Research on Chemical Intermediates
https://doi.org/10.1007/s11164-020-04089-9

Introduction of a novel dicationic Brönsted acidic ionic liquid based on pyrazine and its application in the synthesis of xanthenediones and 3, 4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions

Seyyed Erfan Sadati Sorkhi[1] · Mohammad M. Hashemi[1] · Ali Ezabadi[2]

Received: 19 September 2019 / Accepted: 17 January 2020

Abstract
A novel dicationic Brönsted acidic ionic liquid based on pyrazine has been prepared and characterized by FTIR, ^{1}H NMR, ^{13}C NMR, MS, thermal gravimetric and differential thermal gravimetric analysis and also Hammett acidity function. The prepared dicationic ionic liquid is found to be an efficient and reusable catalyst for the synthesis of xanthenediones and 3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions. The merits of the developed procedure include novelty in terms of the ionic liquid, easy preparation of the ionic liquid, easy workup, reusability of the catalyst, high yield, short reaction time and absence of toxic organic solvent.

Keywords Dicationic ionic liquid · Pyrazine · Xanthenediones · 3,4-Dihydropyrimidin-2(1*H*)-ones · Solvent-free

Introduction

Ionic liquids (ILs) are organic salts comprised of organic cations in combination with organic and/or inorganic anions, which exhibit a myriad of remarkable and interesting properties, such as wide liquid range, negligible vapor pressure, simple recovery process, high ionic conductivity, broad electrochemical window and design ability by appropriate modifications of cations or anions in structures [1, 2]. Recently, many researches have been focusing on the development of a new subclass of ILs known as dicationic ionic liquids (DILs), which typically consist of two cationic head groups linked by a rigid or flexible spacer, associated

✉ Mohammad M. Hashemi
mhashemi@sharif.edu

[1] Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran

[2] Department of Chemistry, Faculty of Science, Central Tehran Branch, Islamic Azad University, Tehran, Iran

Published online: 06 February 2020

with two counteranions [3]. Compared to monocationic ILs, multicationic ones can have a higher melting point, viscosity, surface tension, thermal stability, wide liquid range and tenability of chemical and physical properties [4, 5]. Therefore, they have good potential to be used in a wide range of applications including solar cells, fuel cells, batteries, lubricants, reaction media, separation technologies, material preparation, catalysis reactions and, more recently, improving the isomerization degree of *n*-pentane and electrolytes for photo-harvesting [6–8].

Structures containing xanthene moiety are well known to have a wide range of biological and pharmacological activities, such as antibacterial [9], anti-inflammatory [10] and antiviral [11] activities. They are used as an antagonist for paralyzing the action of zoxazolamine [12] and in photodynamic therapy [13]. These heterocyclic compounds are also used as dyes [14], as pH-sensitive fluorescent materials for visualization of biomolecules [15] and in laser technologies because of their valuable spectroscopic properties [16]. In addition, xanthenediones occur as constituent units in a large number of natural products [17].

Therefore, in recent years, many efforts have been focused on the synthesis of xanthenediones by one-pot condensation of aldehydes with 5,5-dimethyl-1,3-cyclohexanedione in the presence of catalysts such as Brönsted–Lewis acidic ionic liquids [18], CuO nanoparticles [19], trichloromelamine [20], secondary amine-based ionic liquid [21], SmI_3 [22], 1-butyl-3-methylimidazolium hydrogen sulfate [bmim] HSO_4 [23], carboxy-functionalized ionic liquid [24], β-cyclodextrin grafted with butyl sulfonic acid [25], cesium salt for phosphotungstic acid [26], titanium aminophosphates [27], $[Et_3NH][HSO_4]$ [28], $SbCl_3/SiO_2$ [29], $ZrOCl_2{\cdot}8H_2O$ [30], Fe_3O_4 nanoparticles [31], $InCl_3$ or P_2O_5 [32], 3-(*N*,*N*-dimethyldodecylammonium) propanesulfonic acid hydrogen sulfate ([DDPA][HSO4]) [33], $[DABCO](SO_3H)_2Cl_2$ [34], imidazol-1-yl-acetic acid [35], $[Et_3N–SO_3H]Cl$ [36], natural acidic ionic liquid immobilized on magnetic silica [37], task-specific dicationic ionic liquids [38], acetic acid [39], amberlite IR-120H [40], cyclodextrin nanosponges [41] and phosphomolybdic acid supported on Schiff-base-functionalized graphene oxide nanosheets [42].

Due to our interest in the design, preparation and use of novel ionic liquids for organic transformations [43–46], herein we report for the first time the development of a new dicationic Brönsted acidic ionic liquid (Fig. 1)-catalyzed synthesis of xanthenediones and 3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions (Schemes 1, 2).

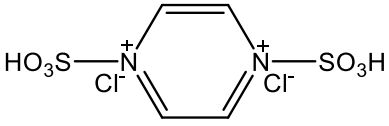
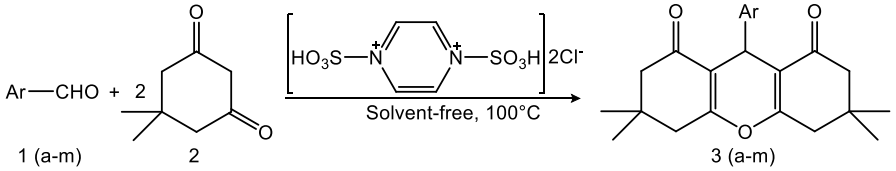
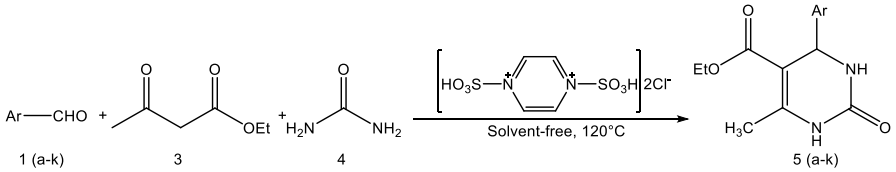


Fig. 1 Structure of the dicationic Brönsted ionic liquid



Scheme 1 Synthesis of xanthenediones catalyzed by {[SO_3H–Pyrazine–SO_3H]Cl_2}d under solvent-free conditions



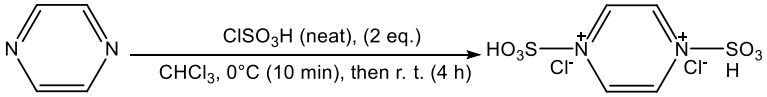
Scheme 2 Synthesis of DHPMs catalyzed by {[SO_3H–Pyrazine–SO_3H]Cl_2} under solvent-free conditions

Experimental section

All reagents and solvents were commercially available and used without further purification. ^{1}H NMR and ^{13}C NMR in DMSO-d_6 were recorded on a Bruker Avance Ultrashield spectrometer at 500 and 125 MHz, respectively. Chemical shifts were reported in parts per millions (δ), relative to the internal standard of tetramethylsilane (TMS). Thermal analysis (TG–DTA) of the DIL was recorded on a STA-1500 Rheometric Scientific TGA. Mass spectrometry (MS) studies were performed using 5957C VL MSD with a triple-axis detector, Agilent Technologies (ion source: electron impact (IE) 70 eV, ion source temperature: 230 °C, analyzer: Quadrupole). FTIR spectrum was taken on a FTIR PerkinElmer Spectrum Version 10.51 with KBr plates. Melting points were recorded on a Mettler Toledo Type FP62 in open capillary tubes.

