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Facile one-pot three-component synthesis of 4,6-diaryl-3,4-dihydropyrimidine-2(1H)-thiones under ultrasonic irradiation

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ABSTRACT

We developed a facile one-pot procedure for the synthesis of 4,6-diaryl-3,4-dihydropyrimidine-2(1H)-thione under ultrasonic irradiation. The method is based on a three components reaction of aldehydes, ketones, and thiourea under basic conditions affording isolated yields of up to 95% within a reaction time of 30–90 min.

GRAPHICAL ABSTRACT

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Biginelli reaction; 4,6-diaryl-3,4-dihydropyrimidine-2(1H)-thiones; multi-component reactions; one-pot synthesis; ultrasound

Introduction

Pyrimidines are among the most prominent heterocyclic compounds that exhibit a range of significant pharmacological and herbicidal activities.^[1,2] They are found in many bioactive natural products as well as numerous nucleoside and non-nucleoside analogs. Pyrimidine derivatives are also important chemical scaffolds in synthetic organic chemistry. In particular, dihydropyrimidine (DHPM) derivatives have been reported to exert a range of interesting biological activities.^[1,3] Recent reports indicated that the potent cytotoxic activity of some 4,6-diaryl-3,4-dihydropyrimidine-2(1H)-thione derivatives could be attributed to their structural analogy to combretastatin A-4 (Figure 1).^[4–6] Accordingly, the design of efficient synthetic routes to this class of compounds has attracted considerable attention from various research groups.

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Figure 1. Cytotoxic 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones and their structural analogy to combretastatin A-4.

Traditionally, these 4,6-disubstituted-pyrimidines have been prepared by cyclocondensation of chalcones with thiourea under the ultrasound,^[7] microwave,^[8] or refluxing conditions in basic media.^[9–12] Notably, these syntheses require the formation and isolation of chalcones before conducting the cyclization step. Alternatively, they can be prepared by one-pot procedure under microwave^[13] or refluxing condition.^[14] As part of an ongoing project in our group aiming for the design of important bioactive compounds derived from 4,6-diaryl dihydropyrimidine-2-thiones, we envisioned the possibility of preparing these compounds in a one-pot protocol from aldehyde and ketone derivatives with thiourea under ultrasound irradiations without the need to isolate the intermediate chalcones. Notably, the one-pot protocol using ultrasound irradiation has been successfully applied to similar Biginelli type reactions to prepare substituted pyrimidines.^[15–17] The one-pot multicomponent reactions have several advantages over the stepwise approaches in terms of efficiency, product purity as well as time and atom economy.^[1,18–21]

The ultrasound technique is broadly used in organic synthesis as a green and eco-friendly method. The ultrasound wave induces cavitations in the reaction mixture as the molecules oscillate around themselves and create a great number of cavitation bubbles that enlarge rapidly and subsequently undergo violent collapse. This collapse increases the temperature of the reaction mixture that is enough to cross the activation energy barrier and the reaction occurs.^[1,18,22] In this paper, we report our endeavor to synthesize a number of 4,6-diaryl-3,4-dihydropyrimidine-2(1*H*)-thiones in a one-pot procedure under ultrasonic irradiation.

Results and discussion

Initially, we attempted to prepare the target dihydropyrimidines **1–11** by the conventional one-pot reaction of aromatic aldehydes, acetophenones, and thiourea in ethanolic KOH under refluxing conditions, however, the reaction required longer times (>16 hr) leading to poor chemical yields and several byproducts. Therefore, we opted to conduct the reaction under ultrasound irradiation as a green and ecofriendly method (Table 1).

After short optimization of the reaction conditions, we were delighted to get the maximum chemical yields under irradiation for 30–90 min at 50 °C (Table 1). At room temperature, inferior chemical yields were obtained even after prolonged reaction time. Under the optimized conditions, a variety of un/substituted dihydropyrimidines were

Table 1. One-pot synthesis of 4,6-diaryl-3,4-dihydropyrimidine-2-(1*H*)thiones **1–11**.

1

1-11

Entry	Products	Reaction time (min)	% Yield	Entry	Products	Reaction time (min)	% Yield
1		40	94	7		50	93
2		50	89	8		40	84
3		30	91	9		50	88
4		60	85	10		80	80
5		50	89	11		90	78
6		30	95

Scheme 1. Plausible mechanism for the formation of the target 4,6-diaryl-3,4-dihydropyrimidine-2-thiones.

efficiently obtained in yields of up to 95%. However, vanillin and nitrobenzaldehydes were not suitable substrates for this reaction. A plausible reaction mechanism is depicted in Scheme 1.^[10,11] We believe the reaction commences with the formation of chalcones **A** which are readily attacked by the deprotonated thiourea via a 1,4-attack. Thereafter, intramolecular cyclization and subsequent dehydration delivered the target compounds. The mechanism supports our observation that aldehydes and ketones

having electron-donating groups required somewhat longer reaction times that is attributed to the slower formation of intermediate chalcones or the slower rate of subsequent cyclization (Table 1, entries 10, 11). On the other hand, aldehydes and ketones bearing electron-withdrawing groups reacted faster owing to the rapid formation of chalcones and the rapid cyclization as well (entries 3, 6).

Conclusion

A green and efficient ultrasound-assisted one-pot three-component reaction for the synthesis of 4,6-diaryl-3,4-dihydropyrimidine-2-(1*H*)thiones has been developed. The method affords up to 95% yield in only 30–90 min under mild heating. Further exploration of the method to the synthesis of highly functionalized heterocycles is ongoing.

Experimental section

General procedure for the synthesis of dihydropyrimidine-2-thiones 1–11

In a round-bottomed flask, a mixture of the appropriate acetophenone (8 mmol), appropriate aromatic aldehyde (8 mmol), thiourea (12 mmol) and potassium hydroxide (80 mmol) in ethanol (20 ml) were placed in an ultrasonic bath at 50 °C for 30–90 min. After completion of the reaction, as monitored by TLC, the reaction volume was reduced to its half under vacuum and then poured into crushed ice. The produced precipitate was filtered off, washed with water, and dried. Crystallization from ethanol afforded the pure products (1–11). Yields: (78–95%).

4,6-Diphenyl-3,4-dihydropyrimidine-2(1*H*)-thione 1.^[10]

Off-white shiny crystals, yield = 94%, mp = 182–184 °C (reported mp = 182–184 °C); ¹H NMR (300 MHz, CDCl₃) δ: 7.76 (s, 1H, NH), 7.38 (s, 5H, Ar-H), 7.36 (s, 5H, Ar-H), 7.07 (s, 1H, NH), 5.26 (s, 1H, H-4), 5.18 (s, 1H, H-5). ¹³C NMR (75 MHz, CDCl₃) δ: 174.75, 141.81, 133.49, 132.82, 129.12, 128.70, 128.56, 128.16, 126.47, 124.77, 100.19, 56.74. Data are in good agreement with those reported.^[10]

Supplementary data (copies of ¹H and ¹³C NMR spectra of all the synthesized compounds) associated with this article can be found via the “Supplementary Content” section of this article’s webpage.

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