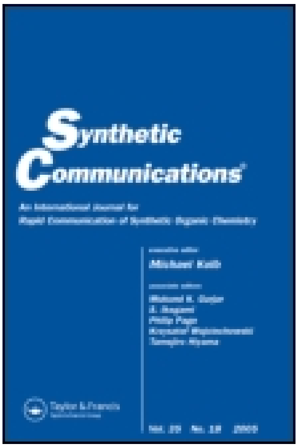


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Microwave-Assisted and Iodine-Catalyzed Synthesis of Dihydropyrimidin-2-thiones via Biginelli Reaction Under Solvent-Free Conditions

Qingjian Liu [a], Ning Pan [a], Jiehua Xu [a], Wenwen Zhang [a] & Fanpeng Kong [a]

[a] College of Chemistry, Chemical Engineering, and Materials Science, Key Laboratory of Molecular and Nano Probes, Engineering Research Center of Pesticide and Medicine Intermediate Clean Production, Ministry of Education, Shandong Provincial Key Laboratory of Clean Production of Fine Chemicals, Shandong Normal University, Jinan, China

Accepted author version posted online: 01 Feb 2012. Version of record first published: 05 Sep 2012

To cite this article: Qingjian Liu, Ning Pan, Jiehua Xu, Wenwen Zhang & Fanpeng Kong (2013): Microwave-Assisted and Iodine-Catalyzed Synthesis of Dihydropyrimidin-2-thiones via Biginelli Reaction Under Solvent-Free Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:1, 139-146

To link to this article: http://dx.doi.org/10.1080/00397911.2011.593289

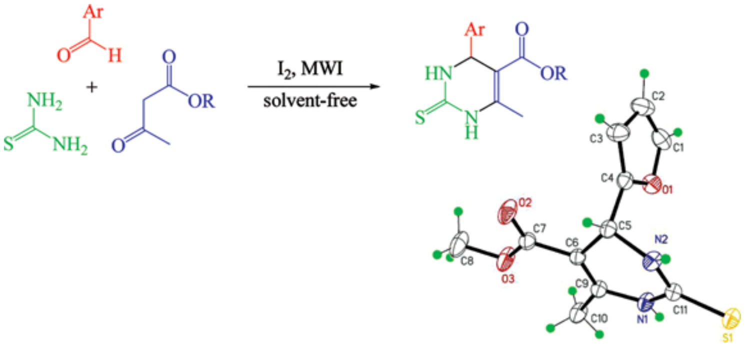
Synthetic Communications®, 43: 139–146, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.593289

MICROWAVE-ASSISTED AND IODINE-CATALYZED SYNTHESIS OF DIHYDROPYRIMIDIN-2-THIONES VIA BIGINELLI REACTION UNDER SOLVENT-FREE CONDITIONS

Qingjian Liu, Ning Pan, Jiehua Xu, Wenwen Zhang, and Fanpeng Kong
College of Chemistry, Chemical Engineering, and Materials Science, Key Laboratory of Molecular and Nano Probes, Engineering Research Center of Pesticide and Medicine Intermediate Clean Production, Ministry of Education, Shandong Provincial Key Laboratory of Clean Production of Fine Chemicals, Shandong Normal University, Jinan, China

GRAPHICAL ABSTRACT



Abstract *Microwave-assisted synthesis of 3,4-dihydropyrimidin-2-thiones via Biginelli reaction from aldehydes, acetoacetates, and thiourea in the presence of iodine under solvent-free conditions has been accomplished in good yields and purity without chromatographic separation.*

Keywords Biginelli reaction; 3,4-dihydropyrimidin-2-thiones; microwave-assisted synthesis; solvent-free reaction

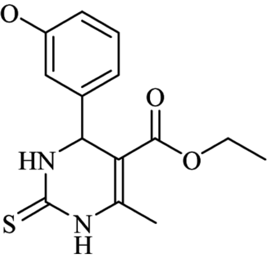
INTRODUCTION

Dihydropyrimidinones (DHPMs) have attracted considerable attention recently in synthetic organic chemistry because of their wide range of biological activities,[1]

Received February 27, 2011.