Preparation of the catalyst

A round-bottom flask (100 mL) was filled with a solution of pyrazine (3.2 g, 0.04 mol) in chloroform (80 mL) and cooled in an ice bath. Then, with intensive stirring, chlorosulfonic acid (5.3 mL, 0.08 mol) was added dropwise over a period of 10 min at 0 °C. After addition, the reaction mixture was removed from the ice bath and stirred for 4 h at room temperature. A white precipitate formed, which was filtered, washed with chloroform (3 × 15 mL) and dried at room temperature in 94% of yield (Scheme 3).



Scheme 3 Preparation of $\{[SO_3H–Pyrazine–SO_3H]Cl_2\}$

Determination of the structure of the catalyst

For determining the structure of the catalyst, several techniques including FTIR, ^{1}H NMR, ^{13}C NMR, TG/DTA and MS were used.

FTIR

FTIR spectrum of the catalyst is depicted in Fig. 2. The presence of some bonds reveals the complete transfer of acidic hydrogen from chlorosulfonic acid to two nitrogen atoms of pyrazinium ring.

- The broad peak at 3400–2400 cm^{-1}. This peak is due to the stretching vibration of O–H bond present in SO_3H group.
- Two peaks at 1617 cm^{-1} and 1487 cm^{-1}. These two peaks belong to C=N and C=C vibrations, respectively.
- Two peaks at 1158 cm^{-1} and 1228 cm^{-1}. These two peaks belong to O–SO_2 symmetric and asymmetric stretching, respectively, and the other band at 1009 cm^{-1} is related to N–SO_2 stretching.

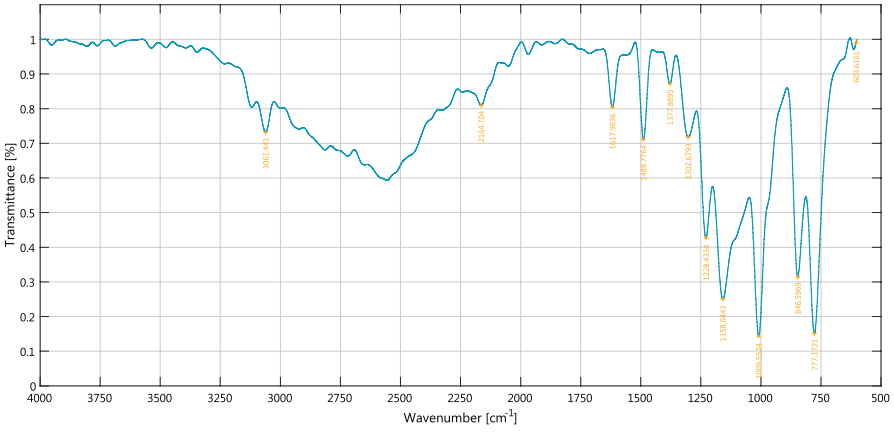


Fig. 2 FTIR spectrum of $\{[SO_3H–Pyrazine–SO_3H]Cl_2\}$

^{1}H NMR

Another evidence for determining the structure of the catalyst is extracted from NMR study. The ^{1}H NMR of the catalyst is shown in Fig. 3. Two singlet signals are observed in ^{1}H NMR spectrum of the catalyst.

- Signal at 8.66 ppm which is related to four hydrogen atoms of pyrazinium ring.
- Signal at 11.95 ppm which is related to two acidic hydrogen atoms of SO_3H groups.

^{13}C NMR

^{13}C NMR of the catalyst is shown in Fig. 4. The spectrum shows only one peak at 145.08 ppm, which clearly indicates the symmetrical structure of the catalyst.

