, CH_3), 4.87 (1H, *d*, *J* = 5.0 Hz, 4–CH) 5.12 (1H, *d*, *J* = 5.0 Hz, 5–CH), 6.91–7.30 (9H, *m*, Ar–H), 8.85 (1H, *bs*, NH), 9.60 (1H, *bs*, NH). ^{13}C--NMR (100 MHz, DMSO-d_6, δ / ppm): 22.3, 56, 101.8, 125.4, 125.8, 127.5, 127.9, 128.7, 129.2, 133.4, 133.8, 134.7, 137.5, 144.3, 175.2; MS (EI) (*m*/*z*): 280 (M^+).

*4-(3-Methylphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**3c**)*. Yellow crystals; m.p.: 183–185 °C; Anal. Calcd. for $C_{17}H_{16}N_2S$: C 72.85, H 5.71, N 10.00 %. Found: C 72.88, H 5.77, N 10.10 %. FTIR (KBr, cm^{-1}): 3169 (NH), 1640 (C=N), 1575, 1482 (C=C), 1194 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / / ppm): 2.08 (3H, *s*, CH_3), 4.85 (1H, *d*, *J* = 5.0 Hz, 4–CH) 5.15 (1H, *d*, *J* = 5.0 Hz, 5–CH), 6.83–7.31 (9H, *m*, Ar–H), 8.85 (1H, *bs*, NH), 9.64 (1H, *bs*, NH). ^{13}C-NMR (100 MHz, DMSO-d_6, δ / ppm): 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. MS (EI) (*m*/*z*): 280 (M^+).

*4-(4-Methylphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**3d**)*. Yellow crystals; m.p.: 198–200 C (lit.[18] m.p. 199–200 °C). FTIR (KBr, cm^{-1}): 3198 (NH), 1644 (C=N), 1566, 1480 (C=C), 1184 (C=S). ^{1}H-NMR (400 MHz,

DMSO-d_6, δ/ ppm): 2.03 (3H, *s*, CH_3), 4.86 (1H, *d*, *J* = 5.0 Hz, 4–CH) 5.14 (1H, *d*, *J* = 5.0 Hz, 5–CH), 6.87–7.29 (9H, *m*, Ar–H), 8.85 (1H, *bs*, NH), 9.64 (1H, *bs*, NH). ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ ppm): 21.2, 56.0, 102.8, 127.4, 127.9, 128.5, 129.5, 130.4, 130.7, 134.9, 138.4, 142.2, 178.1.

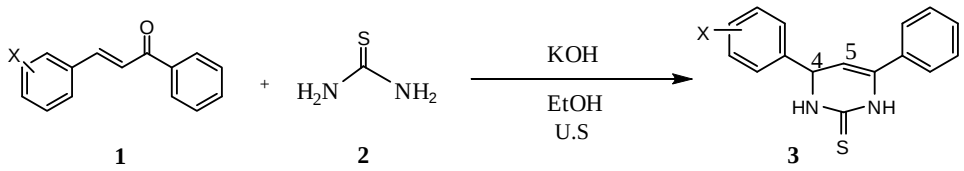
*4-(2-Methoxyphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**3e**)*. White crystals; m.p.: 178–180°C; Anal. Calcd. for $C_{17}H_{16}N_2OS$: C 68.91, H 5.40, N 9.45 %. Found: C 68.99, H 5.50, N 9.39 %. FTIR (KBr, cm^{-1}): 3152 (NH), 1642 (C=N), 1555, 1479 (C=C), 1182 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ ppm): 3.60 (3H, *s*, $-OCH_3$), 5.13 (2H, *m*, 4–CH, 5–CH), 6.93–7.23 (9H, *m*, Ar–H), 8.75 (1H, *bs*, NH), 9.71 (1H, *bs*, NH). ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ ppm): 50.2, 56.0, 100.8, 111.5, 121.1, 126.2, 126.9, 128.8, 129.1, 129.2, 132.1, 133.8, 134.8, 155.73, 177.3. MS (EI) (*m*/*z*): 296 (M^+).

*4-(4-Methoxyphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**3f**)*. White crystals; m.p.: 123–125 C (lit.[19] m.p. 123–124 °C). FTIR (KBr, cm^{-1}): 3149 (NH), 1642 (C=N), 1555, 1479 (C=C), 1182 (C=S). ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ / ppm): 3.60 (3H, *s*, $-OCH_3$), 5.13 (2H, *m*, 4–CH, 5–CH), 6.79–7.25 (9H, *m*, Ar–H), 8.62 (1H, *bs*, NH), 9.60 (1H, *bs*, NH). ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ ppm): 50.2, 56.0, 100.8, 111.6, 121.1, 126.2, 128.8, 129.1, 129.2, 132.1, 134.8, 155.8, 178.2.

