Journal of the Serbian Chemical Society
JSCS-info@shd.org.rs • www.shd.org.rs/JSCS
J. Serb. Chem. Soc. *83* (6) 673–684 (2018) UDC 547.857.4+66.092.000.57:547.48:547.571:547.495.2:547.496.3:547.822.
JSCS–5103 *Original scientific paper*

Three-component reaction of *β*-keto esters, aromatic aldehydes and urea/thiourea promoted by caffeine, a green and natural, biodegradable catalyst for eco-safe Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones derivatives under solvent-free conditions

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(Received 12 July 2017, revised 1 April, accepted 17 April 2018)

Abstract: Caffeine was found to be a natural and green and biodegradable catalyst for the one-pot, three-component condensation Biginelli reaction of *β*-keto esters, aromatic aldehydes and urea/thiourea to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones/thiones derivatives under solvent-free conditions. The remarkable features of this green procedure are high yields, short reaction times, simplicity of operation and work-up procedures, the availability and easy handling of this solid catalyst, avoidance of hazardous or toxic catalysts and organic solvents and economic availability of the catalyst.

Keywords: caffeine; natural and green biodegradable catalyst; Biginelli reaction; 3,4-dihydropyrimidin-2(1*H*)-ones/tihones derivatives; eco-safe procedure; solvent-free conditions.

INTRODUCTION

In recent years, organic chemists have focused their attention towards green chemistry for the synthesis of heterocyclic compounds using multi-component domino reactions (MCRs)[1–6] due to a broad range of notable advantages, such as non-toxic substrate and environmental friendliness. Atom economy, reduction in by-products, number of steps in an organic synthesis, energy cost, produced waste, use of non-hazardous reagents in catalytic protocols are some of the most important goals of green chemistry. Furthermore, organic reactions under solvent-free conditions for green and clean synthesis of organic compounds have attracted the interest of organic chemists.

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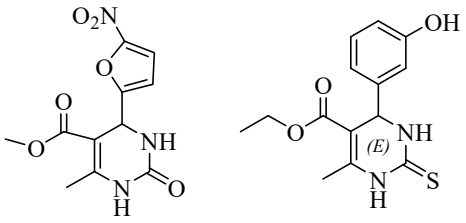
https://doi.org/10.2298/JSC170712041M

Structures containing the pyrimidinones are of interest to organic chemists because of their biological activities. Literature reports have already established pyrimidinones as calcium channel blockers, with antihypertensive,[7] anticancer,[8] anti-HIV agent,[9] antibacterial and antifungal,[10] antiviral,[11] antioxidative[12] and anti-inflammatory effects.[13] Some of structures containing the pyrimidinones with biological activities are shown in Fig 1.



Nitractin Monastrol

Fig. 1. Structures containing the pyrimidinones with biological activities.

In view of the great importance of pyrimidinone derivatives, recently, the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones derivatives was reported using multi-component reactions in the presence of different catalysts, such as calcium fluoride,[15] copper(II) sulfamate,[16] baker's yeast,[17] hydrotalcite,[18] hexaaqua-aluminum(III) tetrafluoroborate,[19] TBAB,[20] and copper(II) tetrafluoroborate,[21] [Btto][*p*-TSA],[22] triethylammonium acetate,[23] and *p*-dodecylbenzenesulfonic acid.[24] Each of these methods has its own merits, but some are limited in terms of the use of expensive catalysts, low yields, long reaction times, tedious work-up procedures and hazardous or toxic catalysts and organic solvents with column chromatographic separation. Consequently, there is a need to develop alternative methods for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones derivatives under mild, green and eco-safe conditions.