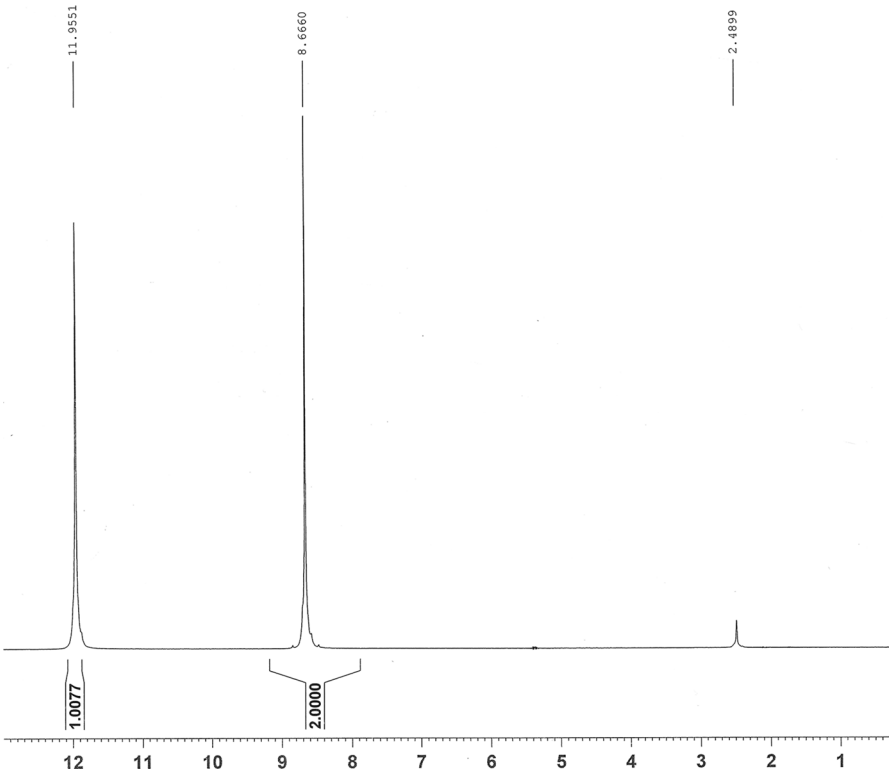


Fig. 3 ^{1}H NMR spectrum of {[SO_3H–Pyrazine–SO_3H]Cl_2}

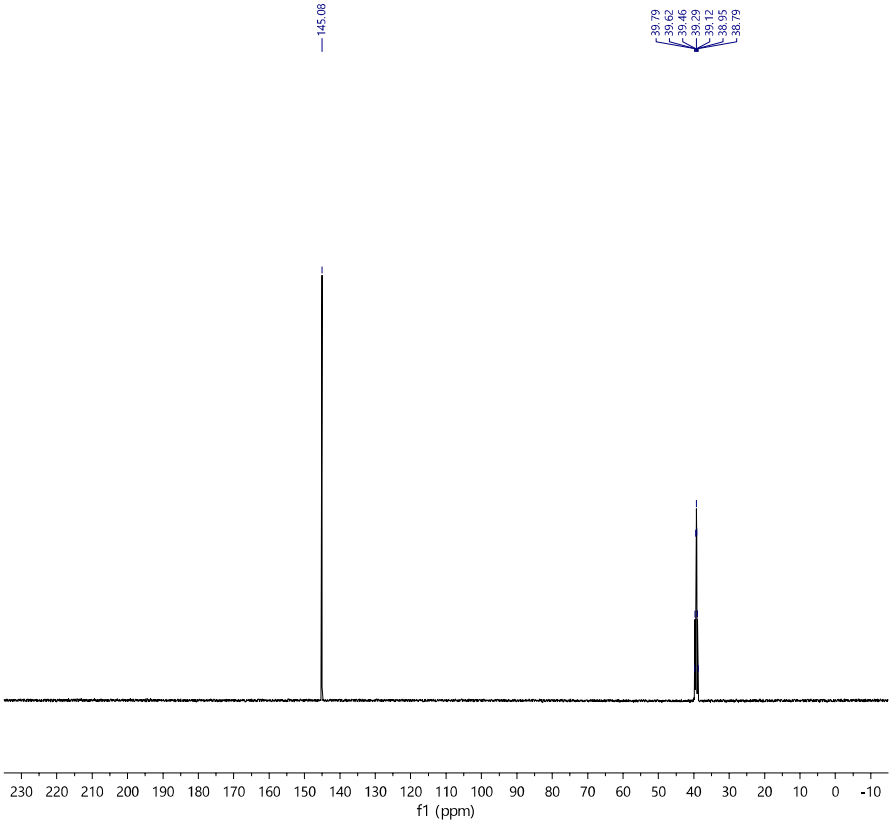


Fig. 4 ^{13}C NMR spectrum of {[SO_3H–Pyrazine–SO_3H]Cl_2}

Mass spectrum

The mass spectrum of the DIL is shown in Fig. 5. In this spectrum, the molecular ion appears at 312 *m/z*. Other ionic peaks are also observed at 277 (M^+–Cl), 150 (M^+–2SO_3H), 115 (M^+–2SO_3H and Cl) and 80 (M^+–2SO_3H, 2Cl).

TG/DTA

The behavior of the DIL against heat change was investigated by thermal gravimetric (TG) and differential thermal gravimetric (DTA) analysis. TG and DTA plots of DIL showed that the weight losses in one step as well as stability at about 285 °C (Fig. 6).

In another study, to prove that {[SO_3H–Pyrazine–SO_3H]Cl_2} was correctly synthesized, we decided to do the halogen test. Therefore, we added silver nitrate solution to the aqueous solution of the dicationic ionic liquid. This addition led to a white solid,

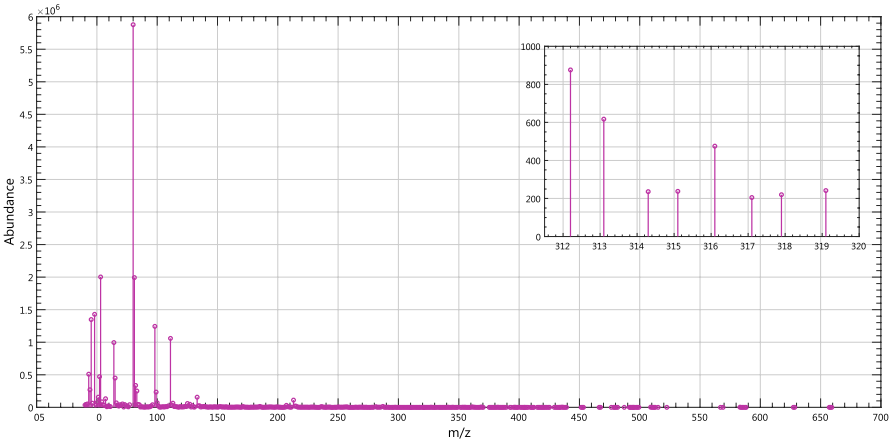


Fig. 5 Mass spectrum of {[SO_3H–Pyrazine–SO_3H]Cl_2}

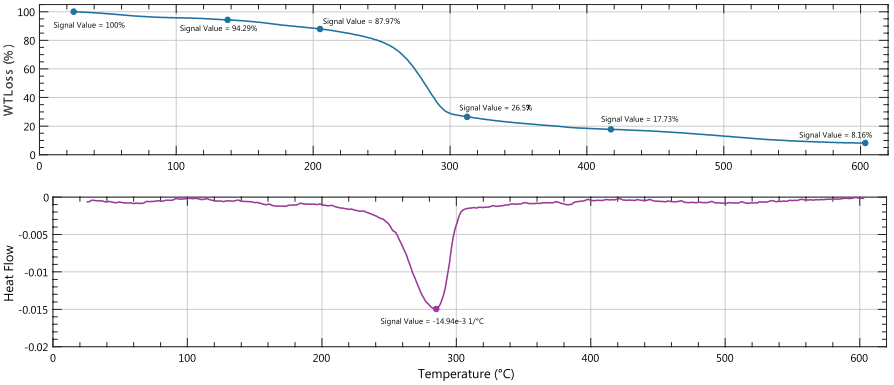


Fig. 6 TG/DTA of {[SO_3H–Pyrazine–SO_3H]Cl_2}

which indicates the formation of silver chloride. This result showed that the DIL contains chloride anions.

Hammett acidity function

The acidity of the synthesized ionic liquid was measured using UV–visible spectroscopy by means of 4-nitroaniline as a basic indicator. The UV absorption of 4-nitroaniline solely as well as mixed with the dicationic Brönsted acidic ionic liquid in water is shown in Fig. 7. The maximum absorbance was observed at 380 nm. Hammett acidity function, H_0 can be calculated using the following equation:

$$H_0 = pK(I)_{aq} + \log\left(\frac{[I]}{[IH^+]}\right)$$

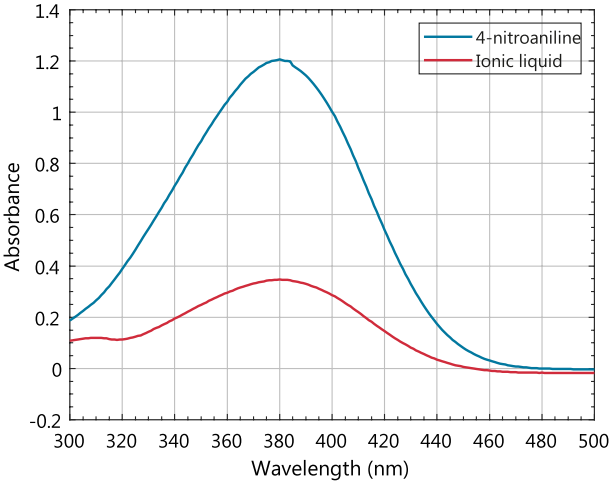


Fig. 7 Hammett acidity function of the {[SO_3H–Pyrazine–SO_3H]Cl_2}

where $pK(I)_{aq}$ is pK_a value of 4-nitroaniline (0.99) and $[IH^+]$ and $[I]$ (I represents indicator) are the molar concentrations of the protonated and unprotonated forms of the indicator, respectively. The $[I]/[IH^+]$ ratio can be determined from absorbance measured before and after the addition of the ionic liquid. The detailed results are given in Table 1.

Results and discussion

To achieve the appropriate reaction conditions, the reaction of 4-chlorobenzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione catalyzed by {[SO_3H–Pyrazine–SO_3H]Cl_2} was chosen as model reaction, and the reaction was carried out under different sets of conditions with respect to solvents, amounts of catalyst and temperatures.

