



Original Research Article

Highly effective synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones using pyridinium-*N*-sulfonic acid bisulfate as a dual-functional catalyst

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ABSTRACT

Acidic ionic liquid pyridinium-*N*-sulfonic acid bisulfate ([Py-SO₃H][HSO₄]) has effectively catalyzed the production of 3, 4-dihydropyrimidin-2 (1H)-ones via the condensation reaction of the arylaldehydes with β-ketoesters and urea under solvent-free conditions. Due to the dual-functionality of [Py-SO₃H][HSO₄] (bearing acidic and basic sites), it was highly effective and general catalyst for the reaction. Additionally, an attractive mechanism for the dual-functionality of the catalyst was proposed.

KEYWORDS

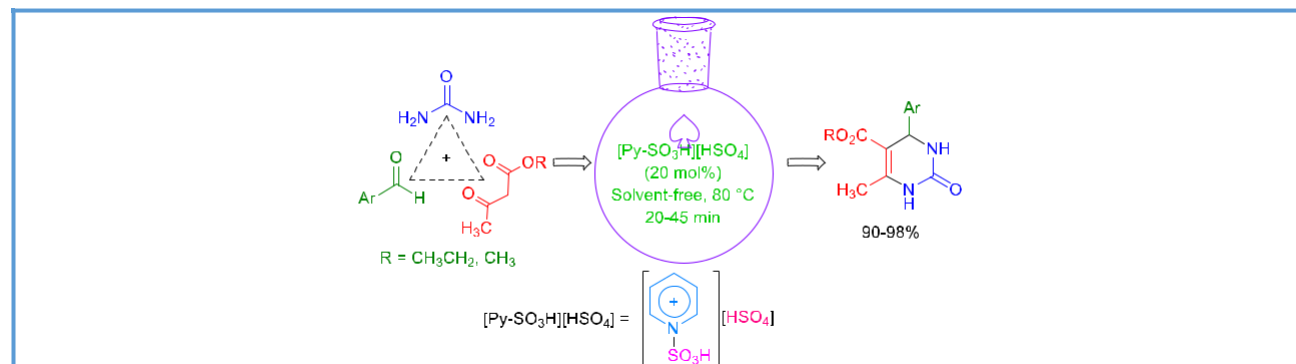
3, 4-Dihydropyrimidin-2 (1H)-one

Acidic ionic liquid Dual-functional catalyst

Pyridinium-*N*-sulfonic acid bisulfate (Py-SO₃H)[HSO₄]

Solvent-free

Graphical Abstract



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Introduction

Room-temperature ionic liquids (RTILs) have extensive applications in industry and chemistry due to their benefit properties including, negligible vapor pressure, non-flammability, reasonable thermal and chemical stability, excellent ionic conductivity, wide electrochemical windows, large liquid range, tunable hydrophobicity, and green nature. Physical properties of the RTILs are adaptable by judicious selection of the cation and anion [1]. In view of the excellent physicochemical characteristics of the ionic liquids, they have been used in lithium batteries [2], electrode position [3], solar cells [4], and electric double layer capacitors [5], and as solvent, reagent and catalyst in organic synthesis [6–23]. Among the ionic liquids, protic acidic ones act as catalysts for a variety of organic transformations [9–23].

Solvent-free conditions has been applied as a valuable technique in green chemistry, as many compounds could be prepared in an efficient and environmentally benign manner by that. Synthesizing compounds under solvent-free conditions has numerous benefits relative to the classical synthetic techniques, which include: (i) shorter reaction time, (ii) higher yield of product, (iii) maximum incorporation of the reactants into the aim product, (iv) higher selectivity in many reactions, (v) easier workup, (vi) fewer energy requirement to promote reaction, (vii) prevention of using harmful and volatile solvents, (viii) safer reaction profile, and (ix) prevention or minimization of waste/by-products [24–28].

