Studies in Synthetic Chemistry 合成化学研究, 2018, 6(2), 29-36
Published Online June in Hans. http://www.hanspub.org/journal/ssc
https://doi.org/10.12677/ssc.2018.62005

Hans汉斯

Brønsted Acid Ionic Liquid Catalyzed Biginelli Reaction to Synthesize 3,4-Dihydropyrimidine-2(1*H*)-(Thio)ones Compounds

Rui Guo, Xiumei Liu, Chenjiang Liu*

Key Laboratory of Oil and Gas Fine Chemicals, Ministry of Education & Xinjiang Uygur Autonomous Region College of Chemistry & Chemical Engineering, Xinjiang University, Urumqi Xinjiang
Email: *pxylcj@126.com

Received: May 22nd, 2018; accepted: Jun. 5th, 2018; published: Jun. 12th, 2018

Abstract

A series of 3,4-dihydropyrimidine-2(1*H*)-(thio)ones were synthesized via the Biginelli reaction of aromatic aldehydes, 1,3-dicarbonyl compounds and urea or thiourea catalyzed by ionic liquid 4-phenyl-3-(3-sulfopropyl)tetrahydrothiazole-2-thione hydrogen sulfate. The experiment method has the advantages of simple operation, mild reaction condition, and convenient treatment. When the ionic liquid catalyst was reused for 6 times, the yield had no obvious change.

Keywords

Ionic Liquid, Biginelli Reaction, Catalysis, 3,4-Dihydropyrimidine-2(1*H*)-(Thio)ones

Brønsted酸性离子液体催化Biginelli反应合成3,4-二氢嘧啶-2(1*H*)-(硫)酮类化合物

郭　瑞，刘秀梅，刘晨江*

石油天然气精细化工教育部&自治区重点实验室，新疆大学化学化工学院，新疆 乌鲁木齐
Email: *pxylcj@126.com

收稿日期：2018年5月22日；录用日期：2018年6月5日；发布日期：2018年6月12日

*通讯作者。

文章引用：郭瑞，刘秀梅，刘晨江. Brønsted酸性离子液体催化Biginelli反应合成3,4-二氢嘧啶-2(1*H*)-(硫)酮类化合物[J]. 合成化学研究, 2018, 6(2): 29-36. DOI: 10.12677/ssc.2018.62005

摘　要

离子液体4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮硫酸氢盐催化芳香醛、1,3-二羰基化合物和脲或硫脲发生Biginelli反应合成了一系列3,4-二氢嘧啶-2(1*H*)-(硫)酮类化合物。本实验方法操作简单、反应条件温和、后处理方便。离子液体催化剂重复使用6次后，产率无明显变化。

关键词

离子液体，Biginelli反应，催化，3,4-二氢嘧啶-2(1*H*)-(硫)酮

1. 引言

1893 年，意大利化学家 Biginelli 首次用浓盐酸作为催化剂，用“一锅法”合成了 3,4-二氢嘧啶-2-酮衍生物(DHPMs)，并将此反应命名为 Biginelli 反应。上世纪 90 年代 Kappe [1]对 DHPMs 进行了详细的综述，研究表明 DHPMs 具有抗病毒、抗菌、消炎、抗肿瘤等重要的生理和药理活性[2]。

用浓盐酸为催化剂的传统合成方法存在环境污染、反应时间长、腐蚀设备等缺点。为了克服这些弊端，研究者改进和优化了 Biginelli 反应的合成方法，如微波促进法[3]、超声促进法[4]、研磨合成法[5]、固相合成法[6]、路易斯酸催化[7]、碱催化[8]、离子液体催化[9]、有机小分子催化[10]等。上述研究丰富了 Biginelli 反应的合成方法，获得了高产率的产物。基于 3,4-二氢嘧啶-2(1*H*)-酮衍生物的重要性，我们实验室在前期研究 Biginelli 反应的基础上[11]，将离子液体 4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮硫酸氢盐应用于催化 Biginelli 反应，并考察了不同反应条件对 Biginelli 反应的影响，同时对催化剂重复使用性进行了研究。

2. 实验部分

2.1. 仪器与试剂

美国 Varian inova-400 型核磁共振仪(TMS 为内标，D_2O 或 DMSO-d_6 为溶剂)；美国 HP1100 液相色谱质谱仪；德国 Bruker Equinox 55 红外光谱仪(KBr 压片)；瑞士 Buchi B-540 型熔点仪；上海嘉鹏 ZF_5 型手提式紫外分析仪。所用试剂均为市售分析纯，用前未经处理。