Address correspondence to Qingjian Liu, College of Chemistry, Shandong Normal University, Jinan 250014, P. R. China. E-mail: liuqj@sdnu.edu.cn

pharmaceutical and therapeutic properties, and antibacterial, antiviral, antitumor, and anti-inflammatory activities.[2] Well-known examples are batzelladine alkaloids, which are potent HIV group-120-CD4 inhibitors,[3] and monastrol, which is the only cell-permeable molecule currently known to specifically inhibit mitotic kinesin Eg5 and can therefore be considered as a lead for the development of new anticancer drugs.[4]



Monastrol

The Biginelli reaction,[5] a one-pot condensation of aldehyde, acetoacetate, and urea under strongly acidic conditions, is one of the most useful multicomponent reactions (MCRs), gaining increasing importance in organic and medicinal chemistry because of its the capacity to generate multifunctionalized products including 3,4-dihydropyrimidin-2-ones, their thiones analogs, and other related heterocyclic compounds. Therefore, many improvements and modifications of the Biginelli reaction have been made, especially in the catalysis of the reaction.[6] A number of new catalysts such as $FeCl_3 \cdot 6H_2O$, $BF_3 \cdot OEt_2$, $LaCl_3$, $La(OTf)_3$, $Yb(OTf)_3$, InX_3, $ZrCl_4$, $Mn(OAc)_3$, $LiClO_4$, or a combination of Lewis acids with transition-metal salts have been reported.[7] Iodine as a nontoxic and readily available catalyst has been used in the Biginelli reaction.[8]

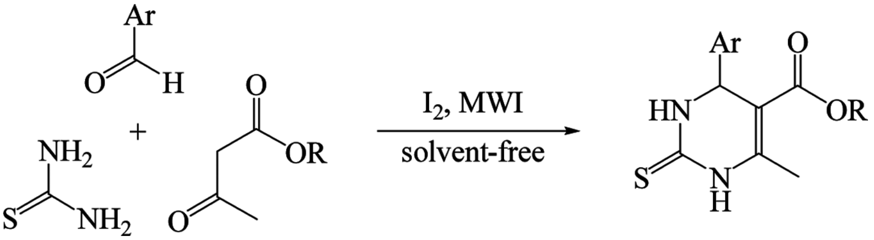
Microwave irradiation (MWI), a nonconventional energy source, has become an important method in organic synthesis.[9] Moreover, many reactions under microwave irradiation can be performed without any solvent.[10]

As increasing environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean processes that can avoid using harmful organic solvents or, even better, do not need solvents at all.

In continuation of our interest in the use of cheap and commercially available catalysts along with MWI for the green synthesis of heterocyclic compounds such as 3,4-dihydropyrimidin-2(1*H*)-thione derivatives, we report herein the microwave-assisted and iodine-catalyzed synthesis of substituted 3,4-dihydropyrimidin-2(1*H*)-thiones via the Biginelli reaction from aldehydes, methyl and ethyl acetoacetates, and thiourea under solvent-free conditions (Scheme 1).

EXPERIMENTAL

In a typical procedure, 2.5 mmol of an aldehyde, 5 mmol of acetoacetate, and 5 mmol of thiourea with a catalytic amount of iodine were mixed and irradiated in a microwave synthesizer (XH-200A, 600 W) at 60 °C for 15–30 min. After completion of the reaction, monitored by thin-layer chromatography (TLC), the resulting mixture was dissolved in ethyl acetate and cooled to precipitate out, then filtered to obtain the crude products in good yield. Recrystallization from ethanol afforded



Scheme 1. Synthesis of 3,4-dihydropyrimidin-2-thiones.

the pure products (Table 1). The best results were observed when the molar ratio of aldehyde, acetoacetate, and thiourea was 1:2:2.

The present microwave-induced and iodine-catalyzed protocol is efficient, convenient, and practical. The prominent aspect is the short reaction time (15–30 min). Iodine works well as an excellent catalyst for this one-pot, three-component synthesis of dihydropyrimidinthiones. It is seen from Table 1 that a wide range of substituents can be incorporated in the 4-aryl ring, including the hydroxyl and the azido groups. This facile procedure represents a valid alternative to the existing methods, especially for aldehydes bearing acid-sensitive groups. Iodine may play a crucial role in accelerating the dehydration step and enolization of the β-ketoester.