Initially, the model reaction was investigated in different solvents (Table 2, entries 1–5). The solvents did not improve the yield of the reaction in the presence of the catalyst. Therefore, we carried out the model reaction under solvent-free

Table 1 Calculation of H_0 value of {[SO_3H–Pyrazine–SO_3H]Cl_2} in water at 298 K

Ionic liquid	Absorbance	$[I]$ (%)	$[IH^+]$ (%)	$[I]/[IH^+]$	H_0
Blank	1.2	100	0	–	–
{[SO_3H–Pyrazine–SO_3H]Cl_2}	0.34	28.3	71.7	0.39	0.58

Condition for UV–visible spectrum measurement: solvent: H_2O, indicator: 4-nitroaniline, 7.5×10^{-5} mol L^{-1}; IL: 3×10^{-3} mol L^{-1}, 25 °C

Table 2 Effect of different reaction conditions on {[SO_3H–Pyrazine–SO_3H]Cl_2}-catalyzed synthesis of xanthenediones

Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Time (min)	Yield[a] (%)
1	CH_2Cl_2	Reflux	25	300	41
2	EtOAc	Reflux	25	300	42
3	Acetone	Reflux	25	300	48
4	EtOH	Reflux	25	300	64
5	H_2O	Reflux	25	300	52
6	Solvent-free	100	25	15	93
7	Solvent-free	90	25	25	88
8	Solvent-free	110	25	10	78
9	Solvent-free	100	20	25	90
10	Solvent-free	100	30	10	91
11	Solvent-free	100	–	15	Very low

Reaction conditions: 4-chlorobenzaldehyde (1 mmol); 5,5-dimethyl-1,3-cyclohexanedione (2 mmol); solvent (15 mL)

[a]Isolated yield

conditions. The result (Table 2, entry 6) indicates that the yield of the reaction under solvent-free conditions was higher and the reaction time was shorter in comparison with solvent conditions.

To optimize the reaction temperature, the model reaction was heated at 90 and 110 °C (Table 2, entries 7, 8). The results shown in Table 2 indicate that the 100 °C led to highest yield; therefore, it was selected as the reaction temperature for all further reactions. Finally, the model reaction was optimized by varying the amounts of catalysts (20 and 30 mol%) at 100 °C under solvent-free conditions (Table 2, entries 9 and 10). The results show that 25 mol% of the catalyst is sufficient for the best results. To determine the role of the catalyst, the model reaction was performed in the absence of the catalyst at the same condition, which results in very low yield of the product (Table 2, entry 11), which indicates the high catalytic activity of {[SO_3H–Pyrazine–SO_3H]Cl_2} in the synthesis.

To evaluate the scope and the limitations of this method, we extended our studies to various aldehydes under the optimized conditions. These results are depicted in Table 3. From the results, we could see that all reactions proceeded smoothly to afford the corresponding xanthenediones in high to excellent yields in the short reaction times. Various functional groups present in the aryl aldehydes such as halogen, methoxy, hydroxy and nitro groups were tolerated (Table 3, entries 1–12). Extension of this methodology to heterocyclic aldehyde was also successful (Table 3, entry 13).

In view of green chemistry, reusability of the catalyst is important. Therefore, some experiments were run under the same optimal conditions mentioned above over the {[SO_3H–Pyrazine–SO_3H]Cl_2}. The results showed that the catalyst could

Table 3 {[SO_3H–Pyrazine–SO_3H]Cl_2}-catalyzed synthesis of xanthenediones

Entry	Aldehyde	Product	Time (min)	Yield[a] (%)	Melting point (°C)	
					Found	Reported [Ref.]
1	4-Chlorobenzaldehyde	**3a**	15	93	234–236	230–232 [23]
2	Benzaldehyde	**3b**	35	93	202–204	204–205 [23]
3	4-Bromobenzaldehyde	**3c**	35	95	239–242	240–241 [23]
4	3-Nitrobenzaldehyde	**3d**	15	95	170–172	170–172 [28]
5	3-Bromobenzaldehyde	**3e**	33	81	191–193	192–194 [24]
6	3-Hydoxybenzaldehyde	**3f**	30	80	220–222	223–225 [29]
7	2-Methoxybenzaldehyde	**3g**	25	96	187–189	189–191 [35]
8	Terephethaldehyde	**3h**	35	97	> 300	> 300 [34]
9	4-Hydroxy-3-methoxybenzaldehyde	**3i**	20	91	226–228	226–228 [28]
10	4-Hydoxybenzaldehyde	**3j**	45	87	251–253	247–248 [30]
11	4-Fluorobenzaldehyde	**3k**	40	90	226–227	226–227 [29]
12	2-Bromobenzaldehyde	**3l**	25	84	226–228	226–229 [30]
13	2-Thiophenecarbaldehyde	**3m**	45	77	163–165	164–165 [30]

Reaction conditions: aromatic aldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2 mmol), {[SO_3H–Pyrazine–SO_3H]Cl_2} (0.25 mmol) at 100 °C under solvent-free conditions

[a]Isolated yield

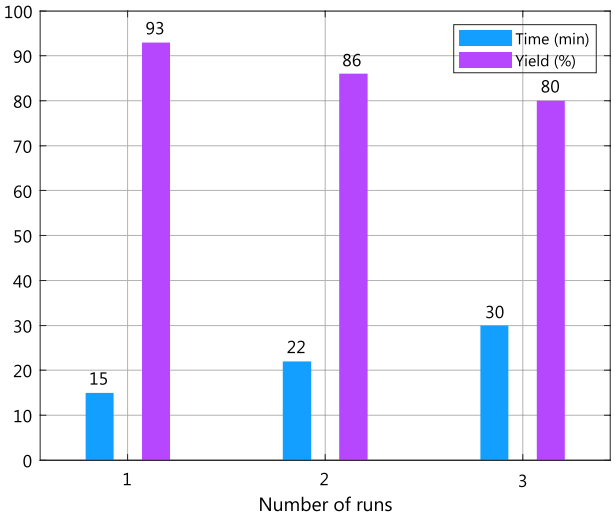
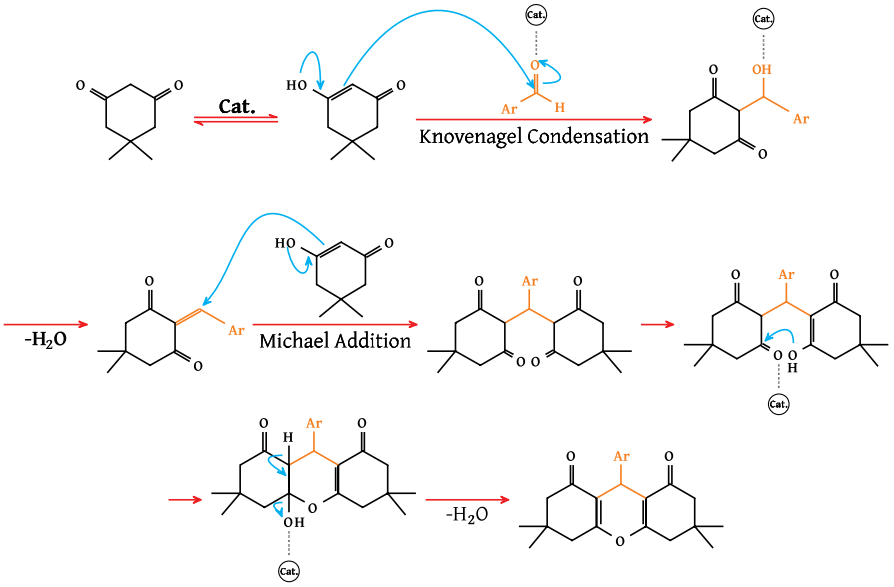


Fig. 8 Reusability of the {[SO_3H–Pyrazine–SO_3H]Cl_2} in the reaction of 4-chlorobenzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione under optimized reaction conditions



Scheme 4 The suggested mechanistic pathway for formation of xanthenediones in the presence of the catalyst

Table 4 Comparison of the efficiency of various catalysts with {[SO_3H–Pyrazine–SO_3H]Cl_2} in the synthesis of **3a**

Entry	Catalyst	Amount of catalyst (mol%)	Conditions	Time (min)	Yield (%)
1	{[SO_3H–Pyrazine–SO_3H] Cl_2}	25	Solvent-free, 100 °C	10	93 (This work)
2	[Et_3NH][HSO_4]	20	Solvent-free, 100 °C	45	87 [28]
3	[DDPA][HSO_4]	10	Solvent-free, 100 °C	90	87 [33]
4	[DDPA][HSO_4]	40	H_2O, 100 °C	210	90 [23]
5	Fe_3O_4 nanoparticles	10	Solvent-free, 100 °C	20	90 [31]
6	[*n*-Pr_2NH_2][HSO_4]	50	Solvent-free, 80 °C	10	85 [21]
7	[Et_3–SO_3H]Cl	25	Solvent-free, 80 °C	40	93 [36]

accelerate the reaction three runs without a significant loss in its catalytic activity (Fig. 8).