2.2. 离子液体 4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮硫酸氢盐(IL)的合成

将 17 mmol 4-苯基-四氢噻唑-2-硫酮[12]与 17 mmol 1,3-丙烷磺酸内酯溶解在乙酸乙酯溶液中，在 90˚C 油浴中加热回流反应 12 h，过滤，固体用乙腈和乙酸乙酯洗涤滤饼，干燥，用玛瑙研钵研细，即得到纯净的 4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮内盐，白色固体，产率：81%，熔点：240˚C~242˚C。

将 20 mmol 4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮内盐与 20 mmol 98%浓硫酸在 100˚C 加热反应 24 h，冷却后将产物用乙醚(3 × 10 mL)浸泡洗涤，然后在 70˚C 下真空干燥 10 h，得到褐色粘稠状离子液体，产率：81%。

离子液体表征如下：

4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮硫酸氢盐(**IL**)：褐色粘稠状液体，^{1}H NMR (D_2O, 400 MHz) δ (ppm) = 2.21~2.30 (m, 2H, CH_2), 2.99~3.07 (m, 2H, CH_2), 3.50 (t, 2H, CH_2, J = 7.3 Hz), 3.75 (dd, 1H, CH, J = 11.7, 8.8 Hz), 4.18 (dd, 1H, CH, J = 11.7, 9.1 Hz), 5.79 (t, 1H, CH, J = 9.0 Hz), 7.39~7.50 (m, 5H, ArH); ^{13}C NMR (D_2O, 100 MHz): δ (ppm) = 24.80, 34.67, 40.55, 49.62, 70.97, 127.27, 127.81, 129.99, 130.12, 130.45, 136.46, 195.26; IR (KBr), υ_{max}/cm^{-1}: 3111, 3014, 1715, 1540, 1456, 1209, 1166, 1039, 900, 769, 699; m/z (%) = 318 (100) $[M]^+$, 97 (100) $[M]^-$。

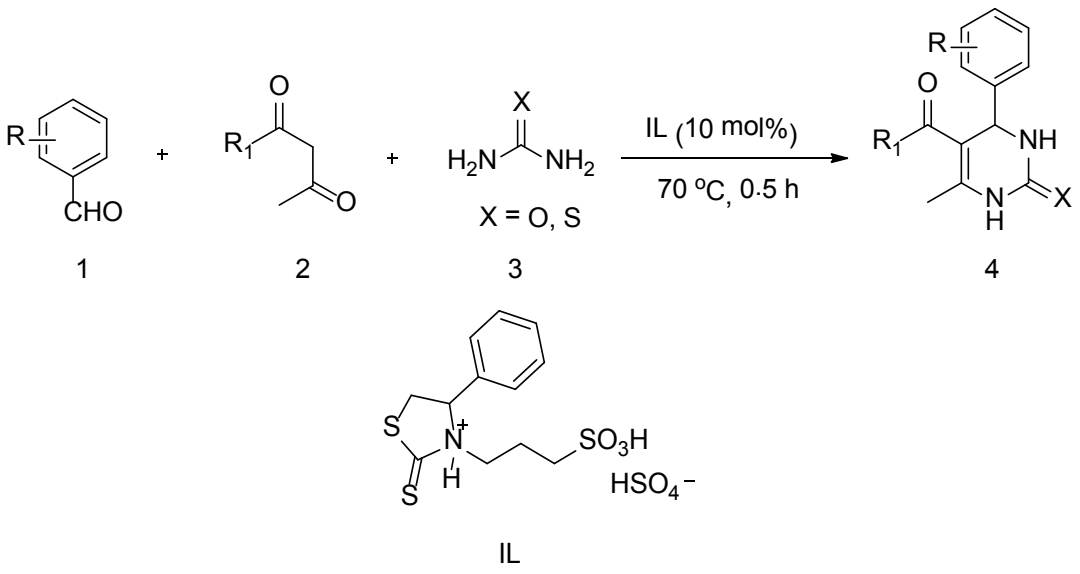
2.3. 3,4-二氢嘧啶-2(1*H*)-(硫)酮类化合物的合成

将芳香醛(2 mmol)、1,3-二羰基化合物(2 mmol)、脲或硫脲(3 mmol)、离子液体 4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮硫酸氢盐(10 mol%)，在 70˚C 下磁力搅拌反应 0.5 h。冷却后加入碎冰，过滤，冰水洗涤固体得到粗产物，经乙醇重结晶即得到纯品，反应式如式 1 所示。化合物结构经 ^{1}H NMR，^{13}C NMR、IR 和 MS 表征。