Caffeine (trimethylxanthine alkaloid, Fig. 2) is chemically related to the adenine and guanine bases of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It is found in the seeds, nuts, or leaves of a number of plants native to South America and East Asia and helps in their protection against predator insects and in the prevention of the germination of nearby seeds. It is the world's most widely consumed psychoactive drug, including Parkinson and Alzheimer's disease.[25–27] There are several known mechanisms of action to explain the effects of caffeine, for example, caffeine augmented the antidepressant-like activity of mianserin and agomelatine in forced swim and tail suspension tests in mice.[28] The most prominent is that it reversibly blocks the action of adenosine on its receptor and consequently, prevents the onset of drowsiness induced by adenosine. Caffeine also stimulates certain portions of the autonomic nervous system.[29]

Caffeine has emerged as a natural, green, cheap and efficient catalyst in various organic transformations.[30,31] In continuation of ongoing work on the dev-

elopment of a useful synthetic methodology for the preparation of these biologically active heterocyclic compounds,[32] herein, a simple and highly efficient procedure for the one-pot, three-component Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones derivatives using caffeine as a green, eco-safe and availabile solid catalyst under solvent-free conditions is presented.

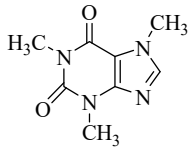


Fig. 2. Structure of caffeine.

The advantages of caffeine as solid catalyst in organic compounds synthesis are friendly environment, mild, inexpensive, non-toxic and biodegradable. Finally, in this procedure, an eco-friendly, simple and mild one-pot approach for synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives using caffeine as a green and cost effective catalyst *via* three-component Biginelli reaction between β-keto esters, aryl aldehyde derivatives and urea/thiourea under solvent-free conditions with excellent yields is reported.

EXPERIMENTAL

Chemicals and apparatus

The melting points of all compounds were determined using an Electrothermal 9100 apparatus. The ^{1}H-NMR spectra were recorded on a Bruker DRX-400 Avance instrument using DMSO-d_6 as the solvent. All reagents and solvents, purchased from Merck, Fluka or Acros Chemical Companies, were used without further purification.

*General procedure for preparation of 3,4-dihydropyrimidin-2(1H)-ones/thiones derivatives (**4a**–**w**)*

A mixture of an aldehyde derivative (**1**, 1.0 mmol), urea/thiourea (**2**, 1.5 mmol) and ethyl/methyl acetoacetate (**3**, 1.0 mmol) was heated under solvent-free conditions at 80 °C for the appropriate time in the presence of caffeine (15 mol %). After completion of the reaction (followed by thin layer chromatography TLC), the mixture was cooled to rt, cold was water added and the formed precipitate was separated by filtration and recrystallized from ethanol to afford the pure products (**4a**–**w**). Supporting information associated with this article can be found, in the online version.

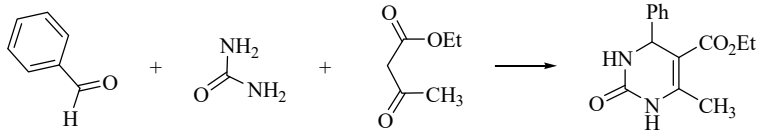
Analytical and spectral data of the synthesized compounds are given in the Supplementary material to this paper.

RESULTS AND DISCUSSION

In pursuit of continued interest in the development of solvent-free and green synthetic procedures, it was decided to explore the use of caffeine as catalyst for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones derivatives *via* Biginelli condensation in high to excellent yields at 80 °C under solvent-free conditions. Initially the reaction between benzaldehyde (1.0 mmol), urea (1.5 mmol) and

ethyl acetoacetate (1.0 mmol) as the model reaction was examined in the presence of varying amount of caffeine as a catalyst and the results are presented in Table I. The best result was achieved by performing the reaction with 0.03 g of catalyst (Table I, entry 4). The use of a higher amount of catalyst did not improve the yield, while a decrease in the amount of catalyst decreases the yield (Table I). In the absence of catalyst, the reaction did not proceed even after a long reaction time (Table I, entry 1). In addition, the effect of temperature was studied by performing the model reaction at different temperatures under solvent-free conditions (room temperature (rt), 40, 60, 70, 80 and 90 °C) and the best results were obtained at 80 °C (Table I, entry 4).