3,4-Dihydropyrimidin-2 (1*H*)-one derivatives have various pharmaceutical and biological activities, and have been used as antihypertensive [29], antibacterial [30], antitumor [31], antiviral [32], calcium channel blockers [33], neuropeptide antagonist [34], α_{1a} -adrenergic antagonists [35], and anti-

inflammatory [36] agents. The general method which has been utilized for production of this class of compounds consists of the condensation reaction of arylaldehydes with β -ketoesters (or compounds containing active methylene) and urea in the presence of a catalyst; for example Mg-Al-CO₃ and Ca-Al-CO₃ hydrotalcite [37] nano- γ -Fe₂O₃@SiO₂ [38], 1-butyl-1,3-thiazolidine-2-thione *p*-toluenesulfate [39], H₄SiMO₁₂O₄₀ [40], 3D printed α -Al₂O₃ [41], silica-supported imidazolium salt [42], TiCl₃OTf-1-butyl-3-methylimidazolium chloride [43], [Co (BPO)₂ (H₂O)₄] (BS)₂ (H₂O)₂ [44], chitosan/graphene oxide [45], (-)-4, 5-dimethyl-3, 6-bis(*o*-tolyl)-1,2-benzenedisulfonimide [46], and Fe₃O₄@mesoporous SBA-15 [47]. Although some catalysts for the synthesis of 3,4-dihydropyrimidin-2 (1*H*)-ones are known, newer catalysts continue to attract attention for solving the drawbacks accompanied with the reported ones, such as harsh conditions, long reaction times, moderate yields, the use of expensive, non-available or toxic catalysts, difficulty in catalyst preparation, and performing the reaction in volatile and toxic organic solvents.

Bearing the above-mentioned subjects in mind, we report here a highly effective and dual-functional ionic-liquid catalyst namely pyridinium-*N*-sulfonic acid bisulfate (Py-SO₃H) [HSO₄]) to produce 3, 4-dihydropyrimidin-2 (1*H*)-ones *via* the condensation reaction between arylaldehydes, β -ketoesters and urea in the absence of solvent. Interestingly, our procedure hasn't the mentioned disadvantages at all.

Experimental

Materials and methods

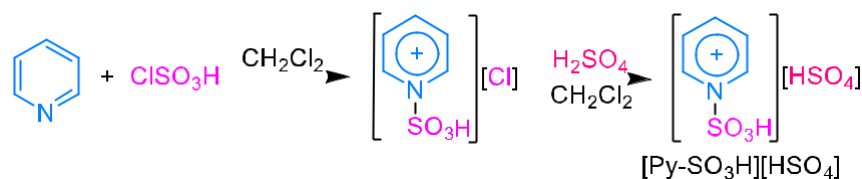
All the chemicals were purchased from Merck and Fluka Chemical Companies. All

known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. Progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel SIL G/UV 254 plates. The ^1H NMR (250 or 400 MHz) and ^{13}C NMR (62.5 or 100 MHz) were run on a Bruker Avance DPX, FT-NMR spectrometers.

Procedure for preparation of $[\text{Py-SO}_3\text{H}][\text{HSO}_4]$

A solution of pyridine (0.395 g, 5 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise to a stirring solution of chlorosulfonic acid (0.580 g,

5 mmol) in dry CH_2Cl_2 (15 mL) over a period of 10 min in an ice-bath. After the addition was completed, the reaction mixture was stirred for 60 min at room temperature [13], and then sulfuric acid (0.490 g, 5 mmol) was added dropwise over a period of 3 min. The resulting mixture was stirred for 4 h at room temperature under nitrogen atmosphere (to remove the produced HCl), and for 1 h in refluxed CH_2Cl_2 . Afterward, the mixture was stand for 3 min, the CH_2Cl_2 was decanted, and the residue was washed with dry CH_2Cl_2 (3×10 mL), and dried under vacuum to give $[\text{Py-SO}_3\text{H}][\text{HSO}_4]$ as a viscous pale yellow oil in 97 % yield (Scheme 1) [14].