The mechanism of the reaction starts with facilitating Knoevenagel condensation due to activating carbonyl group of aldehyde by acidic property of catalyst. In the following, the catalyst again plays a significant role in accelerating the Michael addition and dehydration (Scheme 4).

A comparative study on the catalytic activity of the introduced catalyst in this paper with some reported catalysts was carried out using **3a** as a model compound

(Table 4). From this study, {[SO_3H–Pyrazine–SO_3H]Cl_2} can be regarded as a more powerful catalyst for the synthesis of xanthenediones in terms of the yield and the reaction time.

Multicomponent reactions (MCRs) are defined as one-pot processes that combine at least three reactants to selectively form single complex compounds as well as small heterocycles containing essentially all the atoms of the reactants [47]. Among MCRs, the Biginelli reaction allows for the straight access of multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) through one-pot cyclocondensation of an aldehyde, a β-keto ester and urea in the presence of catalytic amount of acid [48, 49]. Molecules containing DHPM core and its derivatives are of immense biological importance due to a wide range of pharmaceutical and therapeutic properties such as antiviral [50], antitumor [51], antibacterial [52, 53], anti-inflammatory [54], anti-HIV agents [55, 56], mitotic kinesin inhibition [57], calcium channel modulation [58, 59], α_{1a}-adrenergic antagonists [60] and A_2B adenosine receptor antagonists [61]. In the classical Biginelli conditions, low yields and difficult isolation of the products are the main drawbacks due to strongly acidic conditions [62]. Hence, many catalytic methods including Brönsted and Lewis acid [63–73], ionic liquids [74–78], polymer-supported catalyst [79] and nanoparticles [80–84] have been introduced to enhance the efficiency of the synthesis of these important heterocycles.

After obtaining acceptable results from xanthenediones synthesis catalyzed by {[SO_3H–Pyrazine–SO_3H]Cl_2}, we decided to study its efficiency in the synthesis of DHPMs (Scheme 2). In order to obtain the optimized conditions, the model reaction involving cyclocondensation of 4-chlorobenzaldehyde, ethyl acetoacetate and urea was examined. As given in Table 5, the best result was obtained when the reaction was carried out at 120 °C in the presence of 25 mol% of {[SO_3H–Pyrazine–SO_3H]

Table 5 Effect of different reaction conditions on {[SO_3H–Pyrazine–SO_3H]Cl_2}-catalyzed synthesis of DHPMs

Entry	Solvent	Temperature (°C)	Amount of catalysts (mol%)	Time (min)	Yield[a] (%)
1	H_2O	Reflux	25	70	42
2	H_2O/EtOH	Reflux	25	67	50
3	Acetone	Reflux	25	110	64
4	EtOAc	Reflux	25	90	68
5	$CHCl_3$	Reflux	15	105	75
6	CH_3CN	Reflux	15	55	51
7	Solvent-free	120	25	10	92
8	Solvent-free	110	25	17	81
9	Solvent-free	100	25	40	78
10	Solvent-free	120	20	15	85
11	Solvent-free	120	15	38	71

Reaction conditions: 4-chlorobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (2 mmol), solvent (15 mL)

[a]Isolated yield

Cl_2} under solvent-free conditions. After getting the satisfactory reaction condition in hand, the scope and efficiency of this approach were examined with respect to aldehydes, and the obtained results are shown in Table 6. Fortunately, a variety of functional groups, such as halo, methoxy, hydroxy and nitro, were all well tolerated (Table 6, entries 1–10). In addition, heterocyclic aromatic aldehyde afforded the corresponding product with high yield (Table 6, entry 11).

A plausible one-pot reaction pathway for the synthesis of DHPMs catalyzed by {[SO_3H–Pyrazine–SO_3H]Cl_2} is proposed in Scheme 5. Initially, acyl imine intermediate (I) is produced via condensation of aryl aldehyde and urea in the presence of the catalyst as a Brönsted acidic catalyst. Next, ethyl acetoacetate attacks the (I), followed by intramolecular cyclization and dehydration reaction under acidic condition to yield the Biginelli product.

Next, the reusability of {[SO_3H–Pyrazine–SO_3H]Cl_2} was examined in the reaction of 4-chlorobenzaldehyde, ethyl acetoacetate and urea under optimized conditions. As shown in Fig. 9, the catalyst could be reused three times without a significant loss in its catalytic activity. In order to show the efficacy of {[SO_3H–Pyrazine–SO_3H]Cl_2}, a comparison of the present method and some reported methods is shown in Table 7. As revealed from this table, the catalyst can be considered as a more powerful catalyst for the synthesis of DHPMs in terms of the yield and reaction time.

General procedure for the synthesis of xanthenediones under solvent-free conditions

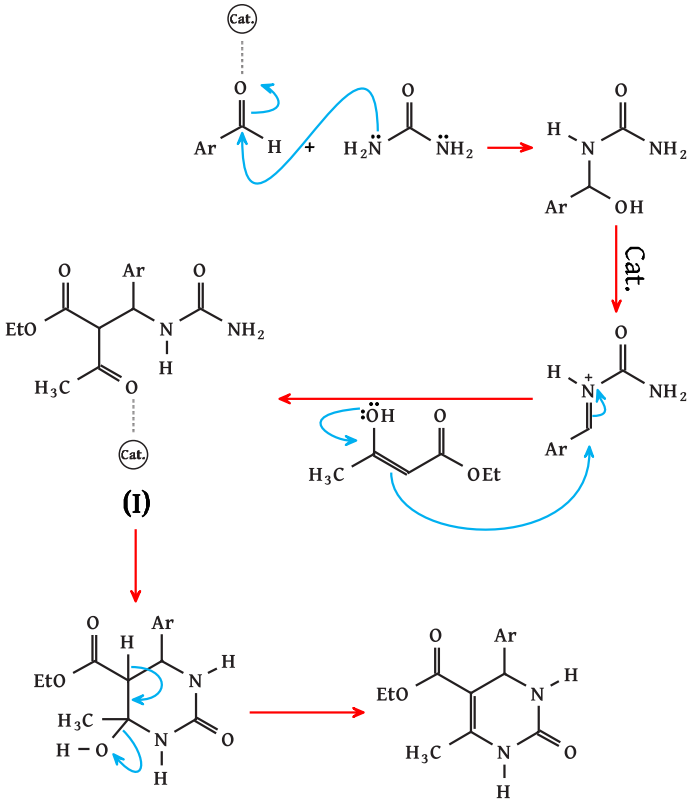
To a mixture of aromatic aldehyde (1 mmol) and 5, 5-dimethyl-1, 3-cyclohexanedione (2 mmol), 25 mol% of {[SO_3H–Pyrazine–SO_3H]Cl_2} (0.25 mmol) was added