TABLE I. Optimization of the reaction condition on the synthesis of **4a**; reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol) and caffeine was heated under various temperatures for an appropriate time



Entry	Catalyst amount, g	t / °C	τ / min	Yield[a] / %
1	Catalyst free	80	360	No product
2	0.01	80	60	47
3	0.02	80	35	73
4	0.03	80	25	91
5	0.03	rt	360	No product
6	0.03	40	70	38
7	0.03	60	45	56
8	0.03	70	30	69
9	0.03	90	25	91
10	0.04	80	25	92

[a]Isolated yield

To study the generality of this process, a wide range of aromatic aldehyde derivatives (**1**, 1.0 mmol), urea/thiourea (**2**, 1.5 mmol) and ethyl/methyl acetoacetate (**3**, 1.0 mmol) were condensed to the corresponding 3,4-dihydropyrimidin-2(1*H*)--ones/thiones derivatives in the presence of a catalytic amount of caffeine and the related 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones derivatives derivatives were obtained in high to excellent yields without the observation of any by-product (Table II and Scheme 1). The structure of the products was characterized by their melting points and nuclear magnetic resonance (^{1}H-NMR) spectral data, which were then compared with those of authentic samples.

The proposed mechanistic route of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones synthesis in the presence of caffeine is shown in Scheme 2. In this mechanism, the reaction of aldehydes (**1**) with urea (**2**) generates an imine intermediate **A**,

which further reacts with the activated 1,3-dicarbonyl compound **B** (the caffeine catalysis is presented in Scheme 2) to produce, after passing a few steps, an open-chain ureide **C**, which undergoes subsequent cyclization and dehydration to give the major product (**4**).[33]

TABLE II. Caffeine catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones derivatives

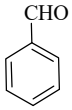
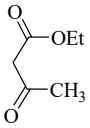
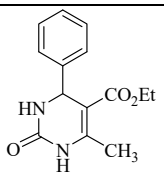
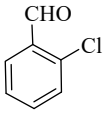
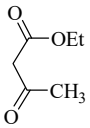
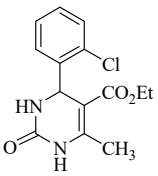
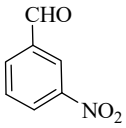
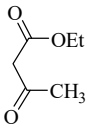
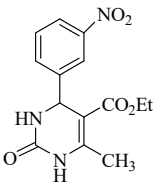
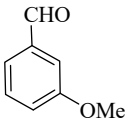
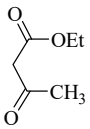
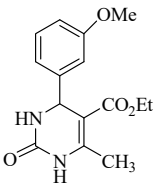
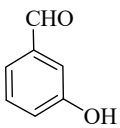
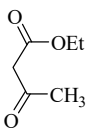
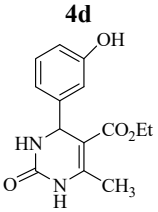
Entry	Ar	R	X	Product	τ min	Yield[a] %	m.p. / °C Found	m.p. / °C Lit.
1			O	 **4a**	25	91	198–200	200–202[19]
2			O	 **4b**	30	82	221–223	220–223[16]
3			O	 **4c**	25	89	223–225	225–227[21]
4			O	 **4d**	30	84	203–205	205–206[17]
5			O	 **4e**	35	81	165–167	163–166[21]