未被报道的化合物结构表征如下：

化合物 **4o**：砖红色粉末，^{1}H NMR (DMSO-d_6, 400 MHz, TMS): δ (ppm) = 0.96 (t, 3H, CH_3, J = 7.1 Hz), 2.29 (s, 3H, CH_3), 3.79~3.91 (m, 2H, CH_2), 5.89 (d, 1H, CH, J = 2.7 Hz), 7.85 (d, 1H, ArH, J = 8.7 Hz), 7.99 (s, 1H, NH), 8.53 (dd, 1H, ArH, J = 8.7, 2.4 Hz), 8.67 (d, 1H, ArH, J = 2.4 Hz), 9.53 (s, 1H, NH); ^{13}C NMR (DMSO, 100 MHz): δ (ppm) = 13.71, 17.79, 49.44, 59.32, 97.17, 119.44, 128.34, 131.04, 145.44, 146.44, 147.01, 150.28, 150.78, 164.40; IR (KBr), υ_{max}/cm^{-1}: 3304, 3111, 2982, 1653, 1599, 1531, 1347, 1056, 833; ESI-MS: m/z (%) = 321 (100) $[M + Na]^+$。

化合物 **4s**：淡黄色粉末，^{1}H NMR (DMSO-d_6, 400 MHz, TMS): δ (ppm) = 1.11 (t, 3H, CH_3, J = 7.1 Hz), 2.31 (s, 3H, CH_3), 3.93~4.11 (m, 2H, CH_2), 5.19 (d, 1H, CH, J = 3.6 Hz), 7.25~7.49 (m, 3H, ArH), 9.68 (s, 1H, NH), 10.44 (s, 1H, NH); ^{13}C NMR (DMSO, 100 MHz): δ (ppm) = 13.87, 17.11, 52.92, 59.60, 99.91, 107.66, 107.87, 116.85, 117.08, 127.60, 127.67, 131.33, 141.43, 141.46, 145.58, 156.30, 158.73, 164.78, 174.15; IR



Scheme 1. Synthesis of 3,4-dihydropyrimidine-2(1*H*)-(thio)ones(4a-4u)
式 1. 3,4-二氢嘧啶-2(1*H*)-(硫)酮(4a-4u)的合成

(KBr), υ_{max}/cm^{-1}: 3308, 3173, 2982, 1669, 1579, 1470, 1333, 1030, 942, 823, 764; ESI-MS: m/z (%) = 375 (100) $[M + Na]^+$。

化合物 **4t**：粉色粉末，^{1}H NMR (DMSO-d_6, 400 MHz, TMS): δ (ppm) = 1.01 (d, 3H, CH_3, J = 6.2 Hz), 1.17 (d, 3H, CH_3, J = 6.2 Hz), 2.23 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 4.78~4.87 (m, 1H, CH), 5.10 (d, 1H, CH, J = 3.3 Hz), 6.80~7.24 (m, 4H, ArH), 7.70 (s, 1H, NH), 9.14 (s, 1H, NH); ^{13}C NMR (DMSO, 100 MHz): δ (ppm) = 17.60, 21.40, 21.69, 54.87, 66.24, 99.32, 112.00, 112.31, 118.18, 129.38, 146.34, 148.06, 152.05, 159.05, 164.73; IR (KBr), υ_{max}/cm^{-1}: 3231, 3107, 2833, 1721, 1699, 1598, 1493, 1091, 923, 866, 788; ESI-MS: m/z (%) = 327 (100) $[M + Na]^+$。

