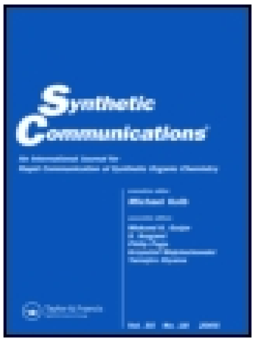

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Green one-pot multicomponent synthesis of pyrrolidinones using planetary ball milling process under solvent-free conditions

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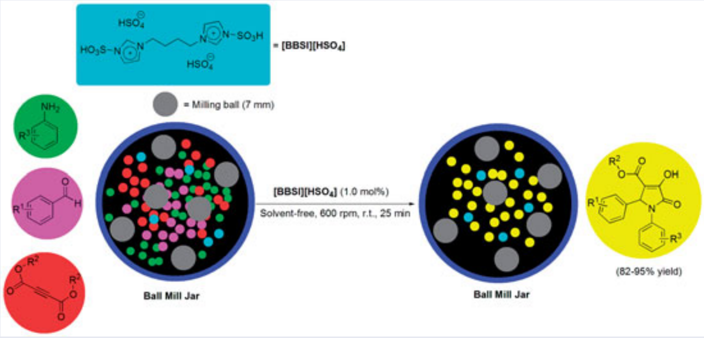
ABSTRACT

This paper presents a novel and efficient protocol for the synthesis of pyrrolidinones using catalytic loading of 1,1′-butylenebis(3-sulfo-3H-imidazol-1-ium) hydrogen sulfate as a recyclable Brönsted acid ionic liquid through ball milling process at room temperature under solvent-free conditions. The developed method provides good to excellent yields of various pyrrolidinones in environmentally friendly conditions. Furthermore, this efficient protocol displays a combination of the synthetic advantage of one-pot multicomponent reaction with ecological benefits and convenience of a mechanochemical procedure.

GRAPHICAL ABSTRACT



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KEYWORDS
Mechanochemistry; pyrrolidinone; ionic liquid; Brönsted acid; eco-friendly conditions

Introduction

The chemists have been broadly interested to the design of new protocols based on some of the essential and sustainable approaches including avoiding toxic and volatile solvents or perform the reaction under solvent-free conditions, load catalytic amounts

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of catalyst instead of stoichiometric amounts and use nontoxic recyclable catalysts.[1,2] The ball milling as a mechanochemical process under solvent-free conditions plays an important role in the academic and industrial transformations which can lead to the reduced amount of catalyst loading, a shorter reaction time, and a higher yield.[3] The applications of the planetary ball mill was broadly reported in the literature for the synthesis of catalysts,[4] metal complexes,[5] heterocycles,[6] *N*-methyl imines,[7,8] catenanes and rotaxanes,[9] metal-organic frameworks (MOFs),[10] and the C–C bond formation reactions, protection functional groups, fullerenes, and redox processes.[11]

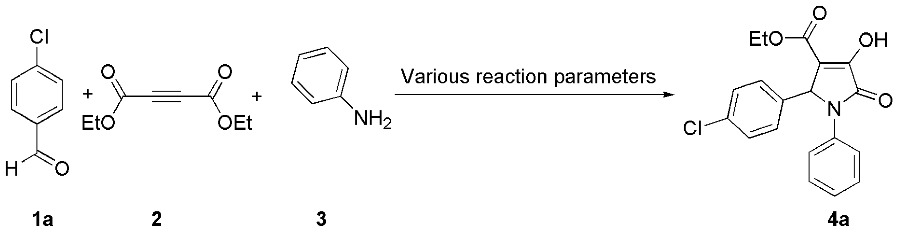
We recently succeeded in the synthesis of two novel binuclear Brönsted acid ionic liquids based on imidazole viz. 1,1′-butylenebis(3-sulfo-3*H*-imidazol-1-ium) chloride (**[BBSI]Cl**) and 1,1′-butylenebis(3-sulfo-3*H*-imidazol-1-ium) hydrogen sulfate (**[BBSI][HSO$_4$]**). Their catalytic applications were demonstrated for the one-pot multicomponent synthesis of bis(indolyl)methanes,[12] xanthenes,[13] and pyrrolidinones under conventional conditions.[14] As part of our studies in developing non-conventional processes for the synthesis of valuable compounds,[7,8] herein, the synthesis of pyrrolidinones is reported in the presence of catalytic amount of **[BBSI]Cl** and **[BBSI][HSO$_4$]** under solvent-free conditions at room temperature using ball milling process. A simple separation and purification of products without the requirement of a chromatography, solvent-free and mild conditions and easy recycling of the catalyst are attractive merits of the current protocol.