TABLE II. Continued

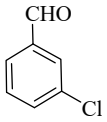
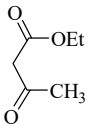
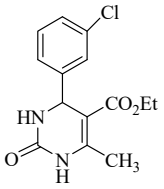
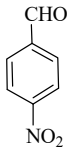
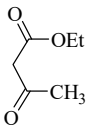
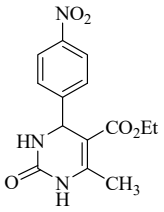
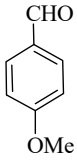
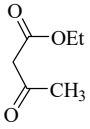
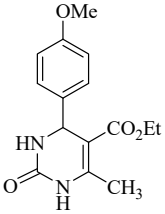
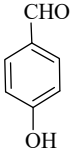
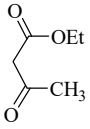
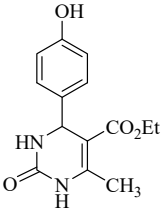
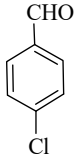
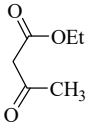
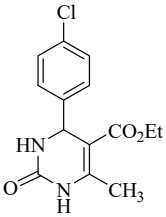
Entry	Ar	R	X	Product	τ min	Yield[a] %	M.p., °C	
6			O	 **4f**	30	80	193–195	191–193[16]
7			O	 **4g**	25	84	209–210	207–209[19]
8			O	 **4h**	30	87	200–202	202–203[18]
9			O	 **4i**	35	79	230–231	230–232[20]
10			O	 **4j**	30	81	215–217	214–215[18]

TABLE II. Continued

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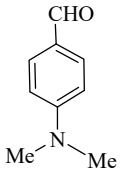
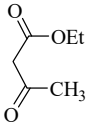
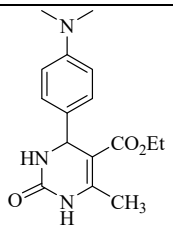
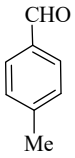
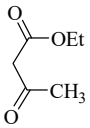
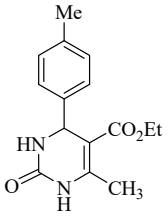
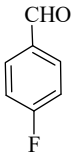
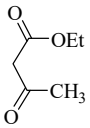
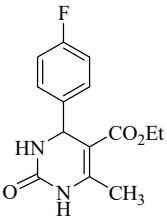
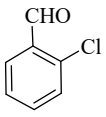
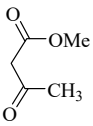
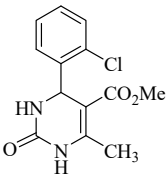
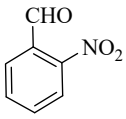
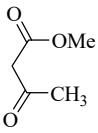
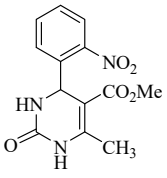
11			O	 **4k**	30	87	257–259	255–257[18]
12			O	 **4l**	25	88	204–206	204–205[17]
13			O	 **4m**	25	93	172–174	174–176[20]
14			O	 **4n**	30	84	251–253	248–252[16]
15			O	 **4o**	25	92	275–277	274–277[21]