Table 6 {[SO_3H–Pyrazine–SO_3H]Cl_2}-catalyzed synthesis of DHPMs

Entry	Aldehyde	Product	Time (min)	Yield[a] (%)	Melting point (°C)	
					Found	Reported [Ref.]
1	4-Chlorobenzaldehyde	**5a**	10	92	213	214–215 [73]
2	3-Chlorobenzaldehyde	**5b**	10	87	189	199.9–201 [78]
3	2-Chlorobenzaldehyde	**5c**	15	88	213	214–215 [73]
4	4-Bromobenzaldehyde	**5d**	13	83	230	211–212 [73]
5	3-Bromobenzaldehyde	**5e**	17	87	190	184–185 [85]
6	2-Bromobenzaldehyde	**5f**	17	89	208	206–208 [86]
7	4-Nitrobenzaldehyde	**5g**	18	81	217	214–216 [87]
8	3-Nitrobenzaldehyde	**5h**	15	83	230	233.5–234.1 [78]
9	4-Fluorobenzaldehyde	**5i**	10	82	183	182–184 [85]
10	Benzaldehyde	**5j**	18	88	212	209.9–212 [78]
11	2-Thiophenecarbaldehyde	**5k**	15	90	210	212–214 [88]

Reaction conditions: aromatic aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (2 mmol) and {[SO_3H–Pyrazine–SO_3H]Cl_2} (0.25 mmol) at 120 °C under solvent-free conditions

[a]Isolated yield



Scheme 5 Plausible mechanism for one-pot synthesis of DHPMs in the presence of the catalyst

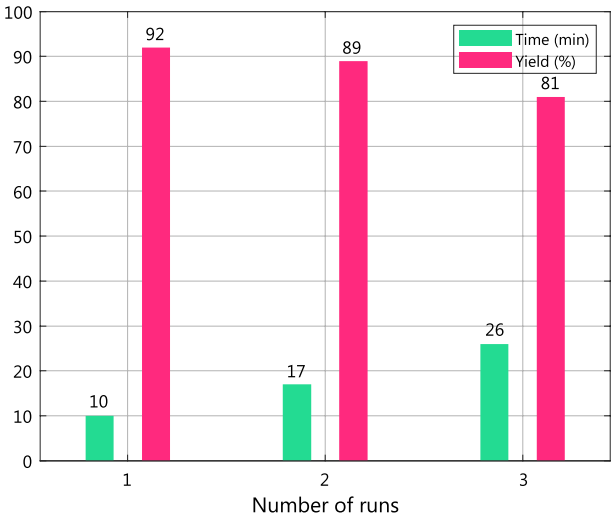


Fig. 9 Reusability of the {[SO_3H–Pyrazine–SO_3H]Cl_2} in the reaction of 4-chlorobenzaldehyde, ethyl acetoacetate and urea under optimized reaction conditions

Table 7 Comparison of the efficiency of various catalysts with {[SO_3H–Pyrazine–SO_3H]Cl_2} in the synthesis of **5a**

Entry	Catalyst	Reaction condition	Time	Yield (%)	References
1	{[SO_3H–Pyrazine–SO_3H]Cl_2} (25 mol%)	Solvent-free, 120 °C	10 min	92	This work
2	Montmorillonite KSF (0.5 g)	Solvent-free, 130 °C	48 h	76	[89]
3	$Al(HSO_4)_3$ (10 mol%)	Solvent-free, 130 °C	55 min	90	[90]
4	Fe_3O_4 @ CM (20 mg)	Water, reflux	60 min	95	[80]
5	Phytic acid (10 mol%)	Solvent-free, 100 °C	3.5 h	86	[78]

and the reaction mixture was heated at 100 °C with stirring. After completion of the reaction monitored by thin-layer chromatography (TLC), the reaction mixture was allowed to cool at room temperature. Water (10 mL) was added and filtered to separate the catalyst. Then, the obtained solid product was filtered and then recrystallized from ethanol to afford the pure product. The products were identified by IR, ^{1}H NMR and physical data (M.P.) with those reported in the literature.

General procedure for the synthesis of DHPMs under solvent-free conditions

To a mixture of aromatic aldehyde (1 mmol), ethyl acetoacetate (1 mmol) and urea (2 mmol), 25 mol% of {[SO_3H–Pyrazine–SO_3H]Cl_2} (0.25 mmol) was added and the reaction mixture was heated at 120 °C with stirring. After completion of the reaction evident from thin-layer chromatography (TLC), the reaction mixture was allowed to cool at room temperature. Water (10 mL) was added and the obtained solid product was filtered and then recrystallized from ethanol. The products were identified by IR, ^{1}H NMR and physical data (M.P.) with those reported in the literature. The spectra data for some selected compounds are presented in the following.

Spectra data of some selected compounds

3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(4-chlorophenyl)-2*H*-xanthene-1,8(5*H*, 9*H*)-dione (3a) ^{1}H NMR (500 MHz, $CDCl_3$): 7.27 (d, 2H), 7.22 (d, 2H), 4.75 (s, 1H), 2.46 (s, 4H), 2.24 (dd, 4H), 6.12 (s, 6H), 6.27 (s, 6H). IR (KBr): 2956, 1661, 1362, 1198, 1007 cm^{-1}.

3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(3-hydroxyphenyl)-2*H*-xanthene-1,8(5*H*, 9*H*)-dione (3f) ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.18 (s, 1H), 6.96 (t, 1H), 6.62 (s, 1H), 6.53 (d, 2H), 6.46 (d, 1H), 4.42 (s, 1H), 2.49 (s, 4H), 2.16 (dd, 4H), 1.04 (s, 6H), 0.90 (s, 6H). IR (KBr): 3330, 2962, 1658, 1598, 1453, 1362, 1255, 1199, 1143 cm^{-1}.

3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(2-thienyl)-2*H*-xanthene-1,8(5*H*, 9*H*)-dione (3m) ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.21 (q, 1H), 6.82 (q, 1H), 6.75 (d, 2H), 4.85 (s, 1H), 2.49 (m, 4H), 2.22 (dd, 2H), 1.03 (s, 6H), 0.953 (s, 6H). IR (KBr): 2957, 2872, 1664, 1360, 1164, 1003 cm^{-1}.

5-Ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidine-2(1*H*)-one (5a) ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.23 (s, 1H), 7.76 (s, 1H), 7.38 (d, 2H), 7.23 (d, 2H), 5.12 (s, 1H), 3.96 (q, 2H, CH_2O), 2.23 (s, 3H), 1.09 (t, 3H). IR (KBr): 3239, 3116, 2977, 1712, 1640, 1461, 1288, 1091, 782 cm^{-1}.

5-Ethoxycarbonyl-6-methyl-4-(4-bromophenyl)-3,4-dihydropyrimidine-2(1*H*)-one (5d) ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.23 (s, 1H), 7.76 (s, 1H), 7.53 (d, 2H), 719 (d, 2H), 5.12 (s, 1H), 3.96 (q, 4H), 2.24 (s, 3H), 1.10 (t, 3H). IR (KBr): 3235, 3116, 2981, 1712, 1616, 1403, 1292, 1222, 1091, 779 cm^{-1}.