Scheme 1. The synthesis of pyridinium-*N*-sulfonic acid bisulfate

General procedure for production of 3, 4-dihydropyrimidin-2 (1H)-ones

A mixture of arylaldehyde (1 mmol), β -ketoester (1 mmol), urea (0.078 g, 1.3 mmol) and $[\text{Py-SO}_3\text{H}][\text{HSO}_4]$ (0.052 g, 0.2 mmol) was initially stirred magnetically at 80 °C, and after solidification of the reaction mixture, it was stirred by a small rod at same temperature. Progress of the reaction was followed by TLC; after completion of the reaction, the mixture was cooled to room temperature, and the resultant solid was purified by recrystallization from ethanol (95%) to give the pure product.

Selected spectroscopic data of 3, 4-dihydropyrimidin-2 (1H)-ones

Ethyl 6-methyl-2-oxo-4-p-tolyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (4)

^1H NMR (400 MHz, DMSO-d_6): δ 1.1 (3H, t, $J = 7.2$ Hz), 2.2 (3H, s), 2.2 (3H, s), 3.9 (2H, q, $J = 7.2$ Hz), 5.12 (1H, s), 7.1 (4H, s), 7.7 (1H, br.), 9.1 (1H, br.). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.6, 18.2, 21.1, 54.1, 59.6, 99.9, 126.6, 129.4, 136.8, 142.4, 148.6, 152.7, 165.8.

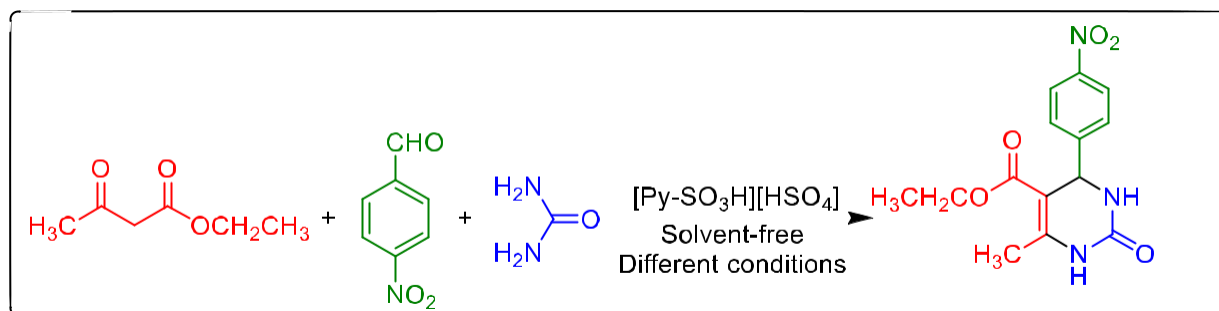
Ethyl 6-methyl-2-oxo-4-(4-dimethylaminophenyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (5)

^1H NMR (400 MHz, DMSO-d_6): δ 1.1 (3H, t, $J = 7.2$ Hz), 2.2 (3H, s), 2.86 (6H, s), 3.97 (2H, q, $J = 7.0$ Hz), 5 (1H, s), 6.6 (2H, d, $J = 8.8$ Hz), 7 (2H, d, $J = 8.8$ Hz), 7.5 (1H, br.), 9.1 (1H, br.). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.6, 18.2, 40.7, 53.8, 59.6, 100.4, 112.7, 127.4, 133.1, 148.0, 150.2, 152.8, 165.9.

Results and Discussion

To obtain the appropriate reaction temperature and catalyst amount, the condensation between the 4-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and urea (1.3 mmol) was chosen as a model reaction (Scheme 2), and examined at the presence of different molar ratios of [Py-

SO₃H][HSO₄] at 70-90 °C in the absence of solvent. The main results are presented in Table 1. As can be seen in Table 1, the suitable temperature and catalyst amount were 70 °C and 20 mol%, correspondingly (Table 1, Scheme 2).