All the products prepared have been characterized by ^{1}H NMR and infrared (IR), and unknown compounds were characterized also by ^{13}C NMR, mass spectrometry (MS), and elemental analysis. The structures of methyl 6-methyl-4-(2-furyl)-1,2,3,4-tetrahydro-2-thioxo-5-pyrimidinecarboxylate **11** and ethyl 6-methyl-4-phenyl-1,2,3,4-tetrahydro-2-thioxo-5-pyrimidinecarboxylate **22** have been unambiguously confirmed by single-crystal x-ray crystallographic analysis (Figs. 1 and 2). In the molecular structures of the crystals **11** and **12**, the 3,4-dihydropyrimidine ring has a boat-type conformation, and the phenyl ring is almost perpendicular to the tetrahydropyrimidin-2-thione, which is similar to the structure of monastrol.[11]

Crystal Data for 11

Methyl 6-Methyl-4-(2-furyl)-1,2,3,4-tetrahydro-2-thioxo-5-pyrimidi-necarboxylate. CCDC reference: 763044, mp 252.3–253.7 °C. $C_{11}H_{12}N_2O_3S$, $M = 252.29$, triclinic, $C2/c$, $a = 7.2590(14)$ Å, $\alpha = 85.691(3)°$, $b = 7.8640(16)$ Å, $\beta = 88.594(2)°$, $c = 10.552(2)$ Å, $\gamma = 80.156(3)°$, $V = 591.8(2)$ A^{3}, $Z = 2$, $D_{\text{calcd}} = 1.416\,\text{mg/m}^{-3}$, $T = 298(2)$ K, radiation = 0.71073 Å, final R indices [$I > 2\text{r}(\text{I})$], $R_1 = 0.0423$, $wR_2 = 0.1159$, R indices (all data), $R_1 = 0.0457$, $wR_2 = 0.1191$, for all data total reflections collected/unique 3107/2156 [$R(\text{int}) = 0.0143$], GOF = 1.035. Diffraction data were measured on a Siemens 4 Circle single-crystal x-ray diffractometer.

Crystal Data for 22: Ethyl 6-Methyl-4-phenyl-1,2,3,4-tetrahydro-2-thioxo-5-pyrimidine-carboxylate

CCDC reference: 763043, mp 187.5–188.2 °C. $C_{14}H_{16}N_2O_2S$, $M = 276.35$, triclinic, $C2/c$, $a = 7.379(2)$ Å, $\alpha = 69.794(4)°$, $b = 9.505(3)$ Å, $\beta = 89.860(4)°$,

Table 1. Microwave-assisted, iodine-catalyzed, and solvent-free Biginelli synthesis of 3,4-dihydropyrimidin-2-thiones[a,b,c]