Results and discussion

Synthesis of pyrrolidinones in the presence of [BBSI]Cl and [BBSI][HSO$_4$]

The condensation reaction of 4-chlorobenzaldehyde (**1a**), aniline, and diethyl acetylenedicarboxylate were investigated as a model reaction for the optimization of the reaction parameters, (Scheme 1).

The model reactants were ground using the planetary ball mill in the absence of a catalyst at room temperature under solvent-free conditions. After 2 hours, the TLC and GC-MS spectra of the reaction mixture showed no respective product, viz. ethyl-2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-*1H*-pyrrole-3-carboxylate (**4a**) (Table 1, entry 1). Then, the model reactants were milled in the presence of **[BBSI]Cl** for two hours. The crude product was extracted with ethyl acetate from grinding jar and purified by recrystallization from hot ethanol which afforded the desired product (**4a**) in 42% yield (Table 1, entry 2). A **[BBSI]Cl** loading to 1.0 mol% showed a more favorable effect on the reaction yield (Table 1, entry 3). However, no significant



Scheme 1. Investigation and optimization of various reaction parameters.

improvement was observed in the yield of **4a** at higher catalyst loading up to 2.0 mol% (Table 1, entry 4). When the reaction time was curtailed to 30 min, no considerable difference was observed in the reaction yield (Table 1, entry 5), while the yield dropped when the reaction time was reduced from 30 min to 20 min (Table 1, entry 6). Then, the influence of technical parameters such as revolution per minute (rpm), number and size of ball mill were studied on the performing of the model reaction. As shown in Table 1, the results displayed that rpm has a vital influence on the yield of the desired product, at which point, the best yield of **4a** was observed at 600 rpm of the planetary ball mill within 30 min (Table 1, entries 5, 7 and 8). While the other parameters were kept constant, the number and the size of the milling balls were changed. As reported in the literature, these parameters directly influence the active surface area and the total mass of the milling balls, which are important variables for the energy transfer and increase of internal temperature and pressure.[15] As expected, a higher yield of **4a** was obtained when the experiment was conducted with a higher number and larger size of milling balls (Table 1, entries 13 and 14). Then, the model reaction was conducted in the presence of **[BBSI][HSO$_4$]** under the aforementioned optimized reaction conditions. The results exhibited that the ionic liquid bearing an acidic and non-coordinating anion had a crucial influence not just on the reaction yield but on the reaction time too (Table 2). Therefore, entry 6 in Table 2 was chosen as the optimized reaction conditions

Table 1. Optimization of the synthesis of ethyl-2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate in the presence of **[BBSI]Cl** using planetary ball mill[a].

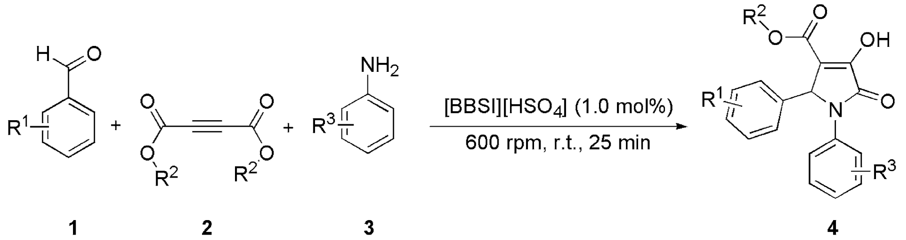
Entry	Loading **[BBSI]Cl** (mol%)	Number of ball mill	Speed (rpm)	Ball mill diameter (mm)	Milling time (min)	Yield (%)[b]
1	0	4	300	7	120	–[c]
2	0.5	4	300	7	120	42
3	1.0	4	300	7	120	58
4	2.0	4	300	7	120	59
5	1.0	4	300	7	30	56
6	1.0	4	300	7	20	47
7	1.0	4	600	7	30	68
8	1.0	4	500	7	30	65
9	**1.0**	**6**	**600**	**7**	**30**	**87**
10	1.0	6	600	5	30	46