Scheme 2. The model reaction for the production of 3, 4-dihydropyrimidin-2 (1*H*)-one

Table 1. Optimizing temperature and the catalyst amount on the model reaction

Entry	Temperature (°C)	Mol% of [Py-SO ₃ H][HSO ₄]	Time (min)	Yield ^a (%)
1	70	20	30	97
2	80	20	20	98
3	90	20	20	98
4	80	17	30	95
5	80	25	20	97

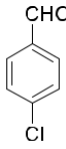
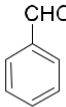
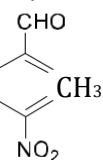
^a Yields refer to isolated pure product

With the aim of recognizing the generality and effectiveness of the catalyst for producing the 3,4-dihydropyrimidin-2 (1*H*)-ones, the reaction of different arylaldehydes (benzaldehyde and electron-rich as well as electron-deficient arylaldehydes) with β -ketoesters and urea was examined in the presence of [Py-SO₃H][HSO₄] in the optimal conditions; the relevant results are summarized in Table 2. As shown in Table 2, the ionic-liquid efficiently catalyzed all reactions to produce the related products in excellent yields and in short reaction times. Thus, [Py-SO₃H][HSO₄] was general and highly efficient catalyst for the synthesis.

In another study, our catalyst was compared with the more recently reported catalysts for the production of 3,4-dihydropyrimidin-2(1*H*)-ones. The results for the synthesis of compounds **3** and **7** were displayed in Table 3. As demonstrated in Table 3, the [Py-SO₃H][HSO₄] was superior related to the reported catalysts in terms of reaction time, yield and/or reaction conditions as well as temperature. Moreover, the purification of the products in our method was easy (recrystallization). The amount of urea used in our protocol was also fewer than most of the reported protocol.

Table 2. The synthesis of 3, 4-dihydropyrimidin-2 (1*H*)-ones using [Py-SO₃H][HSO₄]

Product	Aldehyde	R	Time (min)	Yield _a (%)	M.p. °C (Lit.)
1		Et	35	90	202-204 (202-204) [38]
2		Et	35	91	205-207 (207-209) [43]
3		Et	40	97	203-205 (201-202) [43]
4		Et	35	94	216-218 (216-218) [38]
5		Et	45	97	251-253 (250-253) [39]
6		Et	30	98	224-226 (225-227) [39]
7		Et	20	98	205-207 (207-209) [40]
8		Et	40	97	184-186 (183-185) [39]
9		Et	30	98	211-213 (210-212) [43]
10		Et	30	93	221-223 (222-224) [38]
11		Et	35	90	194-196 (193-195) [43]

12		Et	35	98	205-207 (207-210) [39]
13		CH ₃	30	91	212-214 (211-213) [38]
14			20	97	236-238 (233-236) [40]

^a Yields refer to isolated pure product

Table 3. Comparison of [Py-SO₃H][HSO₄] catalyzed 3,4-dihydropyrimidin-2(1*H*)-ones synthesis with the recently reported catalyzed process

Catalyst (mol%)	Conditions	Time (min)		Yield (%)		Ref
		3 ^a	7 ^b	3 ^a	7 ^b	
[Pyridine-SO ₃ H]HSO ₄	Solvent-free (80 °C)	40	20	97	98	-
Mg-Al-CO ₃ hydrotalcite	Solvent-free (80 °C)	30	60	82	81	[37]
Ca-Al-CO ₃ hydrotalcite	Solvent-free (80 °C)	45	60	61	64	[37]
Mg-Al-CO ₃ hydrotalcite	Solvent-free, MW (390 W)	6	6	82	83	[37]
Ca-Al-CO ₃ hydrotalcite	Solvent-free, MW (390 W)	8	8	63	67	[37]
Nano- γ -Fe ₂ O ₃ @SiO ₂	Solvent-free (60 °C)	- ^c	90	- ^c	82	[38]
Nano- γ -Fe ₂ O ₃ @SiO ₂	Solvent-free, MW (60 °C, 250 W)	- ^c	30	- ^c	95	[38]
[Btto][<i>p</i> -TSA] _d	Solvent-free (90 °C)	30	- ^c	97	- ^c	[39]
H ₄ SiMO ₁₂ O ₄₀	Reflux in CH ₃ CN	90	90	75	80	[40]
H ₄ SiMO ₁₂ O ₄₀	Reflux in EtOH	90	90	69	78	[40]
3D printed α-Al ₂ O ₃	Solvent-free, MW (100 °C)	15 ^e	- ^c	95 ^e	- ^c	[41]
Silica-supported imidazolium salt	Ethanol, reflux	40	20	88	95	[42]
TiCl ₃ OTf-ionic liquid	Solvent-free (140 °C)	- ^c	20	- ^c	95	[43]
[Co(BPO) ₂ (H ₂ O) ₄](BS) ₂ (H ₂ O) ₂	Solvent-free (80 °C)	120	- ^c	98.55	- ^c	[44]
Chitosan/graphene oxide	Solvent-free (110 °C)	50	65	75	78	[45]