Entry	No.	Aldehydes	R	Reaction time (min)	Yield (%)	Mp (lit.) (°C)
1	**1**	C_6H_5	Me	15	95	221.6–223.8 (220–222)[7h]
2	**2**	4-ClC_6H_4	Me	15	88	153.5–155.8
3	**3**	4-BrC_6H_4	Me	15	90	179.7–180.9
4	**4**	4-FC_6H_4	Me	15	95	183.1–184.7
5	**5**	4-$O_2NC_6H_4$	Me	20	88	204.7–207.1
6	**6**	3-$O_2NC_6H_4$	Me	20	95	249.6–251.7
7	**7**	2-$O_2NC_6H_4$	Me	20	84	215.2–217.1
8	**8**	4-$MeOC_6H_4$	Me	15	90	178.3–179.6
9	**9**	3-HOC_6H_4	Me	25	82	217.8–220.2
10	**10**	4-HO-3-$MeOC_6H_3$	Me	15	90	254.6–255.5
11	**11**	2-Furyl	Me	15	90	252.3–253.7
12	**12**	3-ClC_6H_4	Me	15	92	246–247 (243–245)[7i]
13	**13**	3-$N_3C_6H_4$	Me	20	91	176.8–177.2
14	**14**	3,4-$Cl_2C_6H_3$	Me	15	90	204.3–205.7
15	**15**	4-HOC_6H_4	Me	15	93	250.3–251.6
16	**16**	2-HOC_6H_4	Me	20	89	209.3–212.7
17	**17**	4-HO-3,5-$Br_2C_6H_2$	Me	20	88	235.7–236.8
18	**18**	4-$Me_2NC_6H_4$	Me	20	90	232.6–234.4
19	**19**	4-$C_6H_5C_6H_4$	Me	30	78	>306
20	**20**	2-Hydroxyl-1-naphthalyl	Me	20	88	>326
21	**21**	C_6H_5	Et	20	95	206–208 (208–210)[7a]
22	**22**	4-ClC_6H_4	Et	20	93	188–190
23	**23**	4-BrC_6H_4	Et	20	92	190.4–192.7
24	**24**	4-FC_6H_4	Et	20	94	186.6–188.5
25	**25**	4-$O_2NC_6H_4$	Et	30	90	111–112 (109–111)[7a]
26	**26**	3-$O_2NC_6H_4$	Et	20	95	206–207 (206–207)[10g]
27	**27**	2-$O_2NC_6H_4$	Et	30	90	215.4–216.4
28	**28**	4-$MeOC_6H_4$	Et	20	92	147–149 (150–152)[7a]
29	**29**	3-HOC_6H_4	Et	30	89	182–184 (184–186)[12]
30	**30**	4-HO-3-$MeOC_6H_3$	Et	20	94	217.4–219.8
31	**31**	2-Furyl	Et	20	90	220–222 (188–190)[12]
32	**32**	3-ClC_6H_4	Et	20	91	203–205 (192–196)[12]
33	**33**	3-$N_3C_6H_4$	Et	20	92	151.3–153.1
34	**34**	4-IC_6H_4	Et	30	78	180.3–182.3
35	**35**	3,4-$Cl_2C_6H_3$	Et	20	92	110.3–112.0
36	**36**	4-HOC_6H_4	Et	20	93	205–206 (198–200)[7b]
37	**37**	2-HOC_6H_4	Et	20	90	251.6–252.9
38	**38**	4-HO-3,5-$Br_2C_6H_2$	Et	20	90	230.1–230.9
39	**39**	4-$Me_2NC_6H_4$	Et	20	92	207–209 (209–210)[10h]
40	**40**	4-$C_6H_5C_6H_4$	Et	30	77	>310
41	**41**	2-Hydroxyl-1-naphthalyl	Et	20	86	256.1–259.5

[a] The reaction was conducted under solvent-free conditions.

[b] The reaction was conducted under microwave irradiation in the presence of iodine.

[c] 2.5 mmol of an aldehyde, 5 mmol of acetoacetate, and 5 mmol of thiourea with a catalytic amount of iodine were mixed and irradiated in a microwave synthesizer (XH-200A, 600 W) at 60 °C for 15–30 min.

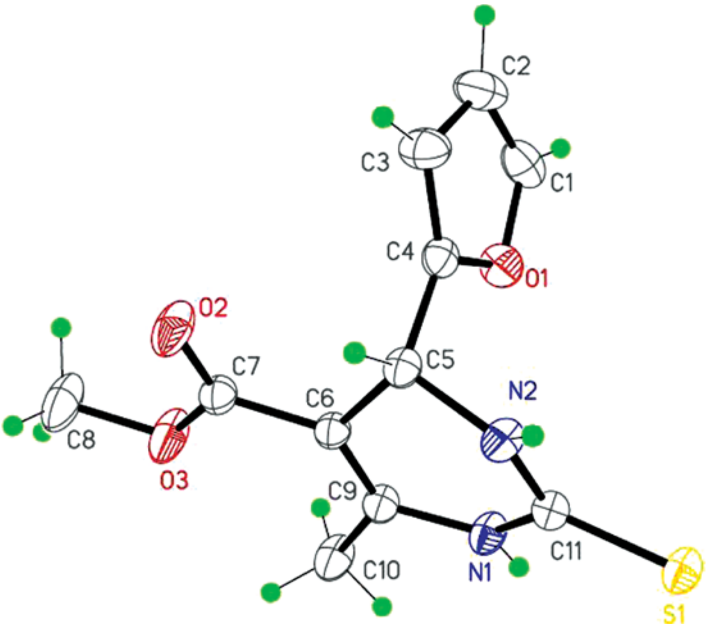


Figure 1. Crystal structure x-ray ORTEP diagram of compound **11**. (Figure is provided in color online.)