*4-(2,4-Dimethoxyphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**3g**)*. White crystals; m.p.: 180–182 °C. Anal. Calcd. for $C_{18}H_{18}N_2O_2S$: C 66.25, H 5.52, N 8.58 %. Found: C 66.29, H 5.43, N 8.67 %. FTIR (KBr, cm^{-1}): 3195 (NH), 1644 (C=N), 1581, 1465 (C=C), 1162 (C=S). ^{1}H-NMR (400 MHz, DMSO--d_6, δ/ ppm): 3.60 (6H, *s*, 2',4'–OCH_3), 5.13 (2H, *m*, 4–CH, 5–CH), 6.83–7.25 (8H, *m*, Ar–H), 8.60 (1H, *bs*, NH), 9.63 (1H, *bs*, NH). ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ ppm): 51.1, 58.2, 101.2, 111.2, 121.2, 125.2, 125.9, 127.3, 129.1, 129.8, 132.6, 134.8, 153.7, 154.6, 177.1. MS (EI) (*m*/*z*): 326 (M^+).

*4-(4-*N,N*-Dimethylphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**3h**)*. Yellow crystals; m.p.: 162–164 °C; Anal. Calcd. for $C_{18}H_{19}N_3S$: C 69.91, H 6.14, N 13.9 %. Found: C 70.03, H 6.19, N 13.95 %. FTIR (KBr, cm^{-1}): 3196 (NH), 1640 (C=N), 1552, 1475 (C=C), 1191 (C=S). ^{1}H-NMR (400 MHz, DMSO--d_6, δ/ ppm): 2.74 (6H, *s*, $N(Me)_2$), 5.00 (2H, *m*, 4–CH, 5–CH), 6.83–7.25 (8H, *m*, Ar–H), 8.64 (1H, *bs*, NH), 9.60 (1H, *bs*, NH). ^{13}C-NMR (100 MHz, DMSO-d_6, δ/ /ppm): 56.5, 79.7, 102.0, 112.2, 125.6, 126.3, 128.0, 128.2, 130.3, 134.5, 138.7, 150.5, 176.1. MS (*m*/*z*): 309 (M^+).

In the present work, chalcone derivatives **1** were treated with thiourea **2** in the presence of potassium hydroxide in ethanol to produce the pyrimidine-2-thione derivatives **3**. The reaction occurred in two steps: first conjugate addition took place on the β-position of carbonyl group and then nucleophilic attack on the carbonyl group followed by dehydration led to the six-membered ring products (Scheme 1).[17,19,20]



1 **2** **3**

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$(Me)_2$

Scheme 1. Approach to the synthesis of pyrimidine-2-thiones under ultrasound irradiation (in **3h** N$(Me)_2$ stands for 4-N$(Me)_2$).

Application of ultrasound shortened the reaction time of the generation of pyrimidines from 6 h under classical conditions to 30 min. In addition, the yields of the products were improved by 20–30 % in comparison with those obtained by the thermal heating method (Table I).

Conventional heating of the sonicating reaction mixture to the same (bulk) temperature did not lead to any significant differences in the yields and times.

In the view of the interest in green chemistry for the synthesis of organic compounds, an optimized procedure for the preparation of pyrimidine-2-thione derivatives was developed. These reactions were realized under milder and cleaner conditions. While with thermal heating these reactions required 6 h at 70–80 °C, the new method was performed at room temperature for shorter times.

CONCLUSIONS

An optimized procedure for the preparation of pyrimidine-2-thione derivatives under mild and clean conditions was described. The advantages of ultrasound in chemical reactions, such as shorter reaction times, higher yields and milder conditions, could be of use in industrial applications in the pharmaceutical or fine chemical industries.

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ИЗВОД

СИНТЕЗА ДИХИДРОПИРИМИДИН-2-ТИОНА УЛТРАОЗВУЧИВАЊЕМ

JAVAD SAFAEI-GHOMI и MOHAMMAD ALI GHASEMZADEH

Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, 51167 Kashan, I. R. Iran

Деривати халкона добијени су кондензацијом различитих супституисаних арил-алдехида и ацетофенона под базним условима у етанолу, а деривати пиримидин-2-тиона добијени су реакцијом халкона и тиоурее, под уобичајеним реакционим условима и ултраозвучивањем. Уочене су предности ултраозвучивања реакционе смеше, као што су повећање приноса и добијање производа за краће реакционо време, 20–30 min. Карактеризација и

одређивање структуре производа извршено је уобичајеним спектроскопским и аналитичким методама.

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