化合物 **4u**：墨绿色粉末，^{1}H NMR (DMSO-d_6, 400 MHz, TMS): δ (ppm) = 1.03 (d, 3H, CH_3, J = 6.2 Hz), 1.16 (d, 3H, CH_3, J = 6.2 Hz), 2.22 (s, 3H, CH_3), 2.84 (s, 6H, 2 × CH_3), 4.81 (m, 1H, CH), 5.02 (d, 1H, CH, J = 3.2 Hz), 6.65~7.03 (m, 4H, ArH), 7.55 (s, 1H, NH), 9.04 (s, 1H, NH); ^{13}C NMR (DMSO, 100 MHz): δ (ppm) = 17.56, 21.47, 21.72, 53.25, 66.08, 100.11, 112.03, 126.80, 132.66, 147.14, 149.62, 152.17, 164.87; IR (KBr), υ_{max}/cm^{-1}: 3238, 3115, 2936, 1719, 1648, 1526, 1526, 1459, 1168, 1090, 920, 812; ESI-MS: m/z (%) = 340 (100) $[M + Na]^+$。

3. 结果与讨论

3.1. 优化反应条件

以苯甲醛(2 mmol)、乙酰乙酸乙酯(2 mmol)、脲(3 mmol)的反应为模型，对反应条件进行了优化，实验结果见表 1。首先考察了无催化剂条件下以及在离子液体催化剂 4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮

Table 1. Optimization of reaction conditions[a]
表 1. 反应条件优化 [a]

Entry	Catcatalyst (mol%)	Solvent	Temperature (˚C)	Time (h)	Yields (%)[b]
1	/	/	90	1	N.R
2	IL (15)	/	90	1	89
3	IL (15)	Water	90	1	33
4	IL (15)	Ethanol	90	1	68
5	IL (15)	Methanol	90	1	70
6	IL (15)	Dichloromethane	90	1	78
7	IL (15)	/	30	1	35
8	IL (15)	/	40	1	47
9	IL (15)	/	50	1	74
10	IL (15)	/	60	1	77
11	IL (15)	/	70	1	91
12	IL (15)	/	80	1	87
13	IL (15)	/	70	0.5	92
14	IL (15)	/	70	2	88
15	IL (15)	/	70	3	89
16	IL (5)	/	70	0.5	88
17	**IL (10)**	**/**	**70**	**0.5**	**93**
18	IL (20)	/	70	0.5	90

[a]反应条件：苯甲醛(2 mmol)，乙酰乙酸乙酯(2 mmol)，脲(3 mmol)，4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮硫酸氢盐(IL)，无溶剂或溶剂(2 mL)；[b]分离产率。

硫酸氢盐存在下反应的效果(表 1, entries 1-2)，结果表明离子液体催化效果较好。其次考察了有无溶剂的条件对反应的影响(表 1, entries 2-6)，结果表明无溶剂条件下产物产率较高。随后考察了温度和时间对该反应的影响(表 1, entries 2, 7-15)，结果显示，在 70˚C 时反应 0.5 h 产物产率较高。最后，我们考察了催化剂的用量对该反应的影响(表 1, entries 16-18)，当催化剂用量为 10 mol%时，催化效率最高，产物产率可达 93% (表 1, entry 17)。因此，反应的最佳条件为：离子液体催化剂 4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮硫酸氢盐用量 10 mol%，无溶剂条件下 70˚C 反应 0.5 h。

3.2. 反应底物普适性研究

在最佳反应条件下，对反应底物的普适性进行了研究，结果见表 2。研究发现，当芳香醛上连接-CH_3，-OCH_3，-$N(CH_3)_2$ 等供电子基团(表 2, entries **4b-4e**)和吸电子的卤素、硝基等基团(表 2, entries **4f-4o**)时，反应都能顺利地进行。当芳香醛上连接一个或者两个羟基(表 2, entries **4p-4q**)时，反应也可以正常进行。当硫脲代替脲参与反应时(表 2, entries **4r-4s**)，也能顺利的得到目标产物。此外，乙酰乙酸异丙酯作为一种二羰基化合物也可以很好地参与反应，分别以 81%和 90%得到目标化合物(表 2, entries **4t-4u**)。以上结果表明，该反应具有一定的底物普适性。

4. 催化剂的循环使用性研究

催化剂的循环使用研究结果见图 1。具体操作为：将反应结束后抽滤除去粗产物的滤液旋除水，真

Table 2. Research of substrate scope[a]
表 2. 底物的普适性研究 [a]