[a] Reaction conditions: 4-chlorobenzaldehyde (**1a**) (5.0 mmol), aniline (5.0 mmol), and diethyl acetylenedicarboxylate (5.0 mmol), room temperature.
[b] Isolated yield.
[c] Monitored by GC-MS.
[d] Bold values signify the optimize reaction conditions.

Table 2. The synthesis of ethyl-2-(4-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate in the presence of **[BBSI][HSO$_4$]** using planetary ball mill.[a]

Entry	Loading **[BBSI][HSO$_4$]** (mol%)	Number of ball mill	Speed (rpm)	Ball mill diameter (mm)	Milling time (min)	Yield (%)[b]
1	1.0	6	600	7	30	92
2	0.5	6	600	7	30	64
3	1.0	4	600	7	30	76
4	1.0	6	600	5	30	58
5	1.0	6	600	7	20	72
6	**1.0**	**6**	**600**	**7**	**25**	**92**

[a] Reaction conditions: 4-chlorobenzaldehyde (**1a**) (5.0 mmol), aniline (5.0 mmol), and diethyl acetylenedicarboxylate (5.0 mmol), room temperature.
[b] Isolated yield.
[c] Bold values signify the optimize reaction conditions.



Scheme 2. Synthesis of pyrolidinones in the presence of [BBSI][HSO4] under optimal conditions.

Table 3. The one-pot multicomponent synthesis of pyrolidinone derivatives **4(a-o)** using ball mill process in the presence of **[BBSI][HSO$_4$]** under optimized reaction conditions[a].

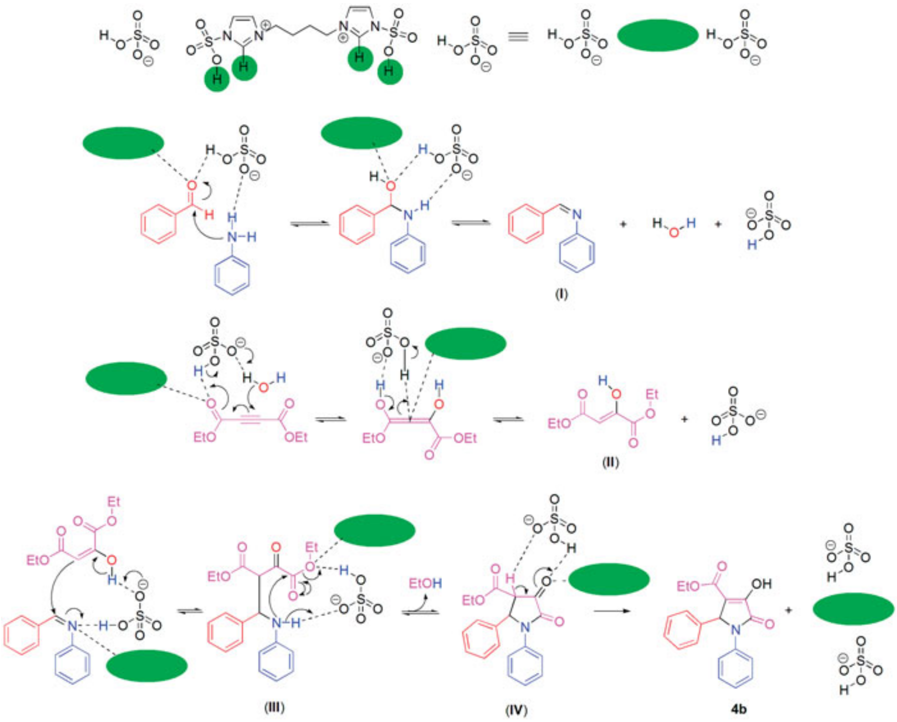
Entry	R^1 (**1**)	R^2 (**2**)	R^3 (**3**)	Product (**4**)	Yield (%)[b]
1	4-Cl	Et	H	a	92
2	H	Et	H	b	90
3	4-CH_3	Et	H	c	88
4	4-CF_3	Et	H	d	96
5	4-NO_2	Et	H	e	92
6	4-CH_3O	Et	H	f	87
7	4-OH	Et	H	g	85
8	2-NO_2	Et	H	h	95
9	2-Cl	Et	H	i	84
10	2-CH_3O	Et	H	j	82
11	H	Me	H	k	90
12	4-CH_3	Me	H	l	86
13	4-CF_3	Et	4-CH_3	m	84
14	4-CF_3	Et	4-NO_2	n	82
15	4-CF_3	Et	4-CH_3O	o	87