5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidine-2(1*H*)-one (5k) ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.30 (s, 1H, NH), 7.89 (s, 1H, NH), 6.88-7.35 (m, ArH), 5.41 (s, 1H), 2.21 (s, 3H), 1.18 (t, 3H). IR (KBr): 3332, 3235, 3116, 2977, 1700, 1643, 1419, 1307, 1226, 1095, 786 cm^{-1}.

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidine-2(1*H*)-one (5g) ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.34 (s, 1H), 8.22 (d, 2H), 7.88 (s, 1H, NH), 7.51 (s, 1H), 5.27 (s, 1H), 4.006 (q, 4H), 2.26 (s, 3H), 1.10 (t, 3H). IR (KBr): 3232, 3120, 2981, 1704, 1643, 1523, 1349, 1299, 1318, 1095, 782 cm^{-1}.

Conclusion

In this research, we have described the preparation, characterization and catalytic application of {[SO_3H–Pyrazine–SO_3H]Cl_2} in the synthesis of xanthenediones and DHPMs under solvent-free conditions. Ease of preparation and handling of the catalyst, generality, easy workup procedure, high yields, short reaction times, reusability of catalyst and absence of organic solvents are the attractiveness of the developed procedure.

References

1. R.L. Vekariya, J. Mol. Liq. **227**, 44 (2017)
2. M. Parveen, S. Azaz, A.M. Malla, F. Ahmad, P.S.P. da Silva, M.R. Silva, New J. Chem. **39**, 469 (2015)
3. M. Talebi, R.A. Patil, D.W. Armstrong, J. Mol. Liq. **256**, 247 (2018)
4. S. Steudte, S. Bemowsky, M. Mahrova, U. Bottin-Weber, E. Tojo-Suarez, P. Stepnowski, S. Stolte, RSC Adv. **4**, 5198 (2014)
5. A.N. Masri, M.A. Mutalib, N.F. Aminuddin, J.-M. Leveque, Sep. Purif. Technol. **196**, 106 (2018)
6. N. Daneshvar, M. Nasiri, M. Shirzad, M.S.N. Langarudi, F. Shirini, H. Tajik, New J. Chem. **42**, 9744 (2018)
7. J. Chen, L. Yang, W. Zhou, L. Zhu, Y. Zhou, Y. Xiang, D. Xia, Energy Fuels **32**, 5518 (2018)
8. A. Dhar, N.S. Kumar, M. Asif, R.L. Vekariya, New J. Chem. **42**, 6990 (2018)
9. T. Hideo, Chem. Abstr. **95**, 80922b (1981)
10. J.P. Poupelin, G. Saintruf, R. Lacroix, G. Narcisse, O. Foussardblanpin, G. Uchidaernouf, Eur. J. Med. Chem. **13**, 381 (1978)
11. R.W. Lambert, J.A. Martin, J.H. Merrett, K.E.B. Parkes, G. Thomas, Chem. Abstr. **126**, p212377y (1997)

12. G. Saintruf, J.P. Poupelin, Naturwissenschaften **62**, 584 (1975)
13. R.-M. Ion, A. Planner, K. Wiktorowicz, D. Frackowiak, Acta Biochim. Pol. **45**, 833 (1998)
14. V.R. Narayana, Z. Pudukulathan, R. Varala, Organ. Commun. **6**, 110 (2013)
15. P. Iniyavan, S. Sarveswari, V. Vijayakumar, Res. Chem. Intermed. **41**, 7413 (2015)
16. M. Seyyedhamzeh, P. Mirzaei, A. Bazgir, Dyes Pigm. **76**, 836 (2008)
17. A. Rahmati, Chin. Chem. Lett. **21**, 761 (2010)
18. F. Abbasi, N. Azizi, M. Abdoli-Senejani, J. Iran. Chem. Soc. **14**, 2097 (2017)
19. G.R. Chaudhary, P. Bansal, N. Kaur, S. Mehta, RSC Adv. **4**, 49462 (2014)
20. B. Maleki, A. Davoodi, M.V. Azghandi, M. Baghayeri, E. Akbarzadeh, H. Veisi, S.S. Ashrafi, M. Raei, New J. Chem. **40**, 1278 (2016)
21. P.J. Das, J. Das, RSC Adv. **5**, 11745 (2015)
22. A. Ilangovan, S. Malayappasamy, S. Muralidharan, S. Maruthamuthu, Chem. Cent. J. **5**, 81 (2011)
23. H. Ulusal, G. Fındıkkıran, O. Demirkol, D. Akbaşlar, E.S. Giray, J. Supercrit. Fluid. **105**, 146 (2015)
24. A.N. Dadhania, V.K. Patel, D.K. Raval, J. Saudi Chem. Soc. **21**, S163 (2017)
25. K. Gong, H. Wang, S. Wang, Y. Wang, J. Chen, Chin. J. Catal. **36**, 1249 (2015)
26. A. Thakur, A. Sharma, A. Sharma, Synth. Commun. **46**, 1766 (2016)
27. A. Rajini, C. Suman, A. Ajay Kumar, S. Suresh, N. Venkatathri, Synth. Commun. **46**, 1671 (2016)
28. Z. Zhou, X. Deng, J. Mol. Catal. A: Chem. **367**, 99 (2013)
29. Z.-H. Zhang, Y.-H. Liu, Catal. Commun. **9**, 1715 (2008)
30. H.Y. Lue, J.J. Li, Z.H. Zhang, Appl. Organomet. Chem. **23**, 165 (2009)
31. M.A. Ghasemzadeh, J. Safaei-Ghomi, S. Zahedi, J. Serb. Chem. Soc. **78**, 769 (2013)
32. G.K. Verma, K. Raghuvanshi, R.K. Verma, P. Dwivedi, M. Singh, Tetrahedron **67**, 3698 (2011)
33. D. Fang, J.M. Yang, Z.L. Liu, J. Heterocycl. Chem. **48**, 468 (2011)
34. F. Shirini, M.S.N. Langarudi, M. Seddighi, O.G. Jolodar, Res. Chem. Intermed. **41**, 8483 (2015)
35. S. Nazari, M. Keshavarz, B. Karami, N. Iravani, M. Vafaee-Nezhad, Chin. Chem. Lett. **25**, 317 (2014)
36. A. Zare, A.R. Moosavi-Zare, M. Merajoddin, M.A. Zolfigol, T. Hekmat-Zadeh, A. Hasaninejad, A. Khazaei, M. Mokhlesi, V. Khakyzadeh, F. Derakhshan-Panah, J. Mol. Liq. **167**, 69 (2012)
37. N. Azizi, F. Abbasi, M. Abdoli-Senejani, ChemistrySelect **3**, 3797 (2018)
38. N. Azizi, F. Shirdel, J. Mol. Liq. **222**, 783 (2016)
39. N. Hazeri, A. Masoumnia, M.T. Mghsoodlou, S. Salahi, M. Kangani, S. Kianpour, S. Kiaee, J. Abonajmi Res. Chem. Intermed. **41**, 4123 (2015)
40. M. Nisar, I. Ali, M.R. Shah, A. Badshah, M. Qayum, H. Khan, I. Khan, S. Ali, RSC Adv. **3**, 21753 (2013)
41. S. Sadjadi, M.M. Heravi, M. Daraie, Res. Chem. Intermed. **43**, 843 (2017)
42. M. Rohaniyan, A. Davoodnia, S.A. Beyramabadi, A. Khojastehnezhad, Appl. Organomet. Chem. **33**, e4881 (2019)
43. M. Salami, A. Ezabadi, Res. Chem. Intermed. **45**, 3673 (2019)
44. Z. Abdi Piralghar, M. M. Hashemi, A. Ezabadi. Polycycl. Aromat. Compd. 1 (2019)
45. Z. Ehsani-Nasab, A. Ezabadi, Comb. Chem. High Throughput Screening **21**, 602 (2018)
46. Z.A. Piralghar, M.M. Hashemi, A. Ezabadi, Comb. Chem. High Throughput Screening **21**, 526 (2018)
47. M. Puripat, R. Ramozzi, M. Hatanaka, W. Parasuk, V. Parasuk, K. Morokuma, J. Org. Chem. **80**, 6959 (2015)
48. P. Biginelli, Gazz. Chim. Ital. **23**, 360 (1893)
49. G.C. Tron, A. Minassi, G. Appendino, Eur. J. Org. Chem. **2011**, 5541 (2011)
50. G. Maiti, P. Kundu, C. Guin, Tetrahedron Lett. **44**, 2757 (2003)
51. A. Khorshidi, K. Tabatabaeian, H. Azizi, M. Aghaei-Hashjin, E. Abbaspour-Gilandeh, RSC Adv. **7**, 17732 (2017)
52. M. Brands, R. Endermann, R. Gahlmann, J. Krüger, S. Raddatz, Bioorgan. Med. Chem. Lett. **13**, 241 (2003)
53. B. Tozkoparan, M. Ertan, P. Kelicen, R. Demirdamar, Il Farmaco **54**, 588 (1999)
54. G.J. Grover, S. Dzwonczyk, D.M. McMullen, D.E. Normandin, C.S. Parham, P.G. Sleph, S. Moreland, J. Cardiovasc. Pharmacol. **26**, 289 (1995)
55. A. Debache, M. Amimour, A. Belfaitah, S. Rhouati, B. Carboni, Tetrahedron Lett. **49**, 6119 (2008)
56. U.K. Sharma, N. Sharma, R. Kumar, A.K. Sinha, Amino Acids **44**, 1031 (2013)
57. T.M. Kapoor, T.U. Mayer, M.L. Coughlin, T.J. Mitchison, J. Cell Biol. **150**, 975 (2000)
58. Y. Yu, D. Liu, C. Liu, G. Luo, Bioorg. Med. Chem. Lett. **17**, 3508 (2007)