TABLE II. Continued

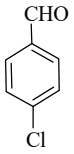
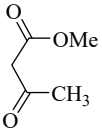
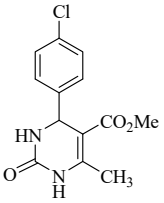
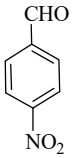
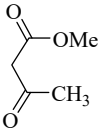
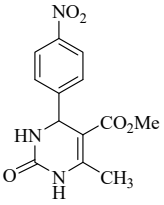
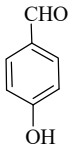
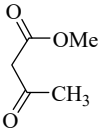
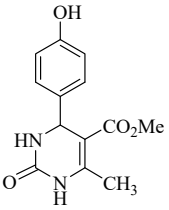
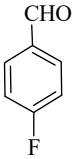
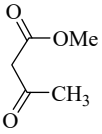
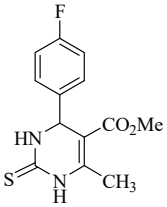
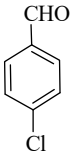
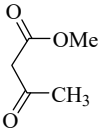
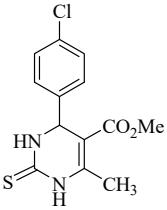
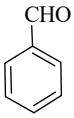
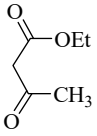
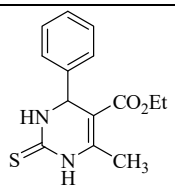
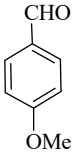
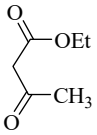
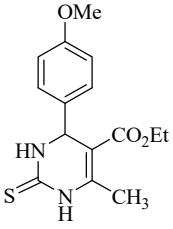
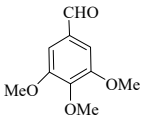
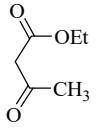
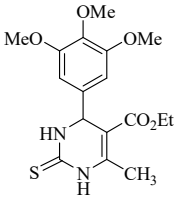
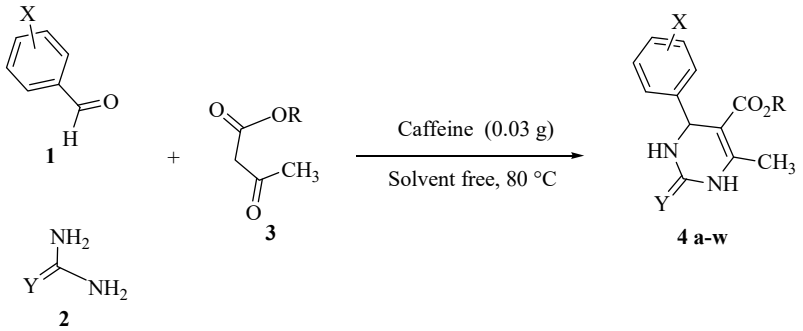
Entry	Ar	R	X	Product	τ min	Yield[a] %	M.p., °C	
16			O	 **4p**	30	84	206–208	205–206[23]
17			O	 **4q**	25	89	215–217	214–216[19]
18			O	 **4r**	35	83	244–246	245–246[16]
19			S	 **4s**	25	92	210–212	208–210[20]
20			S	 **4t**	30	86	193–195	191–195[15]

TABLE II. Continued

Entry	Ar	R	X	Product	τ min	Yield[a] %	M.p., °C	
21			S	 **4u**	25	88	208–209	208–210[19]
22			S	 **4v**	30	85	151–153	150–152[19]
23			S	 **4w**	30	83	195–197	b

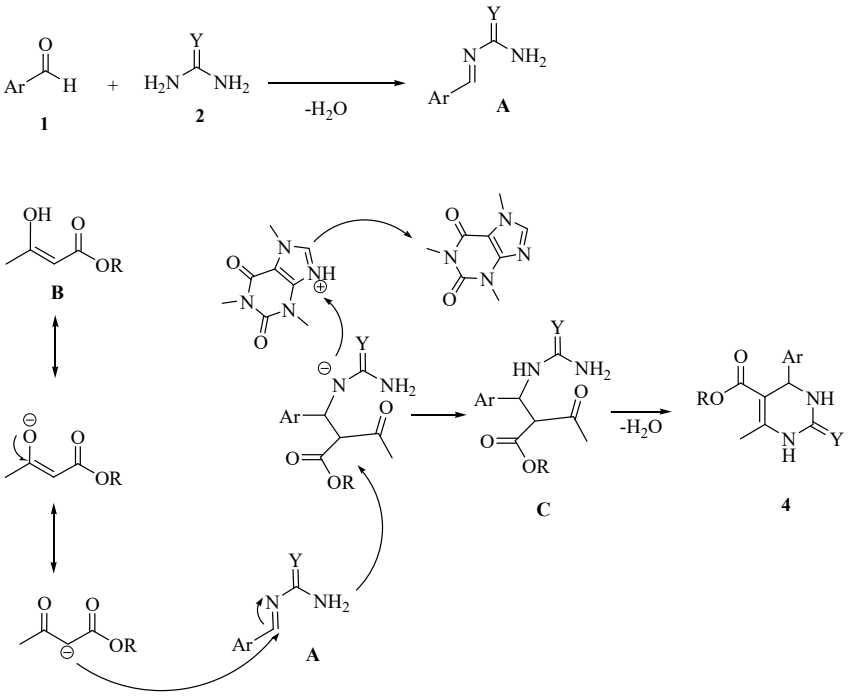
[a]Isolated yield; [b]the new compound synthesized in this work



Scheme 1. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones derivatives.