[a] Reaction conditions: aryl aldehyde (**1**) (5.0 mmol), dialkyl acetylenedicarboxylate (**2**) (5.0 mmol), aniline or its derivatives (**3**) (5.0 mmol), **[BBSI][HSO$_4$]** (0.05 mmol), six milling ball (diameter 7 mm), revolution rate (600 rpm), room temperature, milling time (25 min).
[b] Isolated yield.

and the scope and generality of the present protocol for the preparation of pyrrolidinones was evaluated (Scheme 2).

A broad range of pyrrolidinone derivatives was prepared in good to excellent yield under optimal reaction conditions (Table 3). The reaction proceeded smoothly with aldehydes bearing electron-withdrawing or electron-donating substituents in the aromatic ring. The anilines bearing electron-withdrawing substituents in *para*-position afforded a slightly lower yield of the desired product than electron-donating substituents at the same position due to the deactivation of the amino group (Table 3, entries 13-15). All the known products have spectral and physical data consistent with those reported in the literature.[14] It is worth mentioning that the proton of the 4-hydroxyl group in all of the respective pyrrolidinones showed the most downfield broad peak at ~9 ppm (^1H NMR, $CDCl_3$). It is probably due to the anisotropy of carbonyl groups resulting from the β-interaction with one amino carbonyl function, and a γ-interaction with the carboxylate function.

A possible mechanism was previously reported in the presence of **[BBSI]Cl** in the literature.[14] The [BBSI]Cl and [BBSI][HSO4] have the same cation moiety, and the experimental results exhibited that the anion moiety plays a vital role in the yield and



Scheme 3. A possible mechanism for the one-pot multicomponent synthesis of 4 b in the presence of [BBSI][HSO4].

the reaction time. Therefore, a possible mechanism was proposed for the illustration of this concept (Scheme 3). The sulfonic acid groups and CH-2 of imidazole rings on the cation moiety and hydrogen sulfate anion of **[BBSI][HSO$_4$]** simultaneously activate benzaldehyde and aniline to initiate the condensation reaction through the hydrogen bond (HB). The imine (**I**) is formed through the attack of aniline to the carbonyl group of benzaldehyde followed by removing a water molecule. As shown in the Scheme 3, the IL cation and hydrogen sulfate anion can promote the second reaction step viz. the addition of water molecule from the first reaction step or medium to diethyl acetylene dicarboxylate by the formation of HB. The intermediate (**III**) is afforded through the Michael addition of imine (**I**) and intermediate (**II**). An intermolecular cyclization (**IV**) and the elimination of one ethanol molecule (**V**) along with tautomerization will give the final product. The IL cation and HSO_4^- as a good HB donor-acceptor and proton exchanger can prompt the third reaction step too.

Table 4 exhibits the superiority of the current protocol in comparison with a few other methods reported in the literature in terms of solvent-free condition, catalyst loading, yield, reaction time, and recyclability of the catalyst.