Entry	R	R_1	X	Yields (%)[b]	Mp (˚C)	
					Found	Reported [lit.]
4a	/	OEt	O	87	200~201	200~201 [13]
4b	4-CH_3	OEt	O	93	212~214	215~216 [14]
4c	2-OCH_3	OEt	O	74	257~259	256~257 [15]
4d	3-OCH_3	OEt	O	85	204~208	206~208 [16]
4e	4-$N(CH_3)_2$	OEt	O	87	252~255	256~257 [17]
4f	2-F	OEt	O	93	230~236	235~237 [18]
4g	3-F	OEt	O	82	205~207	209~211 [19]
4h	4-F	OEt	O	87	176~178	175~177 [20]
4i	2-Cl	OEt	O	82	213~215	213~215 [21]
4j	2,3-$(Cl)_2$	OEt	O	87	212~215	215~216 [22]
4k	2-Br	OEt	O	86	197~199	205~207 [23]
4l	3-Br	OEt	O	73	180~182	178~179 [24]
4m	2-Cl-6-F	OEt	O	78	247~249	246~248 [25]
4n	2-NO_2	OEt	O	69	213~216	213~215 [21]
4o	2,4-$(NO_2)_2$	OEt	O	77	204~206	
4p	4-OH	OEt	O	81	223~225	227~228 [14]
4q	3,4-$(OH)_2$	OEt	O	90	229~231	233~235 [26]
4r	2-F	OEt	S	93	86~92	87~90 [27]
4s	3-Br-4-F	OEt	S	84	208~210	
4t	3-OCH_3	i-PrO	O	81	189~191	
4u	4-$N(CH_3)_2$	i-PrO	O	90	241~243	

[a]反应条件：芳香醛(2 mmol)，1,3-二羰基化合物(2 mmol)，脲或硫脲(3 mmol)，离子液体 4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮硫酸氢盐(10 mol%)，70˚C，0.5 h；[b]分离产率。

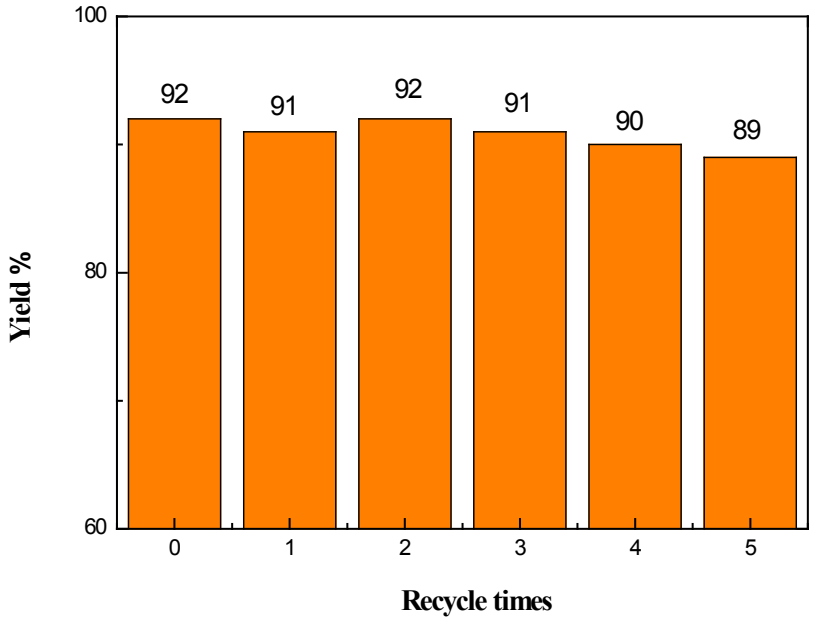


Figure 1. Recycling research of IL
图 1. IL 的循环性研究

空干燥至恒重后回收的离子液体直接用于下一次循环实验。离子液体重复使用 6 次的产率分别为 92%，91%，92%，91%，90%，89%。表明离子液体具有良好的循环使用效果。

5. 总结

本文以离子液体 4-苯基-3-丙基磺酸基四氢噻唑-2-硫酮硫酸氢盐为催化剂催化芳香醛、1,3-二羰基化合物、脲或硫脲发生 Biginelli 反应高产率地合成了一系列的 3,4-二氢嘧啶-2(1*H*)-(硫)酮类化合物，该反应方法具有操作简单、时间短、催化剂可以高效循环使用等特点。

基金项目

“万人计划”后备人选培养项目(No. wr2016cx0145)；国家自然科学基金(No. 21572195)。

参考文献 (References)

[1] Oliver, K.C. (1993) 100 Years of The Biginelli Dihydropyrimidine Synthesis. *Tetrahedron*, **49**, 6937-6963. https://doi.org/10.1016/S0040-4020(01)87971-0

[2] Kappe, C.O. (2000) Biologically Active Dihydropyrimidones of the Biginelli-Type: A Literature Survey. *European Journal of Medicinal Chemistry*, **35**, 1043-1052. https://doi.org/10.1016/S0223-5234(00)01189-2

[3] Nazeruddin, N.G.M. and Mahesh, S.P. (2010) Microwave Assisted One Pot Synthesis of Substituted Dihydropyrimidine-2(1*H*) Ones Using 5-Sulphosalicyclic Acid as a Catalyst. *Der Chemica Sinica*, **1**, 15-20.