59. B. Jauk, T. Pernat, C. Kappe, Molecules **5**, 227 (2000)
60. C.O. Kappe, J. Org. Chem. **62**, 7201 (1997)
61. A. Crespo, A. El Maatougui, P. Biagini, J. Azuaje, A. Coelho, J. Brea, M.I. Loza, M.I. Cadavid, X. García-Mera, H. Gutiérrez-de-Terán, ACS Med. Chem. Lett. **4**, 1031 (2013)
62. B.C. O'Reilly, K.S. Atwal, Heterocycles **26**, 1185 (1987)
63. N.Y. Gorobets, Y.V. Sedash, K.S. Ostras, O.V. Zaremba, S.V. Shishkina, V.N. Baumer, O.V. Shishkin, S.M. Kovalenko, S.M. Desenko, E.V. Van der Eycken, Tetrahedron Lett. **51**, 2095 (2010)
64. J. Světlík, V. Kettmann, Tetrahedron Lett. **52**, 1062 (2011)
65. H. Cho, Y. Nishimura, Y. Yasui, S. Kobayashi, S.-I. Yoshida, E. Kwon, M. Yamaguchi, Tetrahedron **67**, 2661 (2011)
66. Z. Hassani, M.R. Islami, M. Kalantari, Bioorg. Med. Chem. Lett. **16**, 4479 (2006)
67. T. Shu-Jiang, Z. Xiao-Tong, F. Fang, Z. Xiao-Jing, Z. Song-Lei, L. Tuan-Jie, S. Da-Qing, W. Xiang-Shan, J. Shun-Jun, Chin. J. Chem. **23**, 596 (2005)
68. L.M. Ramos, A.Y. Ponce de Leon y Tobio, M.R. dos Santos, H.C. de Oliveira, A.F. Gomes, F.C. Gozzo, A.L. de Oliveira, B.A. Neto, J. Org. Chem. **77**, 10184 (2012)
69. O.M. Singh, N.S. Devi, J. Org. Chem. **74**, 3141 (2009)
70. E.H. Hu, D.R. Sidler, U.-H. Dolling, J. Org. Chem. **63**, 3454 (1998)
71. M. Pramanik, A. Bhaumik, ACS Appl. Mater. Interfaces. **6**, 933 (2014)
72. C.K. Khatri, D.S. Rekunge, G.U. Chaturbhuj, New J. Chem. **40**, 10412 (2016)
73. H.G. Alvim, T.B. de Lima, H.C. de Oliveira, F.C. Gozzo, J.L. de Macedo, P.V. Abdelnur, W.A. Silva, B.A. Neto, ACS Catal. **3**, 1420 (2013)
74. N. Sharma, U.K. Sharma, R. Kumar, A.K. Sinha, RSC Adv. **2**, 10648 (2012)
75. F. Dong, L. Jun, Z. Xinli, Y. Zhiwen, L. Zuliang, J. Mol. Catal. A: Chem. **274**, 208 (2007)
76. F. Heidarizadeh, E.R. Nezhad, S. Sajjadifar, Sci. Iran. **20**, 561 (2013)
77. Q. Zhang, X. Wang, Z. Li, W. Wu, J. Liu, H. Wu, S. Cui, K. Guo, RSC Adv. **4**, 19710 (2014)
78. R.V. Patil, J.U. Chavan, D.S. Dalal, V.S. Shinde, A.G. Beldar, ACS Comb. Sci. **21**, 105 (2019)
79. H.Z. Mohammad, S. Javanshir, B. Hemmati, Z. Dolatkhah, M. Fardpour, Chem. Cent. J. **12**, 108 (2018)
80. D.P. Narayanan, A. Gopalakrishnan, Z. Yaakob, S. Sugunan, B.N. Narayanan. Arab. J. Chem. **13**, 318 (2020)
81. M. Nasr-Esfahani, M. Taei, RSC Adv. **5**, 44978 (2015)
82. M. Sheykhan, A. Yahyazadeh, Z. Rahemizadeh, RSC Adv. **6**, 34553 (2016)
83. N.H. Thi Nguyen, P.P. Thi Nguyen, T.D. Thi Nguyen, M.N. Thi Tran, T.N. Thi Huynh, P.H. Tran, ChemistrySelect **2**, 3932 (2017)
84. J. Safari, S. Gandomi-Ravandi, New J. Chem. **38**, 3514 (2014)
85. A.R. Hajipour, M. Seddighi, Synth. Commun. **42**, 227 (2012)
86. A. Zhu, Q. Li, L. Li, J. Wang, Catal. Lett. **143**, 463 (2013)
87. A. Debache, R. Boulcina, R. Tafer, A. Belfaitah, S. Rhouati, B. Carboni, Chin. J. Chem. **26**, 2112 (2008)
88. F. Bigi, S. Carloni, B. Frullanti, R. Maggi, G. Sartori, Tetrahedron Lett. **40**, 3465 (1999)
89. H.R. Shaterian, A. Hosseinian, M. Ghashang, F. Khorami, N. Karimpoor, Phosphorus, Sulfur Silicon Relat. Elem. **184**, 2333 (2009)