The feasibility of the present method on gram scaled experiment was studied through the reaction of the 4-chlorobenzaldehyde (0.05 mol), diethyl acetylene dicarboxylate (0.05 mol), aniline (0.05 mol), and **[BBSI][HSO$_4$]** (5 mmol) under optimized reaction conditions which afforded **4a** in 87% isolated yield within 25 min.

Table 4. The comparative study of present vs. previously reported methodology for the synthesis of **4b**.

Entry	Catalyst	Catalyst loading (mol%)	Solvent	Temp. (°C)	Reaction time (h)	Yield (%)	Recyclable	Ref.
1	[BBSI]Cl	1.0	Ethanol (96%)	r.t.	30 min	86	Yes	[14]
2	–	–	Ethanol/H_2O (1:1 v/v)	r.t.	15	87	–	[16]
3	Citric acid monohydrate	200	Ethanol	r.t.	10	85	No	[17]
4	Citric acid monohydrate	200	Ethanol (US 100W)	40	20 min	90	No	[17]
5	*p*-toluenesulfonic acid	20	Ethanol	r.t.	48	62	No	[18]
6	Lactic acid (Solvent)	1 mL (1140)	Lactic acid (85% wt/wt)	30	2	60[a]	No	[19]
7	Glacial acetic acid	1 mL (1746)	Glacial acetic acid	30	2	24[a]	No	[19]
8	[BBSI]Cl	1.0	Solvent-free (Ball milling)	r.t.	30 min	87	Yes	This work
9	[BBSI][HSO_4]	1.0	Solvent-free (Ball milling)	r.t.	25 min	90	Yes	This work

[a] 4-methyl benzaldehyde.

Reusability of [BBSI][HSO_4]

Two procedures were carried out to evaluate the recyclability of **[BBSI][HSO_4].** In the first procedure involved, the extraction of the product with ethyl acetate several times. Then, the remained IL was concentrated and the reaction jar was recharged with new model reactants for another run. The product **4a** was obtained in an average 92–90% yield for three subsequent runs. Furthermore, the chemical structure of the IL showed no significant change under the present workup.

In the other procedure, the **[BBSI][HSO_4]** was washed with deionized water followed by evaporation of water from an aqueous solution containing the IL. The recovered IL was successfully reused for the subsequent runs without significant loss of catalytic activity. The results demonstrated that both procedures were practical for the recovering of **[BBSI][HSO_4]** after reactions.

Experiment

General

Unless specified, all chemicals were analytical grade and purchased from Merck, Aldrich, and Fluka Chemical Companies and used without further purification. Products were characterized by their physical constant and IR, NMR and elemental analysis. The purity determination of the substrates and reaction monitoring were accompanied by TLC using silica gel SIL G/UV 254 plates. The FT-IR spectra were recorded on a Perkin Elmer 781 Spectrophotometer using KBr pellets for solid and neat for liquid samples in the range of 4000–400 cm^{-1}. In all the cases, the ^1H and ^{13}C NMR spectra were recorded with Bruker Avance III 600 MHz and 400 MHz instrument. All chemical shifts are quoted in parts per million (ppm) relative to TMS using deuterated solvent.

Microanalyses were performed on a Perkin- Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. Ball-milling was performed in a Retsch PM100 planetary ball mill using a 10 mL and 25 mL stainless steel chamber and four-six stainless steel balls (diameter: 5 or 7 mm) with 300–600 revolution per minute (rpm).

The typical procedure for the synthesis of ethyl-1-phenyl-2-(4-chlorophenyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (4a)

A mixture of 4-chlorobenzaldehyde (5.0 mmol) (1), dialkyl acetylene dicarboxylate (5.0 mmol), aniline (5.0 mmol), and **[BBSI][HSO$_4$]** ionic liquid (0.05 mmol, 1.0 mol%) was ground stirred in milling jar at 600 rpm for 25 min in the presence of six milling ball (diameter 7 mm). The crude products were extracted by EtOAc (3 × 10 mL) and the collected extracted organic phases were dried on anhydrous Na_2SO_4 and the solvent was removed under vacuum and the product purified by recrystallized from hot ethanol to get the pure ethyl-1-phenyl-2-(4-chlorophenyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**4a**).