Moreover, a comparison of the catalytic ability of some of the catalysts reported in the literature for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones derivatives is presented in Table III. This study reveals that caffeine shows an extraordinary potential to be an alternative green, natural, biodegradable and cost effective catalyst for the Biginelli reaction. In addition, the use of solvent-free

conditions together with excellent yields and short reaction times in the reaction with both urea and thiourea are notable advantages of the herein presented methodology.



Scheme 2. Proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones.

TABLE III. Comparison of catalytic ability of some of catalysts reported in the literature for the synthesis of **4a** based on the reaction of benzaldehyde, ethyl acetoacetate and urea

Entry	Catalyst	Solvent, *t* / °C	*τ* / min/Yield, %
1	baker's yeast	Room temperature	1440/84[17]
2	hydrotalcite	Solvent-free, 80	35/84[18]
3	$[Al(H_2O)_6](BF_4)_3$	MeCN, reflux	1200/81[19]
4	$Cu(BF_4)_2{\cdot}xH_2O$	Room temperature	30/90[21]
5	[Btto][*p*-TSA]	Solvent-free, 90	30/96[22]
6	triethylammonium acetate	Solvent-free,70	45/90[23]
7	*p*-dodecylbenzenesulfonic acid	Solvent-free, 80	180/94[24]
8	caffeine	Solvent-free, 80	25/91[a]

[a]This work

CONCLUSIONS

In conclusion, it was demonstrated that a naturally green and biodegradable catalyst, caffeine, could be used as a highly efficient catalyst for the one-pot

Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones under solvent--free conditions. The use of the inexpensive and easy to handle caffeine as a mild natural green catalyst, leading to high to excellent yields, with short reaction times, high catalytic efficiency, straightforward work-up with no column chromatographic separation, environmentally benign nature of the procedure and solvent-free conditions are the notable advantages of this eco-safe and simple protocol. □

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

Acknowledgement. We gratefully acknowledge the financial support from the Young Researchers and Elite Club Islamic Azad University of Shiraz.

ИЗВОД

ТРОКОМПОНЕНТНА РЕАКЦИЈА β-КЕТО ЕСТАРА, АРОМАТИЧНИХ АЛДЕХИДА И УРЕЕ/ ТИОУРЕЕ КАТАЛИЗОВАНА КОФЕИНОМ: ЕКОЛОШКИ И ПРИРОДНИ БИОДЕГРАДАБИЛНИ КАТАЛИЗАТОР У ЕКО-БЕЗБЕДНОЈ BIGINELLI-СИНТЕЗИ ДЕРИВАТА 3,4-ДИХИДРОПИРИМИДИН-2(1*H*)-ОНА/ТИОНА, У УСЛОВИМА БЕЗ ПРИСУТНОГ РАСТВАРАЧА

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Утврђено је да кофеин као природни биодеградабилни производ и еколошки прихватљиво једињење катализује трокомпонентну кондензацију, која се одвија у једном реакционом кораку. Бињинели (Biginelli)-реакцијом β-кето естара, ароматичних алдехида и урее/тиоурее добијени су одговарајући 3,4-дихидропиримидин-2(1*H*)-они/тиони без присуства растварача. Изузетне особине овог еколошки прихватљивог поступка су висок принос производа, кратко реакционо време, једноставна обрада реакционе смеше, доступност и лака употреба овог чврстог катализатора, избегавање опасних и отровних катализатора и органских растварача.

(Примљено 12. јула 2017, ревидирано 1. априла, прихваћено 17. априла 2018)

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