(-)-4,5-dimethyl-3,6-bis(<i>o</i> -tolyl)-1,2-benzene disulfonimide	Solvent-free (50 °C)	120	360	90	85	[46]
Fe ₃ O ₄ @mesoporous SBA-15	Ethanol, reflux	420	300	82	84	[47]

^a Compound **3**

^b Compound **7**

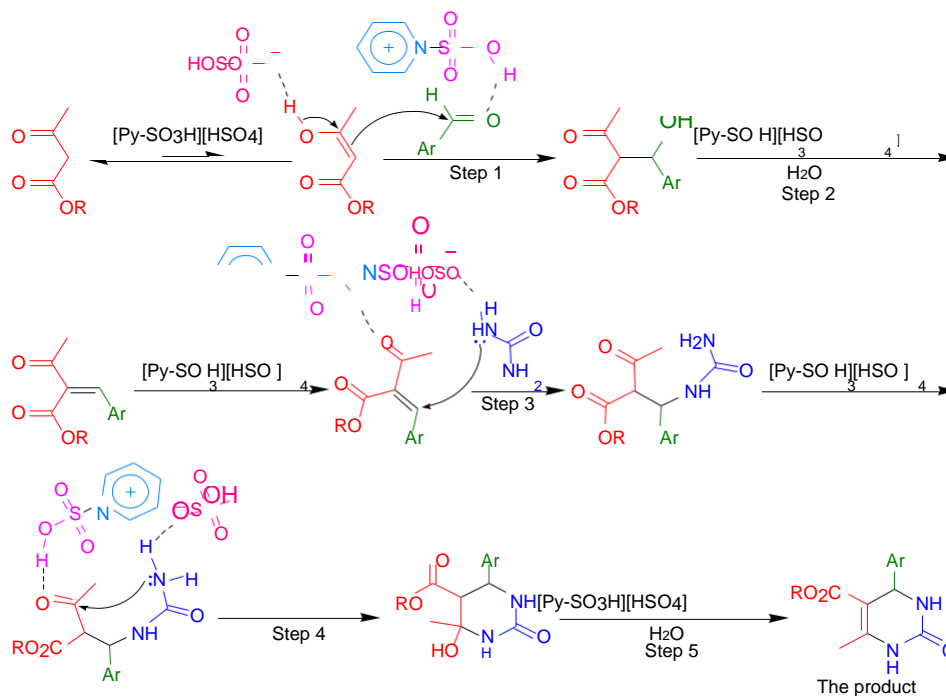
^c In the paper, the synthesis of this compound has not been reported

^d 1-Butyl-1,3-thiazolidine-2-thione *p*-toluenesulfate

^e The results are related to

A plausible mechanism considering the dual-functionality of the catalyst is illustrated in Scheme 3, which is supported by some research studies [43, 47]. The acidic site of the [Py-SO₃H][HSO₄] assists to promote the reaction by activating the carbonyl groups to accept a nucleophilic attack (steps 1, 3 and 4), and

activation of hydroxyl group for removing H₂O molecule (steps 2 and 5). The weak basic site of the catalyst (negative oxygen of bisulfate) accelerates the reaction by abstracting a proton (steps 1, 3 and 4). High efficacy of the [Py-SO₃H][HSO₄] can be attributed to the dual-functionality, and also having two acidic sites.