*Ethyl-1-phenyl-2-(4-chlorophenyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**4a**)*: 1.65 g (yield 92%); mp 189–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20 (t, $J = 7.0$ Hz, 3H), 4.20 (q, $J = 7.0$ Hz, 2H), 5.72 (s, 1H), 7.11–7.17 (m, 3H), 7.22–7.30 (m, 4H), 7.43 (d, $J = 8.0$ Hz, 2H), 9.04 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.6, 60.5, 61.1, 112.5, 122.0, 125.8, 128.6, 128.7, 128.9, 133.4, 134.1, 135.8, 156.3, 162.4, 164.6 ppm; Anal. Calcd. for $C_{19}H_{16}ClNO_4$: C, 63.78; H, 4.51; N, 3.91; Found: C, 63.73; H, 4.49; N, 3.86%.

All the known products have spectral and physical data consistent with those reported in the literature as well as the samples prepared from previously reported methods.[14]

Recycling catalyst

After extraction of the crude products, the remaining IL was concentrated and the reaction jar was recharged with new model reactants for the next run.

Conclusion

The catalytic efficiency of **[BBSI][HSO$_4$]** was demonstrated for the synthesis of pyrrolidinones through ball mill process under mild and solvent-free conditions. The current protocol has the advantages such as solvent-free process, good to excellent yield of the desired products within short reaction times, a broad substrate-scope, and recyclability of the catalyst. The achieved experimental data for the synthesis of pyrrolidinones shows that **[BBSI][HSO$_4$]** can be an efficient Brönsted acid ionic liquid catalyst for the one-pot multicomponent reactions and we hope that our work will encourage further research in this area with promising results for future applications of **[BBSI][HSO$_4$]**.

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Disclosure statement

There are no conflicts of interest to declare.

Supporting information

Full experimental detail along with yield, melting point, ^{1}H and ^{13}C NMR spectra, elemental analysis data, and ^{1}H NMR and ^{13}C NMR copies of 4a, 4d, 4 g, 4 l, 4 m, 4n, and 4o can be found via the "Supplementary Content" section of this article's webpage.

References

[1] Tanaka, K.; Toda, F. Solvent-Free Organic Synthesis. *Chem. Rev.* **2000**, *100*, 1025–1074. DOI: 10.1021/cr940089p.

[2] Wenda, S.; Illner, S.; Mell, A.; Kragl, U. Industrial Biotechnology—The Future of Green Chemistry? *Green Chem.* **2011**, *13*, 3007–3047. DOI: 10.1039/c1gc15579b.

[3] Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. Solvent-Free Heterocyclic Synthesis. *Chem. Rev.* **2009**, *109*, 4140–4182. DOI: 10.1021/cr9001098.

[4] Kubias, B.; Fait, M. J. G.; Schlogl, R. Mechanochemical Methods. In *Hand Book of Heterogeneous Catalysis*, 2nd ed.; Ertl, G., Knozinger, H., Schuth, F., Weitkamp, J., Eds.; Wiley-VCH: Weinheim, **2008**, pp. 571–583.

[5] Garay, A. L.; Pichon, A.; James, S. L. Solvent-Free Synthesis of Metal Complexes. *Chem. Soc. Rev.* **2007**, *36*, 846–855. DOI: 10.1039/b600363j.

[6] M'hamed, M. O. Ball Milling for Heterocyclic Compounds Synthesis in Green Chemistry: A Review. *Synth. Commun.* **2015**, *45*, 2511–2528. DOI: 10.1080/00397911.2015.1058396.

[7] Khaligh, N. G.; Abbo, H. S.; Salam, S. J. J. Synthesis of *N*-Methyl Imines in the Presence of Poly(N-Vinylpyridine) as a Reusable Solid Base Catalyst by a Mechanochemical Process. *Res. Chem. Intermed.* **2017**, *43*, 901–910. DOI 10.1007/s11164-016-2672-y. DOI: 10.1007/s11164-016-2672-y.