$c = 11.068(3)$ Å, $\gamma = 69.931(4)°$, $V = 678.3(3)$ A^3, $Z = 2$, $D_{calcd} = 1.353\,mg/m^{-3}$, $T = 298(2)$ K, radiation $= 0.71073$ Å, final R indices $[I > 2r(I)]$, $R_1 = 0.0515$, $wR_2 = 0.1286$, R indices (all data), $R_1 = 0.0615$, $wR_2 = 0.1355$, for all data total

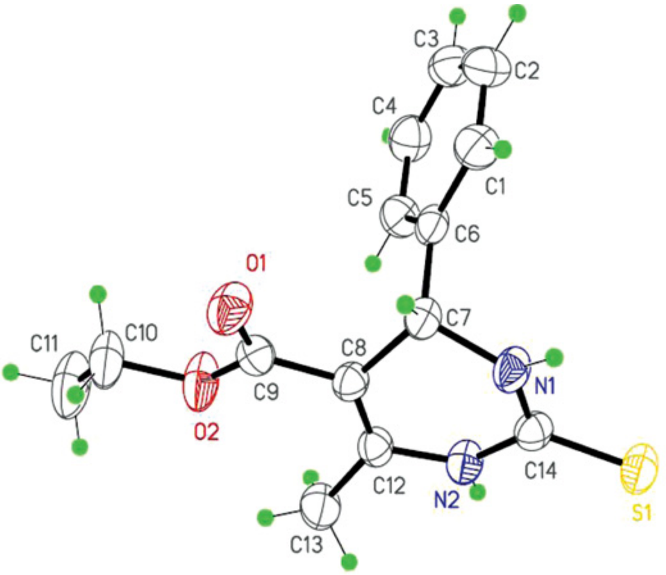


Figure 2. Crystal structure x-ray ORTE diagram of compound **22**. (Figure is provided in color online.)

Table 2. Hydrogen bonds for 11 (A and deg)

D-H . . . A	d(D-H)	d(H . . . A)	d(D . . . A)	<(DHA)
N(2)-H(2A).. . . S(1)#1	0.86	2.62	3.3834 (18)	147.9
N(1)-H(1A).. . . O(2)#2	0.86	2.13	2.969 (2)	165.5

reflections collected/unique 3574/2483 [*R*(int) = 0.0153], GOF = 1.030. Diffraction data were measured on a Siemens 4 Circle single-crystal x-ray diffractometer.

There are two molecules in the asymmetric unit linked by intermolecular N-H...S and N-H...O hydrogen bonds (Table 2), forming a netted three-dimensional structure along the *b* axis leading to a ladder pattern, which stabilized the crystal packing.

In summary, we have developed a facile, simple, and general procedure for the synthesis of 3,4-dihydropyrimidin-2-thiones from aldehydes, acetoacetates, and thiourea using iodine as catalyst under microwave irradiation and solvent-free conditions. The present environmentally benign protocol has short reaction times, good yields, and simple and easy workup and without chromatographic separation.

SUPPORTING INFORMATION

Structural characterization data and NMR spectra are available. Crystal data (excluding structural factors) of compounds **11** and **22** have been deposited with the Cambridge Crystallographic Data Centre, CCDC 763044 for **11** and 763043 for **22**, respectively. This material is available free of charge via the Internet at http://www.ccde.cam.ac.uk.

ACKNOWLEDGMENTS

Support of this work by the College of Chemistry, Chemical Engineering, and Materials Science, and Shandong Normal University is acknowledged.

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