Scheme 3. The proposed mechanism for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones

Conclusions

In this work, we introduced a new acidic ionic-liquid catalyst namely pyridinium-*N*-sulfonic acid bisulfate for the reaction of

arylaldehydes with β -ketoesters and urea to produce 3,4-dihydropyrimidin-2(1*H*)-ones, with the following benefits: generality, effectiveness, excellent yields, short reaction times, easy workup and purification of the

products, easy preparation of the catalyst from available reactants, clean reaction, dual-functionality of the catalyst, avoid of using organic solvents as reaction media, and goof agreement with green chemistry protocols.

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Disclosure statement

No potential conflict of interest was reported by the author.

References

- [1]. Wua T.Y., Su S.G., Gung S.T., Lin M.W., Lin Y.C, Ou-Yang W.C., Sun I.W., Lai C.A. *J. Iran Chem. Soc.*, 2011, **8**:149
- [2]. Sakaebe H., Matsumoto H. *Electrochem Commun*, 2003, **5**: 594
- [3]. Gou S.P., Sun I.W. *Electrochim Acta*, 2008, **53**:2538
- [4]. Ue M., Takeda M., Toriumi A., Kominato A., Hagiwara R., Ito Y.J. *Electrochem Soc.*, 2003, **150**: A499
- [5]. Chang J.K., Lee M.T., Tsai W.T., Deng M.J., Sun I.W. *Chem. Mater.*, 2009, **21**:2688
- [6]. Hasaninejad A., Zare A., Shekouhy M., Ameri Rad. *J. J. Comb. Chem.*, 2010, **12**: 844
- [7]. Youseftabar-Miri L., Hosseinjani-Pirdehi H. *Asian J. Green Chem.*, 2017, **1**:56
- [8]. Zolfigol M.A., Khazaei A., Moosavi-Zare A.R., Zare A., Kruger H.G., Asgari Z., Khakyzadeh V., Kazem-Rostami M. *J. Org. Chem.*, 2012, **77**:3640
- [9]. Sajjadifar S., Mohammadi-Aghdam S. *Asian J. Green. Chem.*, 2017, **1**:1
- [10]. Abshirini Z., Zare A. *Z. Naturforsch*, 2018, **73b**:191
- [11]. Vekariya R.L. *J. Mol. Liq.*, 2017, **227**:44
- [12]. Rezayati S., Hajinasiri R., Hossaini Z., Abbaspour S. *Asian J. Green Chem.*, 2018, **2**:268
- [13]. Moosavi-Zare A.R., Zolfigol M.A., Zarei M., Zare A., Khakyzadeh V., Hasaninejad A. *Appl Catal A: Gen*, 2013, **467**:61
- [14]. Mohammadi S., Abbasi M. *Res. Chem. Intermed*, 2015, **41**:8877
- [15]. Moosavi-Zare A.R., Zolfigol M.A., Khaledian O., Khakyzadeh V. Darestani Farahani M., Gerhardus Kruger H. *New J. Chem.*, 2014, **38**:2342
- [16]. Rezayati S., Rezaee Nezhad E., Hajinasiri R. *Chin Chem. Lett.*, 2016, **27**:974
- [17]. Youseftabar-Miri L., Hosseinjani-Pirdehi H. *Asian J. Green Chem.*, 2017, **1**:56
- [18]. Rezayati S., Salehi E., Hajinasiri R., Afshari Sharif Abad S. *C. R. Chim.*, 2017, **20**:554
- [19]. Das P.J., Das D. *Asian J. Green Chem.*, 2018, **2**:11
- [20]. Rezayati S., Sheikholeslami-Farahani F., Hossaini Z., Hajinasiri R., Afshari Sharif Abad S. *Comb. Chem.*, 2016, **19**:720
- [21]. Poyafar F., Fallah-Mehrjardi M., Banitaba SH. *Asian J. Green Chem.*, 2018, **2**:96
- [22]. Moosavi-Zare A.R., Zolfigol M.A., Khaledian O., Khakyzadeh V. *Chinese Journal of Catalysis*, 2014, **35**:573
- [23]. Rezayati S., Sheikholeslami-Farahani F., Rostami-Charati F., Afshari Sharif Abad S. *Rese. Chem. Intermed.*, 2016, **42**:4097
- [24]. Himaja M., Poppy D., Asif K. *Int. J. Res. Ayurveda Pharm*, 2011, **2**:1079
- [25]. Arzehgar Z., Sajjadifar S., Fekri M.H. *Asian J. Nanosci Mater*, 2019, **2**:251
- [26]. Karami M., Zare A. *Org. Chem. Res.* 2018, **4**:174
- [27]. Heravi M.M., Karimi N., Pooremami S. *Adv. J. Chem.*, 2019, **A 2**:73
- [28]. Kazemi E., Davoodnia A., Nakhaei A., Basafa S., Tavakoli-Hoseini N. *Adv. J. Chem. A.*, 2018, **1**:96
- [29]. Kappe C.O. *Eur. J. Med. Chem.*, 2000, **35**:1043
- [30]. Aron Z.D., Overman L.E. *Chem. Commun*, 2004, 253