[8] Khaligh, N. G.; Ling, O. C.; Mihankhah, T.; Johan, M. R.; Ching, J. J. Mechanosynthesis of *N*-Methyl Imines Using Recyclable Imidazole-Based Acid-Scavenger: *In Situ* Formed Ionic Liquid as Catalyst and Dehydrating Agent. *Aust. J. Chem.* **2018**, *72*, 194–199. DOI: 10.1071/CH18408.

[9] Hsu, C. C.; Chen, N. C.; Lai, C. C.; Liu, Y. H.; Peng, S. M.; Chiu, S. H. Solvent-Free Synthesis of the Smallest Rotaxane Prepared to Date. *Angew. Chem. Int. Ed.* **2008**, *47*, 7475–7478. DOI: 10.1002/anie.200803056.

[10] Wilke, M.; Klimakow, M.; Rademann, K.; Emmerling, F. Fast and Efficient Synthesis of a Host Guest System: A Mechanochemical Approach. *CrystEngComm.* **2016**, *18*, 1096–1100. DOI: 10.1039/C5CE01868D.

[11] Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B. Ball Milling in Organic Synthesis: Solutions and Challenges. *Chem. Soc. Rev.* **2011**, *40*, 2317–2329. DOI: 10.1039/c0cs00195c.

[12] Khaligh, N. G.; Mihankhah, T.; Johan, M. R.; Ching, J. J. Two Novel Binuclear Sulfonic Functionalized Ionic Liquids: Influence of Anion and Carbon-Spacer on Catalytic Efficiency for One-Pot Synthesis of Bis(Indolyl)Methanes. *J. Mol. Liq.* **2018**, *259*, 260–273. DOI: 10.1016/j.molliq.2018.03.044.

[13] Khaligh, N. G. Synthesis and Characterization of Novel Binuclear Task-Specific Ionic Liquid: An Efficient and Sustainable Sulfonic-Functionalized Ionic Liquid for One-Pot Synthesis of Xanthenes. *Res. Chem. Intermed.* **2018**, *44*, 4045–4062. DOI: 10.1007/s11164-018-3354-8.

[14] Khaligh, N. G.; Chong, K. F.; Mihankhah, T.; Titinchi, S.; Johan, M. R.; Ching, J. J. An Efficient Synthesis of Pyrrolidinone Derivatives in the Presence of 1,1'-Butylenebis(3-Sulfo-3*H*-Imidazol-1-Ium) Chloride. *Aust. J. Chem.* **2018**, *71*, 566–572. DOI: 10.1071/CH18246.

[15] Schneider, F.; Stolle, A.; Ondruschka, B.; Hopf, H. The Suzuki – Miyaura Reaction under Mechanochemical Conditions. *Org. Process Res. Dev.* **2009**, *13*, 44–48. DOI: 10.1021/op800148y.

[16] Zonouz, A. M.; Eskandari, I.; Notash, B. Efficient Synthesis of 3-Pyrrolin-2-One Derivatives in Aqueous Media. *Synth. Commun.* **2015**, *45*, 2115–2121. DOI: 10.1080/00397911.2015.1065506.

[17] Ahankar, H.; Ramazani, A.; S̀Lepokura, K.; Lis, T.; Joo, S. W. Synthesis of Pyrrolidinone Derivatives from Aniline, an Aldehyde and Diethyl Acetylenedicarboxylate in an Ethanolic Citric Acid Solution under Ultrasound Irradiation. *Green Chem.* **2016**, *18*, 3582–3593. DOI: 10.1039/C6GC00157B.

[18] Sun, J.; Wu, Q.; Xia, E.-Y.; Yan, C.-G. Molecular Diversity of Three-Component Reactions of Aromatic Aldehydes, Arylamines, and Acetylenedicarboxylates. *Eur. J. Org. Chem.* **2011**, *2011*, 2981–2986. DOI: 10.1002/ejoc.201100008.

[19] Yang, J.; Tan, J.-N.; Gu, Y. Lactic Acid as an Invaluable Bio-Based Solvent for Organic Reactions. *Green Chem.* **2012**, *14*, 3304–3317. DOI: 10.1039/c2gc36083g.