[4] Mandhane, P.G., Joshi, R.S. and Nagargoje, D.R. (2010) Gill C.H. An Efficient Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-Ones Catalyzed by Thiamine Hydrochloride in Water under Ultrasound Irradiation. *Tetrahedron Letters*, **51**, 3138-3140. https://doi.org/10.1016/j.tetlet.2010.04.037

[5] Zohdi, H.F., Rateb, N.M. and Elnagdy, S.M. (2011) Green Synthesis and Antimicrobial Evaluation of Some New Trifluoromethyl-Substituted Hexahydropyrimidines by Grinding. *European Journal of Medicinal Chemistry*, **46**, 5636-5640. https://doi.org/10.1016/j.ejmech.2011.09.036

[6] Quan, Z.J.D., Zhang, Y.X. and Wang, X.C. (2009) PS-PEG-SO_3H as an Efficient Catalyst for 3,4-Dihydropyrimidones via Biginelli Reaction. *Catalysis Communications*, **10**, 1146-1148. https://doi.org/10.1016/j.catcom.2008.12.017

[7] Ranu, B.C., Hajra, A. and Jana, U. (2000) Indium(III) Chloride-Catalyzed One-Pot Synthesis of Dihydropyrimidinones

by a Three-Component Coupling of 1,3-Dicarbonyl Compounds, Caldehydesand Urea: An Improved Procedure for the Biginelli Reaction. *Journal of Organic Chemistry*, **65**, 6270-6272. https://doi.org/10.1021/jo000711f

[8] Debache, A., Amimour, M., Belfaitah, A., Rhouati, S. and Carboni, B. (2008) A One-Pot Biginelli Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-Ones/Thiones Catalyzed by Triphenylphosphine as Lewis Base. *Tetrahedron Letters*, **49**, 6119-6121. https://doi.org/10.1016/j.tetlet.2008.08.016

[9] Karthikeyan, P., Kumar, S.S., Arunrao, A.S., Narayan, M.P. and Bhagat, P.R. (2012) A Novel Amino Acid Functionalized Ionic Liquid Promoted One-Pot Solvent-Free Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-Thiones. *Research on Chemical Intermediates*, **39**, 1335-1342. https://doi.org/10.1007/s11164-012-0689-4

[10] Xu, D.Z., Li, H. and Wang, Y. (2012) Highly Enantioselective Biginelli Reaction Catalyzed by a Simple Chiral Primary Amine Catalyst: Asymmetric Synthesis of Dihydropyrimidines. *Tetrahedron*, **68**, 7867-7872. https://doi.org/10.1016/j.tet.2012.07.027

[11] Liu, C.J., Wang, J.D. and Li, Y.P. (2006) One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-(Thio)Ones Using Strontium(II) Nitrate as a Catalyst. *Journal of Molecular Catalysis A*: *Chemical*, **258**, 367-370. https://doi.org/10.1016/j.molcata.2006.07.037

[12] Chen, N., Jia, W. and Xu, J. (2009) A Versatile Synthesis of Various Substituted Taurines from Vicinal Amino Alcohols and Aziridines. *European Journal of Organic Chemistry*, **33**, 5841-5846. https://doi.org/10.1002/ejoc.200900759

[13] Shaabani, A. and Maleki, A. (2007) Three-Component One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-Ones Catalyzed by Bromodimethylsulfonium Bromide. *Chemical Papers*, **61**, 333-336. https://doi.org/10.2478/s11696-007-0043-2

[14] Debache, A., Amimour, M. and Belfaitah, A. (2009) A One-Pot Biginelli Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-Ones/Thiones Catalyzed by Triphenylphosphine as Lewis Base. *Tetrahedron Letters*, **40**, 6119-6121. https://doi.org/10.1002/chin.200904151