- [31]. Haggarty S.J., Mayer T.U., Miyamoto D.T., Fathi R., King R.W., Mitchison T.J., Schreiber S.L. *Chem. Biol.*, 2000, **7**:275
- [32]. Yarim M., Sarac S., Kilic F.S., Erol K. *IL Farmaco*, 2003, **58**:17
- [33]. Rovnyak G.C., Kimball S.D., Beyer B., Cucinotta G., Dimarco J.D., Gougoutas J., Hedberg A., Malley M., McCarthy J.P. *J. Med. Chem.*, 1995, **38**:119
- [34]. Bruce M.A., Pointdexter G.S., Johnson G. *PCT. Int. Appl WO.*, 1998, **98**:33791
- [35]. Sidler D.R., Larsen R.D., Chartrain M., Ikemoto N., Roberge C.M., Taylor C.S., Li W., Bills G.F. *PCT Int Appl WO.*, 1991, **99**:07695.
- [36]. Naik N.S., Shastri L.A., Joshi S.D., Dixit S.R., Chougala B.M., Samundeeswari S., Holiyachi M., Shaikh F., Madar J., Kulkarni R., Sunagar V. *Bioorg. Med. Chem.*, 2017, **25**:1413
- [37]. Lala J., Sharma M., Guptab S., Parashara P., Saha P., Agarwala D.D. *J Mol Catal A: Chem.*, 2012, **352**:31
- [38]. Kolvari E., Koukabi N., Armandpour O. *Tetrahedron*, 2014, **70**:1383
- [39]. Zhang Y., Wang B., Zhang X., Huang J., Liu C. *Molecules*, 2015, **20**:3811
- [40]. Saher L., Makhoulfi-Chebli M., Dermeche L., Boutemeur-Khedis B., Rabia C., Silva A.M.S., Hamdi M. *Tetrahedron Lett.*, 2016, **57**:1492
- [41]. Azuaje J., Tubío C.R., Escalante L., Gómez M., Guitián F., Coelho A., Caamaño O., Gil A., Sotelo E. *Appl Catal A: Gen.*, 2017, **530**:203
- [42]. Davarpanah J., Sayahi M.H., Ghahremani M., Karkhoe S. *J. Mol. Struct.*, 2019, **1181**:546
- [43]. Farhadi A., Noei J., Aliyari R.H., Albakhtiyari M., Takassi M.A. *Res. Chem. Intermed.*, 2016, **42**:1401
- [44]. Wang J-H., Zhang E., Tangn G-M., Wangn Y-T., Cui Y-Z., Ng S.W. *J. Solid State Chem.*, 2016, **241**:86
- [45]. Maleki A., Paydar R. *React Funct Polym.*, 2016, **109**:120
- [46]. Barbero M., Cadamuro S., Dughera S. *Green Chem.*, 2017, **19**:1529
- [47]. Mondal J., Sen T., Bhaumik A. *Dalton Trans*, 2012, **41**:617

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