[15] Ramalingan, C. and Kwak, Y.W. (2008) Tetrachlorosilane Catalyzed Multicomponent One-Step Fusion of Biopertinent Pyrimidine Heterocycles. *Tetrahedron*, **64**, 5023-5031. https://doi.org/10.1016/j.tet.2008.03.078

[16] Kefayati, H. and Khanjanian, R. (2012) 1-Methylimidazolium Hydrogen Sulfate/Chlorotrimethylsilane: An Effective Catalytic System for the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Hydroquinazoline-2,5-Diones. *Journal of Molecular Liquids*, **172**, 147-151. https://doi.org/10.1016/j.molliq.2012.01.019

[17] Tu, S., Fang, F. and Miao, C. (2003) One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones Using Boric Acid as Catalyst. *Tetrahedron Letters*, **34**, 6153-6155. https://doi.org/10.1016/S0040-4039(03)01466-7

[18] Gholap, A.R., Venkatesan, K., Daniel, T., Lahoti, R.J. and Srinivasan, K.V. (2004) Ionic Liquid Promoted Novel and Efficient One Pot Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones at Ambient Temperature under Ultrasound Irradiation. *Green Chemistry*, **6**, 147. https://doi.org/10.1039/b314015f

[19] Boumoud, T., Boumoud, B., Mosset, P. and Debache, A. (2011) Gypsum-Catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*) under Solvent-Free Conditions. *Chemistry—A European Journal*, **8**, 312-318. https://doi.org/10.1155/2011/780271

[20] Yadav, J.S., Reddy, B.V.S., Sridhar, P., Reddy, J.S.S., Nagaiah, K. and Lingaiah, N. (2004) Green Protocol for the Biginelli Three-Component Reaction: $Ag_3PW_{12}O_{40}$ as a Novel Water-Tolerant Heteropolyacid for the Synthesis of 3,4-Dihydropyrimidinones. *European Journal of Organic Chemistry*, **3**, 552-557. https://doi.org/10.1002/ejoc.200300559

[21] Sujatha, K., Shanmugam, P., Perumal, P.T., Muralidharan, D. and Rajendran, M. (2006) Synthesis and Cardiac Effects of 3,4-Dihydropyrimidin-2(1*H*)-one-5 Carboxylates. *Bioorganic & Medicinal Chemistry Letters*, **16**, 4893-4897. https://doi.org/10.1016/j.bmcl.2006.06.059

[22] Jiang, C. and You, Q.D. (2007) An Efficient and Solvent-Free One-Pot Synthesis of Dihydropyrimidinones under Microwave Irradiation. *Chinese Chemical Letters*, **18**, 647-650. https://doi.org/10.1016/j.cclet.2007.04.002

[23] Hajipour, A.R. and Seddighi, M. (2012) Pyridinium-Based Brønsted Acidic Ionic Liquid as a Highly Efficient Catalyst for One-Pot Synthesis of Dihydropyrimidinones. *Synthetic Communications*, **42**, 227-235. https://doi.org/10.1080/00397911.2010.523488

[24] Jing, X., Li, Z., Pan, X., Shi, Y. and Yan, C. (2009) $NaIO_4$-Catalyzed One-Pot Synthesis of Dihydropyrimidinones at Room Temperature under Solvent-Free Conditions. *Journal of the Iranian Chemical Society*, **6**, 514-518. https://doi.org/10.1007/BF03246529

[25] Nasr-Esfahani, M., Hoseini, S.J. and Mohammadi, F. (2011) Fe_3O_4 Nanoparticles as an Efficient and Magnetically Recoverable Catalyst for the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones under Solvent-Free Conditions. *Chinese Journal of Catalysis*, **32**, 1484-1489. https://doi.org/10.1016/S1872-2067(10)60263-X

[26] Silva, D.L., Fernandes, S.A. and Sabino, A.A. (2011) *p*-Sulfonic Acid Calixarenes as Efficient and Reusable Organocatalysts for the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones-thiones. *Tetrahedron Letters*, **52**, 6328-6330.

https://doi.org/10.1016/j.tetlet.2011.08.175

[27] Attaby, F.A., Ramla, M.M. and Harukuni, T. (2008) Synthesis and Inhibitory Activity against Epstein-Barr Virus of Some New 1,2,3,4-Tetrahydropyrimidine-2-Thiones. *Phosphorus & Sulfur & the Related Elements*, **183**, 2956-2967. https://doi.org/10.1080/10426500802043152